A Case Control Etiologic Study of Sarcoidosis
ACCESS

PROCEDURES MANUAL
VOLUME I

FEBRUARY 1999

NOTICE

The contents of this Procedures Manual are confidential and are not to be cited or discussed except with individuals to whom it has been distributed on behalf of the ACCESS Steering Committee.

Prepared by:

Clinical Trials & Surveys Corp. (C-TASC)
The Village of Cross Keys
350 West Quadrangle
Baltimore, Maryland 21210

ACCESS PROCEDURES MANUAL - VOLUME 1

TABLE OF CONTENTS

TABLE OF CONTENTS (*Continued*)

TABLE OF CONTENTS (*Continued*)

TABLE OF CONTENTS (*Continued*)

TABLE OF CONTENTS (*Continued*)

ACCESS PROCEDURES MANUAL - VOLUME 1

TABLE OF CONTENTS (*Continued*)

TABLE OF CONTENTS (*Continued*)

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
VOLUME I

PREFACE

The ACCESS Procedures Manual consists of four volumes:

Volume I Clinical Center, Clinical Coordinating Center, and RDD (Random Digit Dialing) Interview Group Activities;

Volume II ACCESS Forms and Detailed Instructions for ACCESS Forms;

Volume III Data Management Procedures for Clinical Centers; and

Volume IV Core and Special Study Laboratory Procedures.

These volumes provide a detailed description of study methods, definitions and procedures used in data collection in each Clinical Center and each Core and Special Study Laboratory. Volume I is intended to provide clear and explicit instructions on how to perform each aspect of the required study examinations including recruitment procedures for cases and controls; providing orientation and obtaining informed consent; obtaining and preparing blood and other biological specimens; performing pulmonary function testing; and completing study forms and responding to edit queries from the Clinical Coordinating Center. The introduction of each chapter in Volume I provides an overview of the content of the chapter. Volume II, Part A contains copies of study forms and Part B contains the detailed instructions for administering and completing the ACCESS forms. Volume III contains the detailed instructions for the Clinical Center data management system and Volume IV contains the detailed methods for each approved Core and Special Study Laboratory.

The goal in ACCESS is to recruit 720 cases with sarcoidosis and 720 controls. Each control is identified by random digit dialing and is matched to a case on the basis of age, gender, and ethnic origin. The cases will be recruited in the interval November 1996 through April 30, 1999,

and the matched control for each case is to be recruited within two months of the case or by June 30, 1999. The primary investigation is the study of etiology comparing the characteristics of 720 patients with sarcoidosis representing both men and women, white and minority race/ethnicity and the spectrum of disease severity with the characteristics of 720 controls matched on age, gender and race/ethnicity and who are recruited through random digit dialing to represent the general population. A prospective cohort study of the first 252 cases (goal was 240 cases) enrolled in the case control study is designed to define categories of outcome, which may be related to the etiology of sarcoidosis, and to describe the clinical course of sarcoidosis.

Ten Clinical Centers, located at major medical centers / hospitals in the United States, are responsible for screening and recruitment of eligible sarcoidosis cases and recruitment of matched controls. The RDD (Random Digit Dialing) Interview Group is responsible for telephoning households in the local community of the case to identify an individual who is the same age (within ± 5 years), gender, and ethnic origin as the case and who is willing to participate in ACCESS as a matched control. The ACCESS Clinical Coordinating Center is responsible for monitoring the Clinical Centers' progress in enrolling cases and controls into the study. The Clinical Coordinating Center is also responsible for monitoring the collection of required data for cases and controls, and developing and maintaining the Clinical Center and Clinical Coordinating Center data management systems for entering, editing and storing study data. The Clinical Coordinating Center plays a key role in preparing data analyses to meet study goals.

CHAPTER 1

RECRUITMENT PROCEDURES AND INFORMATION FLOW CHARTS

1.1 INTRODUCTION

The inclusion/exclusion criteria for cases as well as the procedures to confirm the diagnosis of sarcoidosis are defined in this chapter. The inclusion/exclusion criteria of the controls, who are selected by means of random digit dialing, are also defined. The procedures for screening and enrolling both cases and controls are described.

1.2 INCLUSION/EXCLUSION CRITERIA AND CONFIRMATION OF ELIGIBILITY OF CASES

Only newly diagnosed cases of sarcoidosis with tissue confirmation of granuloma and a clinical course compatible with sarcoidosis, that is, a systemic granulomatosis of unknown etiology, are eligible for ACCESS (see Chapter 3 for additional information). Newly diagnosed cases are of interest for accuracy and consistency of recall. A newly diagnosed case is defined as a patient who has tissue confirmation of granuloma less than six months prior to entry into the study. The date of the biopsy that confirms the presence of sarcoidosis is defined as the date of diagnosis.

The Kveim test may be used to confirm a diagnosis of sarcoidosis in patients with Löfgren's Syndrome (defined by the presence of erythema nodosum), if no other tissue is obtained for biopsy. See Chapters 3 and 6 for the standardized procedures for the use of the Kveim agent.

Patients with chronic beryllium disease are excluded from the study. Potential cases whose occupational histories indicate possible beryllium exposure are excluded from the study unless both blood and bronchoalveolar lavage proliferation studies indicate a negative response to beryllium. Fungal lung disease and tuberculosis must be ruled out. Acid-fast bacillus (AFB) and fungal cultures are performed on all available tissue (exclusive of Kveim biopsy) and slides

appropriately stained for all patients screened for eligibility. In patients undergoing bronchoscopy, bronchial washings or lavage are also obtained specifically for fungal and AFB cultures as clinically indicated. Potential cases who live in areas where histoplasmosis is endemic or who have risk factors for tuberculosis must have appropriate tests performed on tissue specimens (cultures of biopsy specimens required) to exclude tuberculosis and fungal infections (especially histoplasmosis). In particular, adequate samples should be cultured if possible. At a minimum, slides of tissue are stained for mycobacteria and fungi. Fungal serology and measures of H. capsulatum antigen are not expected to contribute to the diagnosis and are not used in ascertaining case eligibility. The pathology slides for cases enrolled after September 1997 are reviewed under polarized light to determine whether birefringent material is present. The slides for cases enrolled prior to September 1997 are reviewed for presence of birefringent materials if the slides are available or can be retrieved.

At the time of enrollment into the study, patients are categorized according to their clinical condition at the time of initial diagnosis (i.e., the date of biopsy confirmation). Table 3-2A outlines the disease categories that were used to describe cases beginning November 1996. An additional revised classification system was used beginning September 1997 and is given in Table 3-2B. the purpose of revising the disease categories was to encourage use of information on facets of the clinical presentation of sarcoidosis that were not readily appreciated in the initial, hierarchical classification of disease categories. This information is used to assess the spectrum of clinical sarcoidosis presentations represented among the ACCESS cases. Initially, cases are recruited at each participating Clinical Center without regard to the proportion in each category. If cases are identified from more than one patient source (e.g., different clinics or practices) within the Clinical Center, efforts are made to enroll every patient from each patient source over the period of the study year. Clinical Coordinating Center staff review the distribution of enrolled cases periodically to ensure that appropriate proportions of cases in each category are enrolled by the end of the recruitment period. Assessment occurs after each 150 incident cases have been enrolled in the

study. Based on these analyses, Clinical Centers may be required to adjust the proportion of cases recruited for each category.

Only individuals 18 years of age or older may be enrolled. Cases must be competent to sign consent forms for study participation and must be willing to participate for the length of the study (two-year follow-up for the cases enrolled in the Clinical Course Study* and baseline evaluation only for the remaining cases). Potential cases may be excluded if there is evidence that they may not comply with all study requirements. Only cases who can respond directly to the questions being asked on the study forms are eligible for inclusion in the study.

1.3 INCLUSION/EXCLUSION CRITERIA OF CONTROLS

Population-based controls are identified through random digit dialing of an unbiased clustered random sample of households with telephones. Controls are matched to cases on age (no more than five years older or younger), gender, and self-designated race (black, white, other).

Potential controls with a past history of sarcoidosis, chronic beryllium disease, fungal disease treated with systemic chemotherapy, granulomatous hepatitis, primary biliary cirrhosis, Bell's palsy, undiagnosed uveitis, Crohn's disease and erythema nodosum of unknown etiology are excluded from the study.

Only individuals 18 years of age or older are enrolled. Controls must be competent to sign consent forms for study participation. Potential controls are excluded if there is evidence that they may not comply with all study requirements. Only controls who can respond directly to the questions on the study forms are eligible for inclusion in the study.

1.4 RECRUITING CASES

1.4.1 Overview

Cases may be recruited from a variety of clinical settings including inpatient, hospital-based outpatient, and non-hospital-based outpatient facilities. A patient brochure is available for distribution to cases who have an interest in participating in ACCESS. The Principal Investigator

*The first 252 cases (goal was 240 cases) were enrolled in the Clinical Course Study.

of each Clinical Center defined, in advance of initiating case and control recruitment, the geographic area from which the center recruits cases (and controls) for the study. Permission to contact patients identified in a clinical setting must be obtained initially from the attending physician of record, in advance of study enrollment. If cases are identified from more than one patient source (e.g., different clinics or practices) within the Clinical Center, efforts are made to enroll every patient from each patient source during each year of recruitment.

All newly diagnosed cases should be considered for enrollment and listed on the Screening Log for Cases. Each case listed on this Screening Log should be assigned an ID (identification) number. Completion of the Screening Log for Cases was discontinued in October 1997. A summary of the procedures to be followed to document the eligibility of a case is depicted in Figure 1-1 and described below.

1.4.2 Medical Record Review

Once a newly diagnosed potential case is identified, the medical records are reviewed to determine if he/she satisfies the inclusion and exclusion criteria for ACCESS. If the patient is found to be ineligible upon review of the medical record, this information should be coded on the Screening Log for Cases, and the patient should be designated as ineligible. As indicated above, completion of the Screening Log for Cases was discontinued in October 1997.

1.4.3 Preliminary Interview

If the information on the medical record does not exclude the patient, the potential case should be contacted by telephone, or in person if he/she is still at the Clinical Center. When contact is made, the interviewer should identify himself/herself and state the purpose of ACCESS. The interviewer briefly describes the information and specimens that will be collected from the patient, and the costs to the patient that are defrayed by the study. If the patient expresses interest in ACCESS, a visit is scheduled unless the case is in the Clinical Center for this interview. At the time of the clinic visit, the informed consent should be signed by the patient and witnessed. Upon completion of this task, the interviewer can begin to interview the patient for ACCESS information.

Specifically, the interviewer completes Form 01 (Participant Information Sheet) and Form 02 (Confirmation of Eligibility - Cases) in this session. As part of the interview, the staff member confirms that a biopsy specimen is being collected for the study (a previous biopsy is acceptable) and the biopsy specimens are sent for pathological examination. As part of the examination, a request is made to screen the slides for tuberculosis and histoplasmosis. Once this information has been collected, the Case Registration Worksheet (Form 03) is completed and the Automated Telephone Response System (ATRS) is called to register the potential case (see Chapter 7).

1.4.4 Final Determination of Eligibility for Cases

Upon receipt of the tissue pathology results, the final determination of eligibility for ACCESS is complete. If the patient has a diagnosis of sarcoidosis and does not have pathological evidence of tuberculosis, histoplasmosis, or other fungal infection, the patient is eligible to be enrolled in ACCESS. If the pathology interpretation is designated as a possible or probable diagnosis of sarcoidosis, the slides are sent to the Clinical Coordinating Center (CCC) where they are sent for an outside review by another pathologist participating in ACCESS. If the second review is positive, the patient is eligible for participation in ACCESS, if the second review is negative, probable or possible, the patient is ineligible to participate in ACCESS unless the Principal Investigator determines the tissue sample sent for review was inadequate for the pathology diagnosis to be made. If it is considered adequate, the patient is ineligible to participate in ACCESS; if it is not, another specimen should be obtained and submitted for pathology review. If a second sample is submitted for review, the CCC staff must be notified so that the next set of pathology forms are accepted into the database. Procedures for pathology review of the second specimen are the same as for the first specimen.

If the biopsy confirms the diagnosis of sarcoidosis, the patient is contacted and asked if he/she is willing to participate in ACCESS and a clinic visit is scheduled to complete the baseline evaluation.

At the beginning of the clinic visit scheduled for completion of the baseline evaluation, the Research Coordinator confirms that the patient is eligible and that the informed consent for participation in the study and follow-up, if that is appropriate, has been signed. The Form 04 Case Enrollment / Non-Enrollment - ATRS) is completed and the ATRS called to register the case as enrolled. The baseline evaluation is completed as described in Chapter 4.

1.4.5 Ineligibility

At any point during the course of documenting that the case is eligible, the case may decide not to participate in the study, or exclusion criteria may be discovered that precludes the potential case's participation in ACCESS. If the potential case was registered on the ATRS, Form 04 (Case Enrollment / Non-Enrollment Worksheet - ATRS) is completed to confirm that the potential case was not enrolled and the ATRS called to declare the case ineligible. Prior to October 1997, the Screening Log for Cases was completed indicating the applicable reasons for the final determination that the potential case was ineligible for their consideration.

1.5 RECRUITING CONTROLS

1.5.1 General Procedures for Recruiting Controls

Prior to beginning recruitment of ACCESS controls, staff responsible for contacting the controls after they are identified by the RDD Interview Group should familiarize themselves with the Protocol so that they can quickly respond to any questions the potential control may have concerning ACCESS. Once a potential control has been identified by the RDD Interview Group, it is important to make contact with the control quickly (within two days is preferable, but for all controls the period between identification and Clinical Center contact should not be more than seven days).

A summary of the procedures for enrolling RDD controls is depicted in Figure 1-2 and described below.

1.5.2 RDD (Random Digit Dialing) Interview Group

The process of recruiting a matched control for a case begins after the demographic data and telephone number of the enrolled ACCESS case are entered into the ATRS. Once the location of the case is identified (by the area code), Clinical Coordinating Center staff request a list of 200 telephone numbers from a subcontractor (Survey Sampling, Inc.) The process of generating these numbers is described in Chapter 9.

The RDD Interview Group identifies potential controls by systematically dialing the numbers on the telephone list and asking the respondents if there is a person at that number of a specified age, gender, and race who would be willing to participate in ACCESS (see Chapter 9 for the procedures and script that are used during the calls). If an individual is identified, the name and number of the individual is sent to the Clinical Center (with a copy to the Clinical Coordinating Center) by facsimile transmission. If the RDD Interview Group does not identify a suitable control by calling all numbers in a batch, another batch (or batches) of numbers is generated as needed.

1.5.3 Clinical Center Screening of Potential Controls

Once Clinical Center staff have been notified by the RDD interview group that a potential control has been identified, Clinical Center staff attempt to call the potential control as soon as possible and a letter (on university letterhead) is sent to the patient thanking them for their interest in ACCESS. It is very important that the subsequent follow-up call to the patient is done quickly (preferably within two days of the RDD notification) and that the letter is sent promptly (see Exhibit 1-1 for model letter).

The Screening Log for Controls is used to chart progress in contacting and recruiting potential controls for ACCESS. Each potential control identified by the RDD Interview Group is assigned an ID (identification) number and listed on this Screening Log. Anytime that a potential control is determined to be ineligible, an entry is made in this Screening Log for Controls to record why the control was ineligible. All reasons for the ineligibility are listed on the Screening Log for Controls, not just the first reason encountered.

1.5.4 Preliminary Telephone Interview

The potential control is contacted by telephone as soon as possible after receiving notification from the RDD Interview Group. When contact is made, the interviewer should identify himself/herself and state the purpose of ACCESS. The interviewer should verify that the potential control matches the case for age (± 5 years), gender, and self-designated race (white, black, other). The interviewer gives the potential control a brief description of the information and specimens that will be collected from the individual, and the costs to the individual that will be defrayed by the study. If the control expresses interest in ACCESS, a visit is scheduled so that the informed consent can be signed by the control and witnessed. The information collected is recorded on Form 05 (Confirmation of Eligibility - Controls).

1.5.5 Clinic, Home or Workplace Visit

If the control agrees to participate in the study and presents for evaluation, the Research Coordinator confirms that the individual satisfies the inclusion and exclusion criteria for ACCESS and obtains consent if the control is eligible. The Research Coordinator completes the Form 01 (Participant Information) and Form 05 (Confirmation of Eligibility - Controls) for all eligible controls. As noted previously, race is self-designated and this question must be asked of the potential control. For all controls who sign the consent form, Form 06 (Control Status Worksheet) is completed and the ATRS called to confirm that a matched control has been enrolled. The baseline evaluation may then be completed at this visit. It is recommended that the interview for the control be in the same location as the interview for the case.

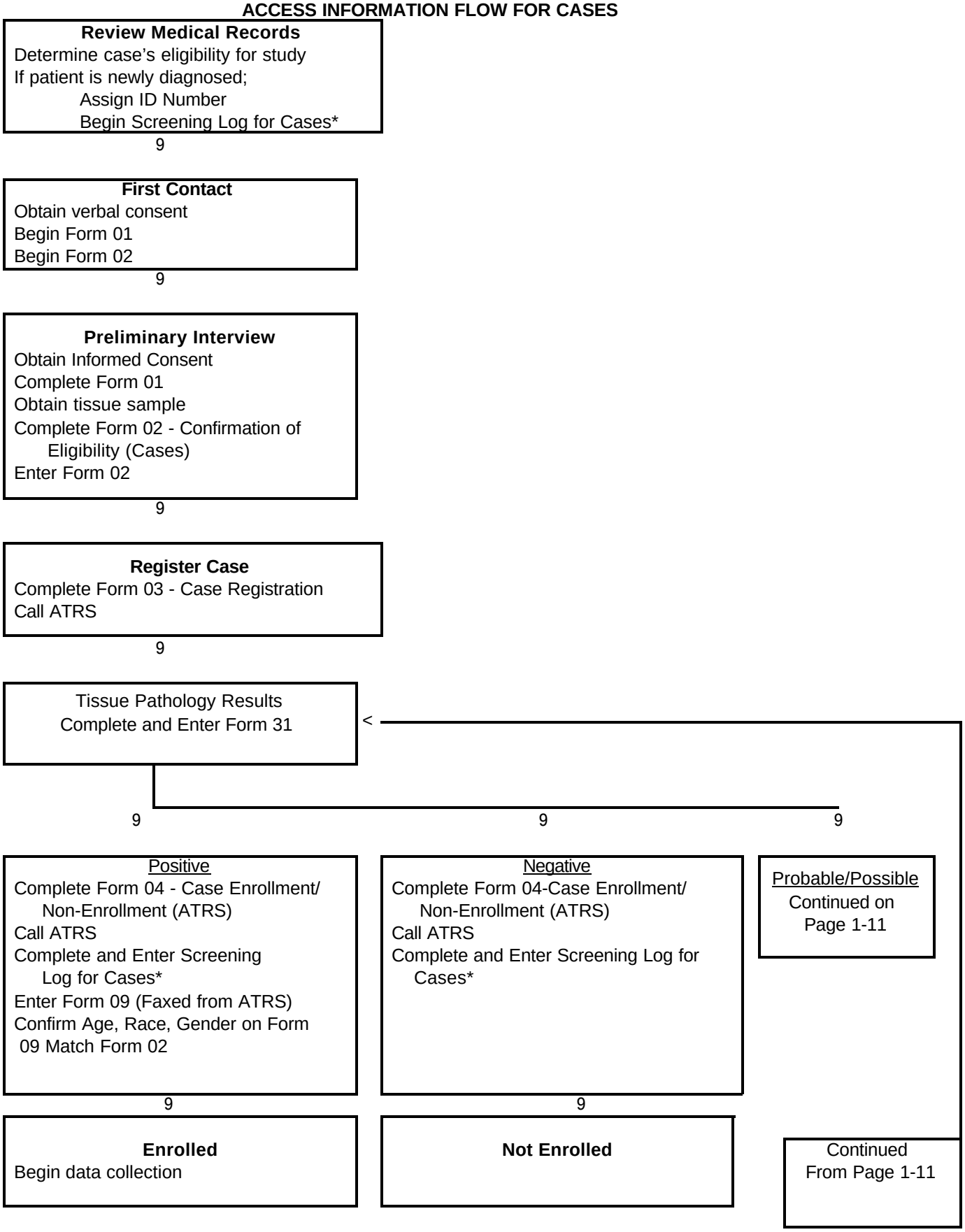
1.5.6 Ineligibility

At any point during the course of establishing that the control is eligible, the control may decide not to participate in the study, or exclusion criteria may be discovered that will preclude the potential control's participation in ACCESS. Form 06 (Control Status Worksheet) is completed and the ATRS called to report the control was ineligible and the reason(s) the control was ineligible

recorded on the Screening Log for Controls. The CCC then contacts the RDD Interview Group to identify a new potential control as described in Section 1.5.2 and Chapter 9.

FIGURE 1-1

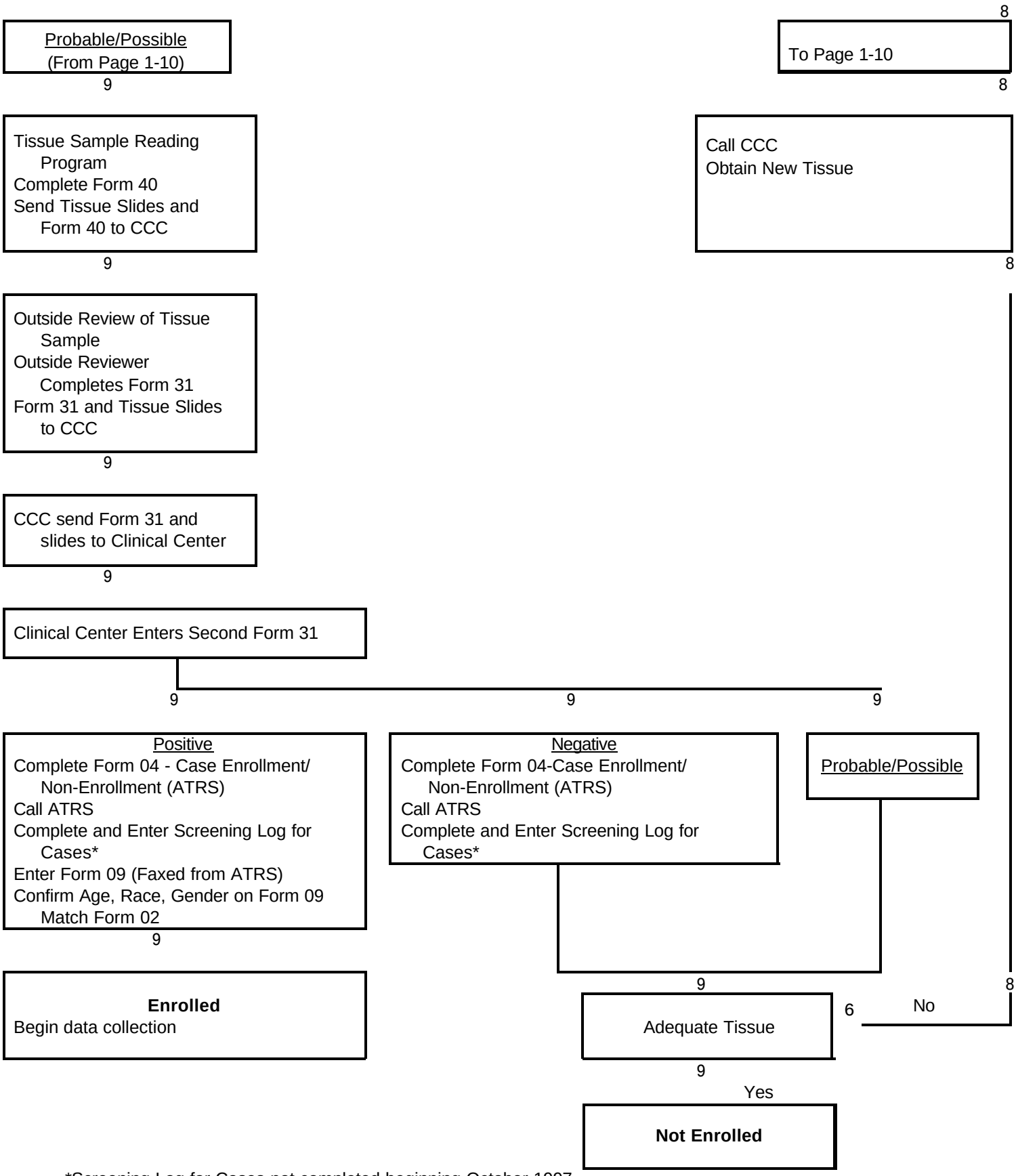
ACCESS INFORMATION FLOW FOR CASES



* Screening Log for Cases not completed beginning October 1997.

FIGURE 1-1 (Continued)

ACCESS INFORMATION FLOW FOR CASES



*Screening Log for Cases not completed beginning October 1997.

FIGURE 1-2

ACCESS INFORMATION FLOW FOR RDD (RANDOM DIGIT DIALING) CONTROLS

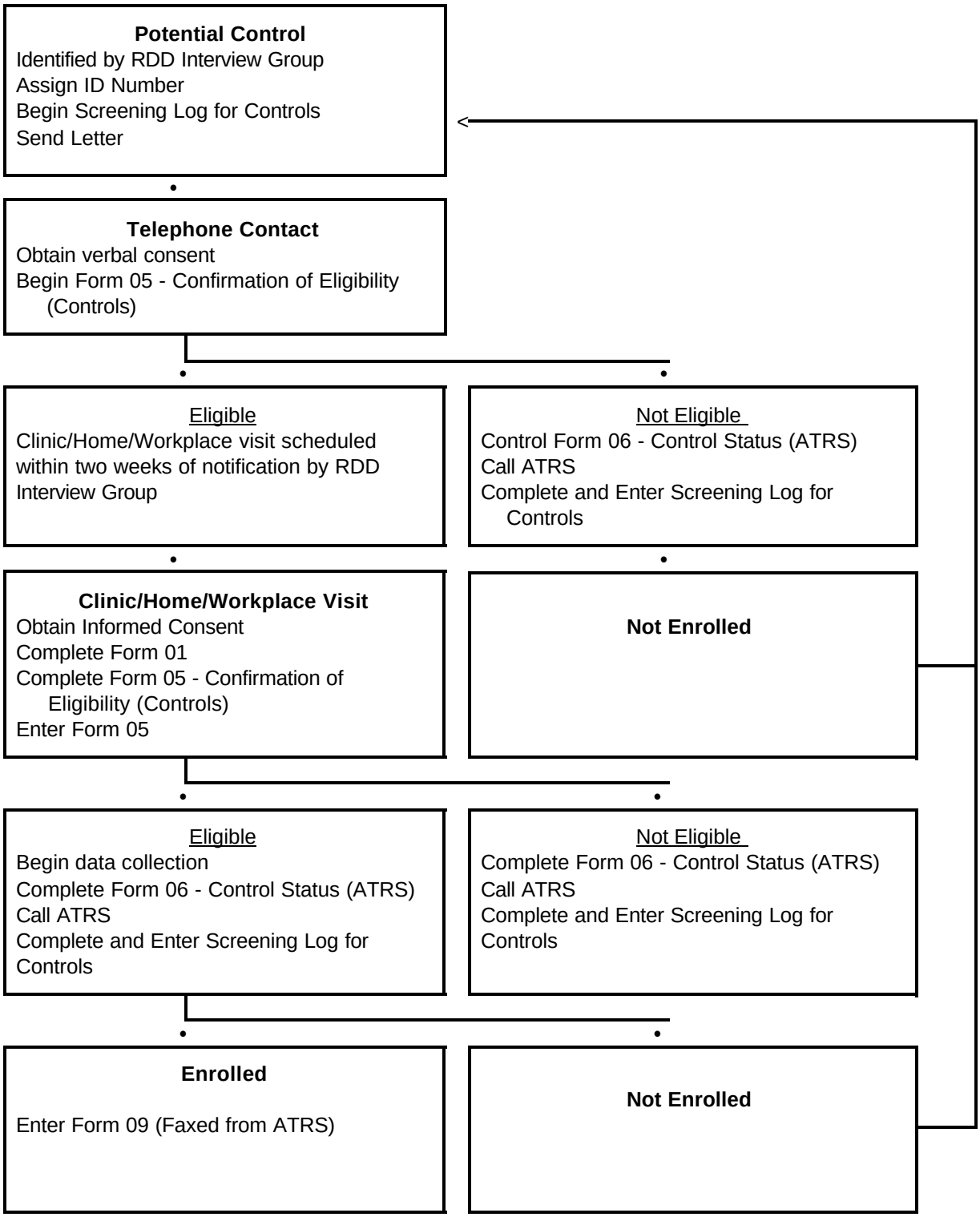


EXHIBIT 1-1

MODEL LETTER FOR POTENTIAL CONTROLS

Thank you for your interest in joining the University of _____ in our effort to help the National Institutes of Health learn the cause of sarcoidosis. You will be one of 720 people from communities across the United States to join the study to answer the research questions and provide a blood sample. We will compare your answers to questions concerning your health and experiences (work history, hobbies, family history) and your blood tests to answer and test results from patients with sarcoidosis to learn what differences may explain their health problems. You will be paid $___ to cover your travel and other efforts upon completion of the visit. You were contacted through a random survey of telephone numbers in our region.

Within the next few days one of the study research staff (or name) from the University of ____ will contact you in order to set up an appointment. The appointment will take about two hours of your time. We are including with this letter some additional information about the study for your interest. If you have any questions about this study, please feel free to call me (or name) at _____. When you talk to the staff at my office, say you are calling about ACCESS; that is the study name. One of the doctors who works with me or I (or We) will be sure to speak with you as soon as we can.

I am grateful that you are willing as a member of the community to help us learn more to improve the health of our neighbors.

Sincerely,

_____, M.D.
Principal Investigator

_____
Clinic Coordinator

CHAPTER 2

ORIENTATION AND CONSENT

2.1 INTRODUCTION

Each case and control enrolled in ACCESS must agree to participate in the study after receiving orientation and signing a consent form. The summary of information to be provided to each case and to each control concerning the study, the goals and objectives of the study, and the procedures to be performed as part of the study are reviewed in this chapter. Drafts of consent forms have also been prepared for use in the Clinical Centers and are included as exhibits.

2.2 PREPARATION OF CONSENT FORMS

Sample consent forms (see Exhibits 2-1A, 2-1B, 2-2 and 2-3) have been prepared for use by each of the ACCESS sites. These forms include:

1. Consent form for cases with sarcoidosis;
2. Consent form for random digit dialing (RDD) controls; and
3. Consent form for obtaining bronchoalveolar lavage fluid during fiber optic bronchoscopy.

Clinical Center Investigators may revise the sample consent forms to make them suitable for their particular institutions; fundamental requirements of consent must be included in all revised forms. The text of each consent form must be comprehensible to persons at an eighth grade reading level. Clinical Center consent forms should be sent to the Clinical Coordinating Center for review and approval by the Executive Committee. Recruitment of cases and controls can begin in a Clinical Center only after formal approval has been received from the local Institutional Review Board (IRB). The original written approval from the IRB should be kept at each Clinical Center, and a copy should be sent to the Clinical Coordinating Center. Confirmation that the local IRB reviewed the study each year after initial approval and approved continuation of the study should also be submitted to the Clinical Coordinating Center.

2.3 OBTAINING CONSENT FROM CASES AND CONTROLS

Informed consent must be obtained from each case and from each control using the appropriate consent form. Consent should be obtained by the Principal Investigator, a Co-Investigator, or the Research Coordinator after the nature of the study has been described to the case or the control.

Each consent form must be signed and dated by one of the above individuals from the Clinical Center, by the case or control, and by a witness to the signatures. Ideally, the witness should not be associated with the study in a way that presents any conflict of interest. Each case or control must check off a block in the consent form either giving or denying permission for use of blood specimens for studies unrelated to sarcoidosis. Specimen collection may not be performed before consent is given.

The original consent form should be kept in the case's study folder or hospital chart at the Clinical Center. A copy should be placed in the case's hospital or office chart. If the original consent form is kept in the hospital chart, a good quality copy of the form must be kept in the case's study folder.

Cases in whom fiber optic bronchoscopy is performed to obtain tissue for a histologic diagnosis of sarcoidosis are potential candidates for providing brochoalveolar lavage fluid obtained during the procedure. Each case who agrees to the collection of brochoalveolar lavage specimens for ACCESS should sign the appropriate consent form. The consent is generally signed before a specific diagnosis has been made and before the case has been formally recruited into the study.

2.3.1 Sarcoidosis Case Orientation

Sarcoidosis patients are informed that this is a research study intended to investigate possible causes and risk factors for sarcoidosis. They are told that the study involves collecting information and biologic samples from patients with sarcoidosis. Information is collected by questionnaire, and blood samples are collected.

Sarcoidosis patients enrolled in the study have an evaluation performed to assess the extent and severity of their sarcoidosis. The evaluation includes a physical examination, chest X-ray, and pulmonary function testing (before and after bronchodilator administration, if clinically indicated). Sarcoidosis patients are informed that this study involves comparing information obtained from them with information that is obtained from control individuals who are matched to them in terms of age, gender, and ethnic origin.

Sarcoidosis patients are informed that enrollment in this study does not involve alteration of their care or their treatment as determined by their usual physician(s). Sarcoidosis patients are recruited for this study only if their usual physicians agree. There are no costs to the patient or to any insurance carrier for any part of the evaluation performed solely for the study and not otherwise part of usual care of patients with sarcoidosis. However, testing that is usually done as part of the care of patients with sarcoidosis is billed according to the usual method of clinical billing. For example, charges for bronchoscopy and transbronchial biopsy or lymph node biopsy and pathological examinations to establish the diagnosis of sarcoidosis remain the patient's responsibility. Patients who have erythema nodosum may be diagnosed with Kveim agent under an Investigational New Drug (IND) Application exemption issued by the U. S. Food and Drug Administration (FDA). The use of Kveim agent requires separate orientation and consent (see Chapter 3 and Chapter 6).

The first 252 sarcoidosis patients (cases) enrolled were informed that the research center will maintain contact by telephone or by mail at intervals of approximately six months. This contact is primarily to ensure accurate and updated information about the patient's address and telephone number. These sarcoidosis patients were informed that they are asked to return for a follow-up evaluation two years after their entry into the study. This evaluation (described in detail in Chapter 4) includes an interview with completion of a questionnaire, a physical examination, a chest X-ray, blood tests, and pulmonary function tests (before and after bronchodilator administration, if clinically indicated).

Patients are informed that they will be reimbursed for their expenses to participate in the study. The amount varies among Clinical Centers and depends upon whether or not the individual has to make a special trip to the Clinical Center. Each individual receives a minimum of $25 for ACCESS-related expenses.

Bronchoscopy and transbronchial biopsy are frequently used procedures in the diagnosis of sarcoidosis. Bronchoalveolar lavage is a routine part of the procedures to obtain specimens for culture and other laboratory analysis. Residual specimens are routinely stored in freezers as part of usual clinical practice by the ACCESS Investigators. Patients with sarcoidosis who enroll in ACCESS are requested to give permission for the central storage and use for research purposes of their residual bronchoalveolar lavage specimens.

2.3.2 Orientation of Controls

Controls are informed of the nature of the study and the method by which they were invited to participate. Potential controls are informed that random digit dialing methods are used to identify individuals with age, gender, and race matching those of a particular patient with sarcoidosis within the same telephone exchange.

Controls are informed that their participation in the study involves an interview with completion of a questionnaire and collection of a blood sample. There are no other procedures, and no follow-up is planned. Controls are informed that they will be reimbursed for their expenses to participate in the study. The amount varies among Clinical Centers and depends upon whether or not the individual has to make a special trip to the Clinical Center. Each individual receives a minimum of $25 for ACCESS-related expenses.

2.4 SAMPLE INFORMED CONSENT FORMS

The following model consent forms are included in Exhibits 2-1 through 2-3. Exhibit 2-1A is the model consent form for patients with sarcoidosis; this form includes a description of the Clinical Course Study Follow-up and was used through September 1997. Exhibit 2-1B is the model consent form for cases in use since October 1997.

Page

2.5 AFFECTED RELATIVES

If a case or control indicates that a first degree relative (parent, sibling or child) over 18 years of age has sarcoidosis, that case or control is asked to assist the ACCESS Investigators to obtain confirmation of the relative's diagnosis. The case or control is provided with a letter and return postcard to send to the relative (see Exhibit 2-4). ACCESS Investigators contact the relative only if the relative first contacts them (by telephone, return postcard or in person) to give permission for the inquires planned. Once a relative has contacted the ACCESS Investigators, inquires are made with the relative to determine the extent to which a diagnosis of sarcoidosis has been documented. If medical records describing sarcoidosis exist (e.g., a hospital chart with a bronchoscopy and biopsy recorded), ACCESS Investigators request the relative's permission to obtain a copy of the relevant parts to document whether or not sarcoidosis was diagnosed. If a possibly affected relative does not contact the Clinical Center, the Clinical Center staff may send a letter to the enrolled case or control asking for assistance in reminding the relative of the opportunity to provide information for ACCESS (see Exhibit 2.5).

EXHIBIT 2-1A

CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. This study will compare facts about patients with sarcoidosis (cases) and people without sarcoidosis (controls) to learn what causes the disease. Ten clinic research centers are in this study.

HOW CASES ARE CHOSEN: Your doctors have recently said that you have sarcoidosis. We are asking patients with newly found sarcoidosis to join this study. Your doctor has given your name to this research team. Your doctor knows that we are asking you if you want to volunteer to be part of the study.

The ten clinics will enroll a total of 720 cases for the study. Also, 720 people without sarcoidosis will enroll in the study as controls. Data and blood samples will be collected from the controls to compare with the data and blood samples from patients with sarcoidosis.

WHAT TO EXPECT: There are five parts of this study. First is an interview to record medical, environmental, and family history. Second is a physical examination by a doctor on the research team. Third, clinic staff will take a sample of your blood. Fourth, clinic staff will perform or review the results of tests that are part of usual care for sarcoidosis. Fifth, clinic staff will contact you every six months for two years and see you in the clinic two years after you join the study.

1. Interview - We will ask you detailed questions about yourself, your medical history, your family, and possible exposures. The interview will take between one and two hours. The interview will be tape recorded. The taping is being done so we can check that we have written down without errors your answers to our questions. We will erase each tape six months after we record it. Only study staff will use these tapes. You may not be able to answer all our questions at first. We may call you so you can give answers later.

2. Physical examination - A doctor on the research team will conduct a routine physical for you. This physical will not include a rectal examination. In women, the physical will not include breast or gynecologic examination (a pelvic or “internal” examination).

3. Blood sample - Study staff will take a blood sample of about three ounces (less than one-half cup) from a vein in your arm. This amount of blood is about one-fifth of the amount that is usually taken when someone donates blood. Part of this sample will be used at the present time; part will be frozen and stored for studies to be planned in the future. The portion of the blood that is frozen will be stored at a central laboratory for the National Institutes of Health. Blood samples will be handled in a manner that protects your privacy.

We will use some of the blood sample to look for gene differences that may play a part in sarcoidosis. Part of the frozen sample will be used in the future for more studies of genes. The genes we want to study may come from you or may have reached your blood from a virus, bacterium, or fungus. If you agree now, doctors in other approved studies may use the frozen samples at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for current or future studies of sarcoidosis. The study will not be giving cases or controls individual results of gene tests.

_____
Initials

EXHIBIT 2-1A (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

Please mark the consent you give for study of your blood and the genes in your blood (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

4. Other tests that are part of the routine care of patients with sarcoidosis - Patients with sarcoidosis usually have several other tests that are part of their care. If one of your usual doctors has done these tests, we will use the results to judge the extent and severity of your sarcoidosis. We will repeat some tests for the study, but there will be no charge to you. If one of your usual doctors has not already done these tests, we will do them as part of your routine care, and you or your insurance provider will be charged. The research team as well as your usual doctor(s) can use these results.

These tests include breathing tests, chest X-ray, and blood tests.

a. Breathing tests (pulmonary function tests) - Breathing tests are a standard method for finding out how much impact sarcoidosis has on your lungs. If not yet done, your breathing tests will be done as part of the testing that patients with sarcoidosis should have. If your own doctor has already done these tests, we will repeat them in the study center so that the breathing tests will be done in the same way for all study patients. If these are repeats of the breathing tests done by your own doctor in the last six months, there will be no charge either to you or to your insurance provider.

   As part of the breathing tests, we will give you a standard bronchodilator to inhale if they could change the results. Then part of the test will be done again. This allows us to find out whether there is any change in your breathing after treatment to open your airways. The treatment is commonly used for this purpose as part of breathing tests.

b. Chest X-ray - A chest X-ray should be part of the testing for any patient with sarcoidosis.

c. Blood tests - Several blood tests (blood cell counts, tests of liver and kidney function, and a calcium level) are usually done in patients with sarcoidosis. If your usual doctor has already done these tests, the research team will not repeat them. If they have not been done, we will perform them on some of the blood from your vein.

5. Follow-up - You will be contacted every six months for two years after you enter the study (either by phone or by mail) so that we will know about any changes in your address or phone number.

A follow-up interview, shorter than the first interview, will be done two years after your entry into the study. During this interview, study staff will ask you about your health. A chest X-ray and breathing tests will also be done as part of your care if they were not done again by your usual doctor(s). If they were done, we will repeat them in the study center to compare with your first tests here. If the testing at the study center is not part of your routine care, there will be no charge either to you or to your insurance provider.

RISKS AND DISCOMFORTS: The tests done as part of this study are all thought to be safe. There may be some discomfort from the needle used to take a blood sample. A skilled technician, nurse, or doctor will take the blood sample. There is practically no risk of infection. Only sterile, disposable materials are used. In the unlikely event that during the examinations you should require medical care, first aid will be available.

_____
Initials

EXHIBIT 2-1A (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

There are no physical risks from the questions. However, the interview is long. You may find that it is tiring. There are some questions about your feelings. You may find that these questions make you feel anxious for a short time.

BENEFITS: There is no direct benefit to you from joining this study. We will give your doctor results of standard blood tests, breathing tests, and chest X-rays. These may be useful for the doctor taking care of you. We will tell your doctor and write a letter about anything urgent for your health care that we find.

This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to you and to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your part in this study is purely voluntary and will not affect your care. You may refuse to join the study. You may leave the study at any time. If you do not become part of the study or if you leave it, doing so will not harm your present or future care at this hospital or clinic.

The study will not provide any treatment for your sarcoidosis. The study will not change the treatment provided by your primary doctor(s).

COST/PAYMENT: We will reimburse you $xx** to cover your expenses in the study. The study will pay for any testing for the study that is beyond the usual standard of care for sarcoidosis. Neither you nor your insurance carrier will be responsible for these costs. The research study will not pay for tests that would usually be part of your care (some listed in section 4 above) if you were not in the study. Either you or your insurance carrier is responsible for the costs of tests that are part of the standard care of patients with sarcoidosis.

No funds are in the study for you to stay overnight in the hospital. We can make no payment from the research study for testing or treatment between now and the time of the two-year follow-up. At the time of follow-up, the study will pay for any testing for the study that would not be part of the usual care of your sarcoidosis. The study will not pay for other testing that would usually be part of the care of patients with sarcoidosis.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Facts about you that we store in the study computer will include your initials, age, gender, weight, and height. Reports from this study will not identify you personally. Your personal medical records, answers to questions, and tape recordings are private. Stored blood samples will be identified only by code numbers that cannot be traced back to you by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). At the end of the study, we will make a computer tape of the study results for future use. It will not include any facts that could identify you directly. We may give facts to the National Institutes of Health, but your name will not be among those facts.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and

**To be supplied by each Clinical Center

Initials

EXHIBIT 2-1A (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Through September 1997

Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the "A Case Control Etiologic Study of Sarcoidosis," will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- "Keeping and Destroying Records."

Initials

EXHIBIT 2-1A (Continued)

A Case Control Etiologic Study of Sarcoidosis (ACCESS)
INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of ACCESS and such risks as are involved. I have asked _____ if any questions have arisen about ACCESS and have given answers to these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the ACCESS study, with its possible benefits, risks and outcomes. I know that I am free to ask any questions. If I have questions about the study later, I may call (Clinical Center Principal Investigator) at (telephone number). My part in this study is voluntary. I am free to withdraw from this study at any time without impact on my care or my relationship with [name of hospital]. I may decline questions that I do not wish to answer in the course of the study.

Study doctors will use my blood sample for studies about sarcoidosis. Other doctors may use my blood samples in future studies of diseases other than sarcoidosis only if I have agreed.

I have a right to privacy. The doctors in this study will take all reasonable measures to protect the privacy of my records. My name and any other facts that might identify me will not appear in any presentation or publication from this study. My name and any other facts that might identify me will not be available to any person or group other than the investigators of this study and the Institutional Review Board of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital protects people who join studies. I may have a copy of this document if I ask for one.

The [name of hospital]'s Institutional Review Board may contact me during or after this study as part of its efforts to check on people in medical studies.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my part in this research study.

_____
Initials

EXHIBIT 2-1A (Continued)

A Case Control Etiologic Study of Sarcoidosis (ACCESS)
INFORMED CONSENT FORM
(Continued)

I agree to take part in this investigation.

I ____ do ____ do not agree to allow my blood sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

EXHIBIT 2-1B
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. This study will compare facts about patients with sarcoidosis (cases) and people without sarcoidosis (controls) to learn what causes the disease. Ten clinic research centers are in this study.

HOW CASES ARE CHOSEN: Your doctors have recently said that you have sarcoidosis. We are asking patients with newly found sarcoidosis to join this study. Your doctor has given your name to this research team. Your doctor knows that we are asking you if you want to volunteer to be part of the study.

The ten clinics will enroll a total of 720 cases for the study. Also, 720 people without sarcoidosis will enroll in the study as controls. Data and blood samples will be collected from the controls to compare with the data and blood samples from patients with sarcoidosis.

WHAT TO EXPECT: There are four parts of this study. First is an interview to record medical, environmental, and family history. Second is a physical examination by a doctor on the research team. Third, clinic staff will take a sample of your blood. Fourth, clinic staff will perform or review the results of tests that are part of usual care for sarcoidosis.

1. Interview - We will ask you detailed questions about yourself, your medical history, your family, and possible exposures. The interview will take between one and two hours. The interview will be tape recorded. The taping is being done so we can check that we have written down without errors your answers to our questions. We will erase each tape six months after we record it. Only study staff will use these tapes. You may not be able to answer all our questions at first. We may call you so you can give answers later.

2. Physical examination - A doctor on the research team will give you a routine physical examination. This physical will not include a rectal examination. In women, the physical will not include breast or gynecologic examination (a pelvic or “internal” examination).

3. Blood sample - Study staff will take a blood sample of about three ounces (less than one-half cup) from a vein in your arm. This amount of blood is about one-fifth of the amount that is usually taken when someone donates blood. Part of this sample will be used at the present time; part will be frozen and stored for studies to be planned in the future. The portion of the blood that is frozen will be stored at a central laboratory for the National Institutes of Health. Blood samples will be handled in a manner that protects your privacy.

We will use some of the blood sample to look for gene differences that may play a part in sarcoidosis. Part of the frozen sample will be used in the future for more studies of genes. The genes we want to study may come from you or may have reached your blood from a virus, bacterium, or fungus. If you agree now, doctors in other approved studies may use the frozen samples at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for current or future studies of sarcoidosis. The study will not be giving cases or controls individual results of gene tests.

Please mark the consent you give for study of your blood and the genes in your blood (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

_____
Initials

EXHIBIT 2-1B (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

4. Other tests that are part of the routine care of patients with sarcoidosis - Patients with sarcoidosis usually have several other tests that are part of their care. If one of your usual doctors has done these tests, we will use the results to judge the extent and severity of your sarcoidosis. We will repeat some tests for the study, but there will be no charge to you. If one of your usual doctors has not already done these tests, we will do them as part of your routine care, and you or your insurance provider will be charged. The research team as well as your usual doctor(s) can use these results.

These tests include breathing tests, chest X-ray, and blood tests.

a. Breathing tests (pulmonary function tests) - Breathing tests are a standard method for finding out how much impact sarcoidosis has on your lungs. If not yet done, your breathing tests will be done as part of the testing that patients with sarcoidosis should have. If your own doctor has already done these tests, we will repeat them in the study center so that the breathing tests will be done in the same way for all study patients. If these are repeats of the breathing tests done by your own doctor in the last six months, there will be no charge either to you or to your insurance provider.

   If the clinic staff think that your breathing test results may be better after inhaling a bronchodilator, they may ask you to repeat the test after the bronchodilator is administered to you. Then part of the test will be done again. This allows us to find out whether there is any change in your breathing after treatment to open your airways. The treatment is commonly used for this purpose as part of breathing tests.

b. Chest X-ray - A chest X-ray should be part of the testing for any patient with sarcoidosis.

c. Blood tests - Several blood tests (blood cell counts, tests of liver and kidney function, and a calcium level) are usually done in patients with sarcoidosis. If your usual doctor has already done these tests, the research team will not repeat them. If they have not been done, we will perform them on some of the blood from your vein.

RISKS AND DISCOMFORTS: The tests done as part of this study are all thought to be safe. There may be some discomfort from the needle used to take a blood sample. A skilled technician, nurse, or doctor will take the blood sample. There is practically no risk of infection. Only sterile, disposable materials are used. In the unlikely event that during the examinations you should require medical care, first aid will be available.

There are no physical risks from the questions. However, the interview is long. You may find that it is tiring. There are some questions about your feelings. You may find that these questions make you feel anxious for a short time.

BENEFITS: There is no direct benefit to you from joining this study. We will give your doctor results of standard blood tests, breathing tests, and chest X-rays. These may be useful for the doctor taking care of you. We will tell your doctor and write a letter about anything urgent for your health care that we find.

This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to you and to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your part in this study is purely voluntary and will not affect your care. You may refuse to join the study. You may leave the study at any time. If you do not become part of the study or if you leave it, doing so will not harm your present or future care at this hospital or clinic.

_____
Initials

EXHIBIT 2-1B (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

The study will not provide any treatment for your sarcoidosis. The study will not change the treatment provided by your primary doctor(s).

COST/PAYMENT: We will reimburse you $xx*** to cover your expenses in the study. The study will pay for any testing for the study that is beyond the usual standard of care for sarcoidosis. Neither you nor your insurance carrier will be responsible for these costs. The research study will not pay for tests that would usually be part of your care (some listed in section 4 above) if you were not in the study. Either you or your insurance carrier is responsible for the costs of tests that are part of the standard care of patients with sarcoidosis.

No funds are in the study for you to stay overnight in the hospital. We can make no payment from the research study for testing or treatment. The study will not pay for other testing that would usually be part of the care of patients with sarcoidosis.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Facts about you that we store in the study computer will include your initials, age, gender, weight, and height. Reports from this study will not identify you personally. Your personal medical records, answers to questions, and tape recordings are private. Stored blood samples will be identified only by code numbers that cannot be traced back to you by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). At the end of the study, we will make a computer tape of the study results for future use. It will not include any facts that could identify you directly. We may give facts to the National Institutes of Health, but your name will not be among those facts.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the “A Case Control Etiologic Study of Sarcoidosis,” will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- “Keeping and Destroying Records.”

***To be supplied by each Clinical Center

_____
Initials

EXHIBIT 2-1B (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of ACCESS and such risks as are involved. I have asked _____ if any questions have arisen about ACCESS and have given answers to these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the ACCESS study, with its possible benefits, risks and outcomes. I know that I am free to ask any questions. If I have questions about the study later, I may call (Clinical Center Principal Investigator) at (telephone number). My part in this study is voluntary. I am free to withdraw from this study at any time without impact on my care or my relationship with [name of hospital]. I may decline questions that I do not wish to answer in the course of the study.

Study doctors will use my blood sample for studies about sarcoidosis. Other doctors may use my blood samples in future studies of diseases other than sarcoidosis only if I have agreed.

I have a right to privacy. The doctors in this study will take all reasonable measures to protect the privacy of my records. My name and any other facts that might identify me will not appear in any presentation or publication from this study. My name and any other facts that might identify me will not be available to any person or group other than the investigators of this study and the Institutional Review Board of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital protects people who join studies. I may have a copy of this document if I ask for one.

The [name of hospital]'s Institutional Review Board may contact me during or after this study as part of its efforts to check on people in medical studies.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my part in this research study.

_____

Initials

EXHIBIT 2-1B (Continued)
CONSENT FORM FOR PATIENTS WITH SARCOIDOSIS
In Use Beginning October 1997

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I agree to take part in this investigation.

I ____ do ____ do not agree to allow my blood sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

EXHIBIT 2-2

CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. This study will compare facts about patients with sarcoidosis (cases) and people without sarcoidosis (controls) to learn what causes the disease. Ten clinic research centers are in this study.

HOW CONTROLS ARE CHOSEN: We are asking you to join this study as a control because you do not have sarcoidosis. You are approximately the same age and are the same gender and race as a patient with sarcoidosis who recently joined the study. We got in touch with you by random number dialing in the same phone exchange as the patient whose age, gender and race match yours.

The ten clinics will enroll a total of 720 people without sarcoidosis in the study as controls. Also, 720 cases will enroll in the study. Data and blood samples will be collected from the controls to compare with the data and blood samples from patients with sarcoidosis.

WHAT TO EXPECT: There will be two main parts of this study. First is an interview to record facts about you. Second, clinic staff will take a sample of your blood.

1. Interview - We will ask you detailed questions about yourself, your medical history, your family, and possible exposures. The interview will take between one and two hours. The interview will be tape recorded. The taping is being done so we can check that we have written down without errors your answers to our questions. We will erase each tape six months after we record it. Only study staff will use these tapes. You may not be able to answer all our questions at first. We may call you so you can give answers later.

2. Blood sample - Study staff will take a blood sample of about three ounces (less than one-half cup) from a vein in your arm. This amount of blood is about one-fifth of the amount that is usually taken when someone donates blood. Part of this sample will be used at the present time; part will be frozen and stored for studies to be planned in the future. The portion of the blood that is frozen will be stored at a central laboratory for the National Institutes of Health. Blood samples will be handled in a manner that protects your privacy.

We will use some of the blood sample to look for gene differences that may play a part in sarcoidosis. Part of the frozen sample will be used in the future for more studies of genes. The genes we want to study may come from you or may have reached your blood from a virus, bacterium or fungus. If you agree now, doctors in other approved studies may use the frozen samples at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for current or future studies of sarcoidosis. The study will not be giving cases or controls individual results of gene tests.

Please mark the consent you give for study of your blood and the genes in your blood (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

Initials

EXHIBIT 2-2 (*Continued*)
CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

RISKS AND DISCOMFORTS: There may be some discomfort from the needle used to take a blood sample. A skilled technician, nurse, or doctor will take the blood sample. There is practically no risk of infection. Only sterile, disposable materials are used.
There are no physical risks from the questions. However, the interview is long. You may find that it is tiring. There are some questions about your feelings. You may find that these questions make you feel anxious for a short time.

BENEFITS: There is no direct benefit to you from joining this study. This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your part in this study is purely voluntary. If you do not become part of the study, doing so will not harm your present or future care at the hospital or clinic.

COST/PAYMENT: You will be reimbursed $xx**** to cover your expenses in the study.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Facts about you that we store in the study computer will include your initials, age, and gender. Reports from this study will not identify you personally. Your personal medical records, answers to questions, and tape recordings will be kept private. Stored blood samples will be identified only by code numbers that cannot be traced back to you by anyone outside of the study. Study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). At the end of the study, we will make a computer tape of the study results for future use. It will not include any facts that could identify you directly. We may give facts to the National Institutes of Health, but your name will not be among those facts.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the "A Case Control Etiologic Study of Sarcoidosis," will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- "Keeping and Destroying Records."

****To be supplied by each Clinical Center

_____
Initials

EXHIBIT 2-2 (*Continued*)
CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of ACCESS and such risks as are involved. I have asked _____ if any questions have arisen about ACCESS and have given answers to these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the ACCESS study, with its possible benefits, risks and outcomes. I know that I am free to ask any questions. If I have questions about the study later, I may call (Clinical Center Principal Investigator) at (telephone number). My part in this study is voluntary. I am free to withdraw from this study at any time without impact on my care or my relationship with [name of hospital]. I may decline questions that I do not wish to answer in the course of the study.

Study doctors will use my blood sample for studies about sarcoidosis. Other doctors may use my blood sample in future studies of diseases other than sarcoidosis only if I have agreed.

I have a right to privacy. The doctors in this study will take all reasonable measures to protect the privacy of my records. My name and any other facts that might identify me will not appear in any presentation or publication from this study. My name and any other facts that might identify me will not be available to any person or group other than the investigators of this study and the Institutional Review Board of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital protects people who join studies. I may have a copy of this document if I ask for one.

The [name of hospital]'s Institutional Review Board may contact me during or after this study as part of its efforts to check on people in medical studies.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my part in this research study.

_____
Initials

EXHIBIT 2-2 (*Continued*)
CONSENT FORM FOR RANDOM DIGIT DIALING CONTROLS FOR THE ACCESS STUDY

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I hereby agree to take part in ACCESS.

I _____ do _____ do not agree to allow my blood sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

EXHIBIT 2-3

CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

PURPOSE OF STUDY: The ACCESS Study (A Case Control Etiologic Study of Sarcoidosis) is a research project of the National Institutes of Health. Sarcoidosis is a chronic disease that often involves the lungs. The cause of sarcoidosis is unknown. In this study we will assess cells and fluid from the lungs of patients with sarcoidosis if the cells and fluid are saved in the course of routine diagnosis. The study doctors have planned to collect lung cells and fluid from approximately 250 of the total of 720 patients with sarcoidosis enrolled in the study. Ten clinic research centers are in this study.

HOW PATIENTS ARE CHOSEN: Patients who are going to have bronchoscopy because they may have sarcoidosis are being asked to agree to use of the bronchoscopy to collect and save the cells and fluid from their lungs. If you have questions about the bronchoscopy, you may discuss them with your doctor before agreeing to the procedure. We are asking you for your agreement to save cells and fluid now because we will not know if you have sarcoidosis until after your bronchoscopy and lab work are done. Only patients who have bronchoscopy in ACCESS hospitals are being asked to agree to saving fluid and cells for this research project.

WHAT TO EXPECT: The doctors who will do your bronchoscopy will obtain your written consent to use a bronchoscope to look into your lungs, rinse a safe fluid into and out of a portion of your lungs to obtain cells and fluid needed for your diagnosis, and to biopsy your lung tissue. The doctors in your hospital will save up to one cup of the rinsed fluid in a freezer after the amount needed has been sent to diagnostic laboratories. We are asking you to agree to allow the fluid and the cells rinsed from your lungs to be collected and saved according to the plans for ACCESS. These plans will assure that the amount of fluid collected is enough for both your diagnosis and research purposes. Making sure that enough fluid is collected will add approximately five to ten minutes to the total time for your bronchoscopy. A typical bronchoscopy lasts less than one hour.

After your diagnosis has been made, ACCESS study doctors will invite you to join this research project if you have sarcoidosis. If you join this research project, the fluid and cells being storied will be sent to the National Institutes of Health to be stored and for research tests related to sarcoidosis. Part of the frozen samples may be used at a later date for studies of diseases other than sarcoidosis. Your agreement or refusal to use the sample in other studies will not affect its use for the current study.

Please mark the consent you give for study of fluid and cells from your lungs (check one):

9 for this sarcoidosis study only.

9 for this sarcoidosis study and for other medical research projects.

If you do not have sarcoidosis, the study doctors will not return to discuss ACCESS with you. If you do not join the study (for example if you do not have sarcoidosis), you and your doctor will have the stored sample used as you and your doctor agree.

RISKS AND DISCOMFORTS: The rinse of fluid and cells from your lungs is a routine part of the diagnosis by bronchoscopy. The increase in risk of infection or reduction in oxygen level due to the procedures to make sure that enough fluid is available for diagnosis and research is small (less than 1%) although it has never been exactly measured. Up to 10% of patients may have a fever for a short time (less than one day) after the procedure.

_____
Initials

EXHIBIT 2-3 (*Continued*)
CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

BENEFITS: There is no direct benefit to you from joining this study. We will tell your doctor and write a letter about anything urgent for your health care that we find.

This study may help us learn the causes and risk factors for sarcoidosis. So, there may be benefit in the future to you (if you have sarcoidosis) and to other people who have sarcoidosis now or later. We will send a brief account of the study findings to you at the end of the study.

YOUR CHOICES AND CARE: Your agreement to let us collect and save the fluid and cells rinsed from your lungs is purely voluntary and will not affect your care. You may refuse to permit this procedure and still be in the study. You may leave the study at any time. If you do not become part of ACCESS or if you leave it, doing so will not harm your present or future care at the hospital or clinic.

The study will not provide any treatment for you. The study will not change the treatment provided by your primary doctor(s).

COST/PAYMENT: There will be no cost and there will be no payment to you for the fluid and cells collected. Neither you nor your insurance carrier will be responsible for extra costs related to the fluid and cells collected for research. The study will not pay for the bronchoscopy, biopsy or obtaining fluid and cells that would usually be part of your care if you were not in the study. Either you or your insurance carrier is responsible for the cost of tests which are part of your usual care.

CONFIDENTIALITY: In this study, only the research staff at the clinic where you are being studied will know your name. Stored fluid and cells will be identified only by code number that cannot be traced back to you by anyone outside of the study. The study staff will not give private information to anyone outside the study except to comply with legal demands (such as a court subpoena). If you agree to the saving of fluid and cells that your doctor obtains during this bronchoscopy for use in the ACCESS research project, please sign this consent form.

The records collected in this study will be subject to the Privacy Act. Records collected in this study can be obtained pursuant to a written request by, or with the prior consent of, the individual to whom the record pertains. The request should be made in writing to the Privacy Act Coordinator, NHLBI, NIH, Building 31, Room 5A10, 9000 Rockville Pike, Bethesda, MD 20892. Records will not be disclosed to any person or agency, unless the individual to whom the record pertains provides a written request or prior consent, except as disclosure of the record fits the criteria described in Section 3(b) of 5 U.S.C. 552a, The Privacy Act of 1974 or in the Privacy Act System Notice 0925-0126 -- Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI. In order to safeguard the records, only authorized users will have access to the records, the records will be maintained in offices that are locked when not in use, and access is strictly controlled. Robert A. Musson, Project Officer for the “A Case Control Etiologic Study of Sarcoidosis,” will be responsible for monitoring contractor compliance with the Privacy Act. Except for the data tape that will not contain personal identifiers (e.g., name, social security number), contractor records pertinent to this study will be destroyed by shredding or burning within six years and three months after final payment under the contract, as described in NIH Manual Chapter 1743, Appendix 1 -- “Keeping and Destroying Records.”

_____
Initials

EXHIBIT 2-3 (*Continued*)
CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM

I have explained to_____, the nature and purpose of the saving of fluid and cells rinsed from the lungs and such risks as are involved. I have asked _____ if any questions have arisen regarding the procedure and have answered these questions to the best of my ability.

_____

Investigator's Signature Date

I have been informed about the above procedure, with its possible benefits, risks and consequences. I recognize that I am free to ask any questions. If I have questions about the study, I may call (Clinical Center Principal Investigator) at (telephone number). My participation in this study is voluntary, and I am free to withdraw from this study at any time without affecting my care or my relationship with [name of hospital].

I have a right to privacy, and the investigators on this study will take all reasonable measures to protect the confidentiality of my records. My name and any other information which might identify me will not appear in any presentation or publication resulting from this study. My name and any other information which might identify me will not be available to any person or group other than the investigators of this study and the Committee on Clinical Investigation of the [name of hospital], which oversees all studies.

I will receive a copy of this Consent Form. [Name of hospital] maintains an "Institutional Assurance of Compliance," a document which explains how the hospital provides for protection of human subjects, a copy of which is available on request.

I may be contacted by the [name of hospital]'s Institutional Review Board during or after my participation in this study as part of its efforts to monitor the experience of subjects in clinical investigations.

In the event physical injury occurs to me, resulting from the research procedures, medical treatment will be available, if appropriate, at [name of hospital]. However, no special arrangements have been made for compensation or for payment for treatment solely because of my participation in this research study.

I hereby agree to participate in this investigation.

_____

Patient's Signature Date

_____

Initials

EXHIBIT 2-3 (*Continued*)
CONSENT FORM FOR USE OF CELLS AND FLUID RINSED FROM THE LUNGS

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

INFORMED CONSENT FORM
(Continued)

I agree to my doctor's saving for research purposes up to one cup of fluid and cells rinsed from my lungs.

I _____ do _____ do not agree to allow my cells and fluid sample to be used at a later date for studies of diseases other than sarcoidosis.

_____

Patient's Signature Date

I have witnessed the explanations made by the Investigator and heard the responses to questions.

_____

Witness's Signature Date

For any questions regarding the rights of a research participant, or information regarding treatment of research-related injuries, please contact [name of research administrator] at [telephone #].

Date submitted to Committee:_____

EXHIBIT 2-4

LETTER TO RELATIVE TO REQUEST INFORMATION FOR ACCESS

Draft 4/3/92

Dear _____
(your relative name)

I recently participated in a study (named ACCESS) about the cause of sarcoidosis. Part of my participation involved giving a family history. I told the doctors doing the study that you were a relative who may have or may have had sarcoidosis. I did not tell them your name but I did tell them you are my _____ (enter the relationship with your relative - child, parent, brother, or sister). I am writing to ask you to give the doctors permission to collect some additional information from you over the telephone.

It is important that the doctors doing this study confirm all reported cases of sarcoidosis in my family. Your participation is voluntary and should take about five minutes. Any information they collect from you will remain confidential and will be used only for research purposes. Only if you have or had sarcoidosis will the study retain the additional information you provide. In order to insure that your confidentiality is protected, it is necessary that I send this letter, instead of the doctors contacting you directly. The doctors doing this study cannot contact you and collect important information for their study until you sign this letter and return it to them. You are not obligated to give information to the study or to reply to this letter. The researchers doing the study will appreciate any assistance you volunteer.

If you are interested in helping in this research, please:

1. Print and sign your name and enter the date below.
2. Write your address and telephone number in the space provided.
3. Circle the day and time that it is best for them to contact you.
4. Send this letter back in the enclosed self-addressed stamped envelope.

Sincerely,

_____
your name

EXHIBIT 2-4 *(Continued)*

LETTER TO RELATIVE TO REQUEST INFORMATION FOR ACCESS

CONSENT TO CONTACT:

I agree to allow an interviewer for ACCESS to call me and ask a short questionnaire about my disease history over the phone. This information will remain confidential and only be used for research purposes.

PRINT NAME: _____

Signature: _____ Date: _____

Address: _____

_____

Telephone Number: (____ ____ ____) ____ ____ ____ - ____ ____ ____ ____

A good day and time to reach me is (please circle a day and time):

DAY: Monday Tuesday Wednesday Thursday Friday Saturday

TIME OF DAY: AM 8 9 10 11 PM 12 1 2 3 4 5 6 7 8 9

EXHIBIT 2-5

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

AFFECTED RELATIVE REMINDER LETTER
(Sent to Case or Control)

Dear **Case/Control's Name:**

Thank you for your recent participation in A Case-Control Etiology Study of Sarcoidosis. During the Review of your family history, you reported a **name type of relative** who had a history of sarcoidosis. We have not yet received the letter from your **name type of relative** indicating his or her willingness to participate in this study. It is important that the doctors doing this study confirm all reported cases of sarcoidosis in families.

As we stated before, the participation of your **name of type of relative** is voluntary, but should only take about five minutes and can be done over the phone. Any information we collect from your **name type of relative** will remain confidential and will be used for only research purposes.

We have enclosed another permission letter to give to your **name type of relative**. The doctors doing this study cannot contact your **name type of relative** until **he** or **she** signs this letter and returns it to them.

Thank you for your help and participation in this study.

Sincerely,

ACCESS Principal Investigator

CHAPTER 3

DIAGNOSIS AND ASSESSMENT PROCEDURES

3.1 INTRODUCTION

Consistency and accuracy in the diagnosis and assessment of patients with sarcoidosis are necessary for the investigation of the etiology of sarcoidosis in ACCESS. The case definition requires the finding of noncaseating granulomata on examination of pathology slides. Chest roentgenogram readings and spirometry measurements are required to classify the cases into homogeneous categories of disease for etiologic evaluation and for clinical course assessment. Among the information collected in ACCESS, pathology data, chest roentgenogram data and spirometry data are particularly dependent upon standardized performance and evaluation. This chapter describes the criteria for interpretation of pathology slides, chest roentgenograms and spirometry tracings in ACCESS.

3.2 DIAGNOSIS OF SARCOIDOSIS

Only newly diagnosed cases are enrolled in the study. A newly diagnosed case is defined as a patient who has had tissue confirmation less than six months prior to entry into the study. Cases may have received systemic treatment for sarcoidosis during this period. The day of the biopsy that confirms the presence of sarcoidosis is defined as the day of diagnosis.

All cases should have a clinical course compatible with sarcoidosis, that is, a systemic granulomatosis of unknown etiology. All cases selected for inclusion in the study have tissue confirmation of granuloma. The Kveim test may be used to confirm a diagnosis of sarcoidosis in patients with Löfgren's Syndrome (defined by the presence of erythema nodosum), if no other tissue is obtained.

Intrathoracic disease documented by mediastinal lymph node or transbronchial biopsies does not require clinical evidence of other organ involvement. A patient with a positive biopsy of a skin lesion requires involvement of at least one other organ as defined in Table 3-1. Table 3-1A provides the categories in use starting November 1996. Revisions to this table were made in April

1998 (Table 3-1B), but did not change the diagnostic criteria (see Section 3.6 below). Cases with uveitis on slit lamp examination require a biopsy of other involved tissue.

The Principal Investigator at each Clinical Center is responsible for documenting that each case has tissue confirmation of a diagnosis of sarcoidosis. The number of transbronchial biopsy attempts should be taken from bronchoscopy reports. If the information is not available from the bronchoscopy report, the number of biopsies may be estimated as the number of biopsy specimens in the pathology report. If there is no reliable count of transbronchial biopsies or specimens, the number of biopsies is recorded as unknown.

3.3 PATHOLOGY

The most commonly used approach for tissue diagnosis of sarcoidosis is bronchoscopy with transbronchial biopsy. Flexible fiberoptic bronchoscopy should be performed according to guidelines outlined by the American Thoracic Society (Sokolowski, et al, 1987). Optimal evaluation of patients undergoing bronchoscopy for suspected sarcoidosis includes bronchoalveolar lavage and transbronchial biopsies. Bronchoalveolar lavage (BAL) is used for cultures and cytopathology, if appropriate. In institutions employing cell differential counts on bronchoalveolar lavage fluid, collection of BAL fluid for this purpose may also be valuable. If the patient consents to collection of BAL specimens for ACCESS, it is strongly recommended that the procedures outlined in Chapter 6 be followed.

Transbronchial biopsies are commonly obtained to establish a diagnosis of sarcoidosis. Although the optimal number of transbronchial biopsies that should be attempted for this evaluation is controversial, most experienced investigators suggest four to six biopsies are sufficient to sample the lung parenchyma. Biopsies of abnormal appearing bronchial mucosa may also be indicated, particularly if a granular or cobblestone appearance is present. In Clinical Centers with expertise in transbronchial needle aspiration biopsy procedures, these procedures can be attempted when there are enlarged paratracheal, subcarinal, or hilar nodes that are potentially reachable by such a procedure.

At least four transbronchial biopsy specimens are recommended for patients whose tissue diagnosis is approached with bronchoscopy and transbronchial biopsy. In patients who have an atypical presentation for sarcoidosis, such as asymmetrical hilar adenopathy or asymmetrical pulmonary infiltrates, a sufficient amount of tissue must be sampled. For patients undergoing mediastinoscopy, it should be determined prior to the procedure which lymph nodes are considered abnormal so that biopsies of those nodes can be obtained rather than normal sized lymph nodes. Biopsy should be obtained of a grossly enlarged lymph node ($\geq$ 2 cm) and not of normal sized lymph nodes.

The Kveim test may be used to confirm a diagnosis of sarcoidosis in patients with Löfgren's Syndrome (defined by presence of erythemia nodosum) if no other tissue is obtained. Investigators using the Kveim agent must adhere to the U.S. Food and Drug Administration (FDA) requirement for use of this agent (see Chapter 6, Section 6-3). The Kveim reaction is characterized by the presence of clear-cut, non-caseating granulomas with no demonstrable foreign substances. This establishes the diagnosis of sarcoidosis. Occasionally the pathologist notes poorly formed granulomas. These equivocal reactions must not be accepted as positive tests, but should prompt the examiner to order further slides for re-examination of the biopsy tissue. It is important to emphasize that a positive test requires demonstration of unmistakable granulomas, indistinguishable from those seen in the naturally occurring disease.

The histopathologic diagnosis of sarcoidosis requires demonstration of unequivocal noncaseating epithelioid granulomas in biopsied tissue (Sheffield and Jones-Williams, 1994). Typically, the granulomas are the same age. In the lung, they may involve the walls of large and small airways as well as the interstitium. In lymph nodes and skin, they are diffusely distributed. The granulomas consist of epithelioid cells, multinucleated giant cells and scanty surrounding lymphocytes. Stains for acid-fast bacilli and fungi must be negative. Inorganic particles should be absent by polarized light.

The pathologic hallmark of sarcoidosis is the presence of discrete non-caseating granulomas. Microscopically, in early nodules, the center is occupied by epithelioid cells which are pale staining, with scattered giant cells of Langerhans type. These cells are surrounded by a ring of lymphocytes and classically, the whole lesion is sharply defined from the surrounding tissue. True caseous necrosis is absent through the center of the nodules. However, a small amount of eosinophilic, necrotic, fibrinoid material may be present. Giant cells may contain a variety of intra-cytoplasmic inclusions which include Schaumann's bodies, asteroid bodies, and centrospheres. Granulomas in sarcoidosis that have undergone some degree of resolution may demonstrate varying degrees of fibrosis leaving a stellate scar or hyalinized ghost of a granuloma. This histopathologic picture is seen in the lung and other organ systems. The granulomatous inflammation present in the heart and liver may be less distinct than classically found in the lung.

Tissue samples are reviewed by a single pathologist at each Clinical Center. The pathologist indicates his/her level of certainty of a pathologic diagnosis that is consistent with sarcoidosis (i.e., definite, probable or possible, or clearly not consistent with a clinical diagnosis of sarcoidosis). If the tissue diagnosis is probable or possible, the slides are sent to the Clinical Coordinating Center for central reading. Any designation other than definite granulomas consistent with a diagnosis of sarcoidosis results in the exclusion of this case from the study. All slides for cases enrolled after September 1997 are reviewed under polarized light to determine whether birefringent material is present. A review for birefringent material on the slides of cases enrolled prior to September 1997 is performed if the slides are available.

A "definitely-positive" reading indicates the biopsy has the histologic features typical for sarcoid granulomas. There should be no evidence of a foreign body reaction in the biopsy area. A "definitely negative" reading indicates the histologic picture is not consistent with granulomatous inflammation. A "probable" diagnosis indicates that many but not all of the typical features for sarcoid granulomata are present. A "possible" reading indicates less certainty or that fewer features of sarcoid granulomatous inflammation are present on the pathology specimen. Classification as

"probable" or "possible" or "uncertain" reading requires sending the slides to the Clinical Coordinating Center for distribution and further review. A minimum of three slides are required: one stained with hematoxylin and eosin; one stained for acid-fast organisms; and one stained for fungus. The pathology slides for a sample of ACCESS cases were selected for review for quality control purposes during the first 20 months of recruitment. Slides submitted for review are labeled similarly whether selected because of possible or probable findings of granulomatous disease or by sampling of enrolled cases' slides. The Johns Hopkins University School of Medicine ACCESS Clinical Center leads the central pathology slide reading program.

Fungal lung disease and tuberculosis are ruled out. Specifically, all cases are required to have acid-fast bacillus (AFB) and fungal cultures of all available tissue performed and appropriately stained slides read unless the diagnosis was confirmed by the Kveim agent. The latter can be used only for cases with Löfgren's Syndrome. In potential cases, undergoing bronchoscopy, bronchial washings should be obtained for fungal and AFB cultures.

Potential cases who live in areas where histoplasmosis is endemic or who have risk factors for tuberculosis should have appropriate tests performed on tissue specimens (cultures of biopsy specimens required) to exclude tuberculosis and fungal infections (especially histoplasmosis). In particular, adequate samples should be cultured, if possible. At a minimum, slides of tissue should be stained for mycobacteria and fungi. Fungal serology and measures of *H. capsulatum* antigen are not expected to contribute to the diagnosis and are not used in ascertaining case eligibility. Potential cases with occupational histories indicating possible exposure to beryllium are not eligible unless both blood and bronchoalveolar lavage proliferation studies indicate a negative response to beryllium.

3.4 CHEST X-RAY

3.4.1 Procurement of a Chest X-ray

Chest roentgenograms are obtained as part of routine clinical evaluation for all sarcoidosis patients enrolling in ACCESS. Interpretation of the postero-anterior (PA) chest roentgenogram is

the responsibility of each Clinical Center's Principal Investigator -- to be performed personally or delegated as appropriate. The roentgenogram is a standard PA film taken with a radiation source six feet from the chest and includes both lung fields. The chest X-ray is reviewed to be sure that all parts of the lung fields can be seen. The quality of the films is graded from unacceptable to acceptable to good. A chest X-ray reading is provided by the Principal Investigator or his/her designee on each of the patients with sarcoidosis.

3.4.2 Characteristics of Chest X-rays to be Evaluated

Two different characteristics of the chest X-rays are evaluated:

A. Scadding Classification System - the chest X-ray is reviewed using the system that Scadding originally proposed (Scadding, 1961). Characteristics of the chest X-ray are as follows:

1. Stage I - Hilar adenopathy either symmetrical or asymmetrical or with peritracheal adenopathy and without any parenchymal involvement is considered as Stage I.
2. Stage II - Chest X-ray shows hilar adenopathy plus parenchymal infiltrates. Parenchymal infiltrates can include a reticulo- nodular infiltrate, alveolar infiltrates, a pseudo-alveolar pattern, or a mixture thereof. The key to Stage II X-rays is the presence of adenopathy plus infiltrates.
3. Stage III - Infiltrates alone with no evidence of adenopathy on the plain PA chest X-ray. Reticulo- nodular alveolar or pseudo-alveolar patterns are all considered pulmonary infiltrates.
4. Stage IV - Infiltrates are fibrocystic changes. In sarcoidosis, these are, classically, of the upper lobes. Those X-rays with minimal changes (less than 10% of the overall chest X-ray appearance) are not considered sufficient for classifying patients as having Stage IV.

It is possible that a patient has mixed characteristics. Commonly, patients who have fibrotic changes may have adenopathy. These patients are considered for consistency with other publications as Stage IV if they have fibrotic changes greater than 10% of the overall infiltrates.

Information obtained by CT scans sometimes biases the interpretations. Patients are not required to have CT scans for entry into this study. However, for some patients with sarcoidosis, this information is available. If a CT scan is obtained, especially if it shows hilar adenopathy which is not present on the plain chest X-ray, it is the plain chest X-ray which is used for characterization of the patient's adenopathy and, hence, staging. The same holds for pulmonary infiltrates that may be seen on CT scan or gallium scan but are not seen on the plain chest X-ray. For the purposes of this study, only the PA chest X-ray is used for interpretation of the staging.

B. Another classification considers the presence or absence on the chest X-ray of specific abnormalities (interstitial infiltrates, alveolar infiltrates, hilar or mediastinal adenopathy, hilar retraction, bullae or blebs/cysts, cardiomegaly, pulmonary artery enlargement, pulmonary fibrosis, pleural abnormalities). For example, pulmonary hypertension is diagnosed in the presence of enlarged pulmonary arteries that are distinctly different from hilar adenopathy. Enlargement of the descending branch of a pulmonary artery to a size greater than 10 mm is used as a criterion for pulmonary hypertension.

3.4.3 Quality Control Plan

Selected original films are requested for review by ACCESS investigators at Steering Committee meetings. The films are read by each investigator and the data recorded on Form 30. The films are scored by the traditional Scadding system: Stage 0 = normal hilum, mediastinum and lung fields; Stage I = with hilar adenopathy; Stage II = hilar adenopathy and infiltrates; Stage III =

infiltrates alone; and Stage IV = fibrosis. For the sake of uniformity, patients with multiple abnormalities (adenopathy plus fibrosis) are staged according to the highest abnormality. Agreement of investigators' readings are reviewed in the Executive Committee. Chest radiographs are also reviewed if Clinical Center investigators request the Clinical Coordinating Center staff to arrange for the review because of some difficult, illustrative or unusual radiographic feature. Chest X-ray reports for cases are reviewed during Site (or Audit) Visits to verify data recorded on study forms.

3.5 SPIROMETRY

Spirometry is performed as part of routine care for all sarcoidosis patients enrolling in ACCESS. Repeat spirometry after bronchodilator administration is performed as clinically indicated. If a patient in ACCESS has had spirometry at another medical center within six months of enrolling in ACCESS, the ACCESS Clinical Coordinating Center performs spirometry at no charge to the patient.

Quality assurance and interpretation of the spirometry are the on-going responsibility of each ACCESS Clinical Center Principal Investigator or physician Co-Investigator(s) certified in ACCESS to whom the Principal Investigator delegates these responsibilities. Each set of tracings for each ACCESS case is to be reviewed by the Clinical Center Principal Investigator or designated Co-Investigator to determine that there is less than 5% variability among the three tracings for each patient. The spirometry tracings for the first three cases enrolled in each Clinical Center are requested by Clinical Coordinating Center staff who arrange for quality assurance review of those tracings. Spirometry records for ACCESS cases are reviewed during Site (or Audit) Visits. The Spirometry Laboratory log is also reviewed during the Site (or Audit) Visits.

A detailed description of ACCESS spirometry performance is attached in Exhibit 3-1 (ACCESS Spirometry Manual).

3.6 SARCOIDOSIS ASSESSMENT SYSTEM

At the time of enrollment into the study, patients are categorized according to their clinical condition at the time of initial diagnosis, i.e., the day of biopsy confirmation. Table 3-2A outlines the disease categories that were used to describe cases beginning November 1996. An additional revised classification system was used beginning September 1997 and is given in Table 3-2B. The purpose of revising the disease categories is to encourage use of information on facets of the clinical presentation of sarcoidosis that were not readily appreciated in the hierarchical, initial classification of disease categories. This information is used in ACCESS to assess the spectrum of clinical sarcoidosis presentations represented among the ACCESS cases.

Multiorgan disease is defined as tissue confirmation in at least one organ, and either clinical or pathological involvement in another organ(s), as outlined in Table 3-1. The record of organ involvement for cases is based on abnormalities ever observed in the set of definitions in use November 1996 - March 1998, and in the revised definitions in use starting April 1998. The revisions made to the criteria for organ involvement in April 1998 were clarifications of wording, deletion of evidence of treatment response as a criterion (because almost none of the ACCESS cases have had a definitive course of treatment at the time of study entry and some of these abnormalities may respond to the same treatment if used for other diseases), and regrouping of the categories into those that are common, those that are unusual but serious, and other organ involvement.

TABLE 3-1A

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS USED BEGINNING NOVEMBER 1996

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy of the organ or one of the clinical conditions in Table 3-1A. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Treatment for sarcoidosis such as corticosteroids, azathioprine chloroquine, or methotrexate associated with improvement in organ function.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NEUROLOGIC	1. Positive MRI with uptake in meninges or brainstem 2. CSF with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's Palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy	1. Other abnormalities on MRI 2. Unexplained neuropathy 3. Positive EMG	1. Unexplained headaches 2. Peripheral nerve radiculopathy
NON-THORACIC LYMPH NODE		1. New palpable node above waist 2. Lymph node > 2 cm by CT scan	1. New palpable femoral lymph node
RENAL	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease
LUNGS	1. Chest roentgenogram with one of the following: -Bilateral hilar adenopathy -Diffuse infiltrates -Upper lobe fibrosis 2. Restriction on PFTs	1. Lymphocytic alveolitis by BAL 2. Any pulmonary infiltrates 3. Isolated reduced DLCO	1. Any adenopathy 2. Obstructive PFTs
CARDIAC	1. Treatment responsive cardiomyopathy 2. EKG showing IVCD or nodal block 3. Positive gallium scan of heart	1. No other cardiac problem and either: -Ventricular arrhythmias -Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: -Cardiomyopathy -Ventricular arrhythmias

TABLE 3-1A (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
USED BEGINNING NOVEMBER 1996

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy of the organ or one of the clinical conditions in Table 3-1A. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Treatment for sarcoidosis such as corticosteroids, azathioprine chloroquine, or methotrexate associated with improvement in organ function.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
SKIN	1. Lupus pernio 2. Annular lesion	1. Macular papular lesions 2. New nodules	1. Keloids 2. Hypopigmentation 3. Hyperpigmentation
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness	1. Glaucoma 2. Cataract
LIVER	1. LFTs > three times normal	1. Compatible CT scan 2. Elevated alkaline phosphatase	
BONE MARROW	1. Granulomas in bone marrow 2. Unexplained anemia 3. Leukopenia 4. Thrombocytopenia		1. Anemia with low MCV
SPLEEN		1. Enlargement by: -Exam -CT scan -Radioisotope scan	
BONE / JOINTS	1. Granulomas in bone biopsy 2. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR / NOSE / THROAT	1. Granulomas in ear, nose or throat	1. Unexplained hoarseness with exam; consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness

TABLE 3-1A (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
USED BEGINNING NOVEMBER 1996

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy of the organ or one of the clinical conditions in Table 3-1A. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Treatment for sarcoidosis such as corticosteroids, azathioprine chloroquine, or methotrexate associated with improvement in organ function.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
PAROTID / SALIVARY GLANDS	1. Biopsy confirmation 2. Symmetrical parotitis with syndrome of mumps 3. Positive gallium scan (“Panda sign”)		1. Dry mouth
MUSCLES	1. Granulomas in muscle 2. Increased CPK/aldolase which decreases with treatment	1. Increased CPK/aldolase	1. Myalgias responding to treatment
HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis - no stone analysis 2. Nephrolithiasis with negative family history for stones

BAL = bronchoalveolar lavage; CPK = creatine phosphokinase; CSF = cerebrospinal fluid; CT = computed tomography; DLCO = diffusing capacity of the lungs for carbon monoxide; EKG = electrocardiogram; EMG = Electromyogram; IVCDs = interventricular conduction defect ; LFT = liver function test; MCV = mean corpuscular volume; MRI = magnetic resonance image; PFTs = pulmonary function tests;

TABLE 3-1B

CRITERIA FOR ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
COMMON INVOLVEMENT
USED BEGINNING APRIL 1998

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy documents definite involvement of the organ; 2) Involvement according to criteria other than biopsy is classified as definite, probable or possible on the basis of clinical evaluation (described in the table below for each organ) and assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease).

ORGAN	DEFINITE	PROBABLE	POSSIBLE
LUNGS	1. Chest roentgenogram with one or more of the following: -Bilateral hilar adenopathy -Diffuse infiltrates -Upper lobe fibrosis 2. Restriction on pulmonary function tests	1. Lymphocytic alveolitis by bronchoalveolar lavage (BAL) 2. Any pulmonary infiltrates 3. Isolated reduced diffusing capacity for carbon monoxide	1. Any adenopathy 2. Obstructive pulmonary function tests
SKIN	1. Lupus pernio 2. Annular lesion	1. Macular/ papular 2. New nodules	1. Keloids 2. Hypopigmentation 3. Hyperpigmentation
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness	1. Glaucoma 2. Cataract
LIVER	1. Liver function tests > three times normal	1. Compatible computer tomography (CT) scan 2. Elevated alkaline phosphatase	
HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis - no stone analysis 2. Nephrolithiasis with negative family history for stones

TABLE 3-1B (Continued)

CRITERIA FOR ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
UNUSUAL, BUT SERIOUS COMPLICATIONS
USED BEGINNING APRIL 1998

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy documents definite involvement of the organ; 2) Involvement according to criteria other than biopsy is classified as definite, probable or possible on the basis of clinical evaluation (described in the table below for each organ) and assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease).

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NEUROLOGIC	1. Positive magnetic resonance imaging (MRI) with uptake in meninges or brainstem 2. Cerebrospinal fluid with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's Palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy	1. Other abnormalities on magnetic resonance imaging (MRI) 2. Unexplained neuropathy 3. Positive electromyogram	1. Unexplained headaches 2. Peripheral nerve radiculopathy
RENAL	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease
CARDIAC	1. Treatment responsive cardiomyopathy 2. Electrocardiogram showing intraventricular conduction defect or nodal block 3. Positive gallium scan of heart	1. No other cardiac problem and either: -Ventricular arrhythmias -Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: -Cardiomyopathy -Ventricular arrhythmias

TABLE 3-1B (Continued)

CRITERIA FOR ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS
OTHER ORGAN INVOLVEMENT
USED BEGINNING APRIL 1998

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy documents definite involvement of the organ; 2) Involvement according to criteria other than biopsy is classified as definite, probable or possible on the basis of clinical evaluation (described in the table below for each organ) and assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease).

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NON-THORACIC LYMPH NODE		1. New palpable node above waist 2. Lymph node > 2 cm by computer tomography (CT) scan	1. New palpable femoral lymph node
BONE MARROW	1. Unexplained anemia 2. Leukopenia 3. Thrombocytopenia		1. Anemia with low mean corpuscular volume (MCV)
SPLEEN		1. Enlargement by: -Exam -Computer tomography (CT) scan -Radioisotope scan	
BONE / JOINTS	1. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR / NOSE / THROAT		1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness
PAROTID / SALIVARY GLANDS	1. Symmetrical parotitis with syndrome of mumps 2. Positive gallium scan (“Panda sign”)		1. Dry mouth
MUSCLES	1. Increased creatine phosphokinase (CK)/aldolase which decreases with treatment	1. Increased creatine phosphokinase (CK)/aldolase	1. Myalgias responding to treatment

TABLE 3-2A

DISEASE CATEGORIES OF CASES USED BEGINNING NOVEMBER 1996

This classification is based on involvement ever (Form 24, Items 82 A-N) and is hierarchical (e.g., pulmonary involvement is given priority over erythema nodosum).

I. Erythema Nodosum (Löfgren's Syndrome)

A constellation of signs including erythema nodosum, fever, swollen tender joints (usually ankles) and an abnormal chest X-ray. Patients need not exhibit every feature of the syndrome, but all should have erythema nodosum. (Approximately 10% of patients with erythema nodosum and sarcoidosis will have a normal chest X-ray).

II. Acute Sarcoidosis (Excluding erythema nodosum) or Chronic Sarcoidosis (Not including the fibrotic lung disease patients)

Signs of sarcoidosis without clinically manifest extrapulmonary disease.

III. Fibrotic lung disease

Patients whose chest X-rays exhibit linear streaks, small and large bullae and retraction of the hilar areas cephalad. Many of these patients manifest obstructive, as well as restrictive, dysfunction. All will have some degree of permanent lung damage resistant to current therapies.

IV. Extrapulmonary sarcoidosis

Patients whose most prominent clinical manifestations that are not pulmonary (e.g., do not have fibrotic lung disease). This group would include major acute or chronic clinically significant extra-pulmonary disease as follows:

A. Ocular - uveitis, glaucoma and/or blindness.

B. Cutaneous (excluding erythema nodosum) granulomatous skin lesions such as lupus pernio, raised erythematous nodules or plaques, or ulcerating lesions.

C. Subcutaneous nodules - palpable nodules which may range from a few millimeters to several centimeters with intact overlying skin.

D. Enlarged liver and/or significantly elevated liver blood chemistries (alkaline phosphatase > 200 IU, ALT, AST > 200 U/L) and/or evidence of portal hypertension.

E. Enlarged spleen with or without evidence of hypersplenism.

F. Neurologic - central nervous system or peripheral nerve involvement.

TABLE 3-2A (Continued)

**DISEASE CATEGORIES OF CASES
USED BEGINNING NOVEMBER 1996**

G. Cardiac - tachycardic or bradycardic dysrhythmias, cardiomyopathy, abnormal gallium or thallium scans.

H. Bone and Joint - clinical and radiographic evidence of bone and/or joint lesions typical of sarcoidosis.

I. Renal - hypercalcemia, nephrocalcinosis, elevated BUN and/or creatine.

Patients with extrapulmonary sarcoidosis are classified in two categories -- those with no pulmonary involvement (i.e., normal chest X-ray or Scadding category I chest X-ray); and those with pulmonary involvement (i.e., Scadding category II or III chest X-ray).

TABLE 3-2B

DISEASE CATEGORIES OF CASES USED BEGINNING SEPTEMBER 1997

This classification counts each involvement (e.g., pulmonary involvement and erythema nodosum) independently and is based on findings at the time of the physical examination (Form 24, Items 83 A-N).

I. Erythema Nodosum (Löfgren's Syndrome)

A constellation of signs including erythema nodosum, fever, swollen tender joints (usually ankles) and an abnormal chest X-ray. Patients need not exhibit every feature of the syndrome, but all should have erythema nodosum. (Approximately 10% of patients with erythema nodosum and sarcoidosis will have a normal chest X-ray).

II. Acute Sarcoidosis or Chronic Sarcoidosis (Not including the fibrotic lung disease patients)

Signs of sarcoidosis without clinically manifest extrapulmonary disease.

III. Fibrotic lung disease

Patients whose chest X-rays exhibit linear streaks, small and large bullae and retraction of the hilar areas cephalad. Many of these patients manifest obstructive, as well as restrictive, dysfunction. All will have some degree of permanent lung damage resistant to current therapies.

IV. Extrapulmonary sarcoidosis

Patients who have prominent clinical manifestations that are not pulmonary. This group would include major acute or chronic clinically significant extrapulmonary disease as follows:

A. Ocular - uveitis, glaucoma and/or blindness.

B. Cutaneous (excluding erythema nodosum) granulomatous skin lesions such as lupus pernio, raised erythematous nodules or plaques, or ulcerating lesions.

C. Subcutaneous nodules - palpable nodules which may range from a few millimeters to several centimeters with intact overlying skin.

D. Enlarged liver and/or significantly elevated liver blood chemistries (alkaline phosphatase > 200 IU, ALT, AST > 200 U/L) and/or evidence of portal hypertension.

E. Enlarged spleen with or without evidence of hypersplenism.

F. Neurologic - central nervous system or peripheral nerve involvement.

G. Cardiac - tachycardic or bradycardic dysrhythmias, cardiomyopathy, abnormal gallium or thallium scans.

TABLE 3-2B (Continued)

**DISEASE CATEGORIES OF CASES
USED BEGINNING SEPTEMBER 1997**

H. Bone and Joint - clinical and radiographic evidence of bone and/or joint lesions typical of sarcoidosis.

I. Renal - hypercalcemia, nephrocalcinosis, elevated BUN and/or creatine.

Patients with extrapulmonary sarcoidosis are classified in three categories -- those with no pulmonary involvement (i.e., normal chest X-ray or Scadding category I chest X-ray); and those with pulmonary involvement (i.e., Scadding category II or III chest X-ray) or fibrosis (i.e., Scadding category IV chest X-ray).

EXHIBIT 3-1

ACCESS SPIROMETRY MANUAL

Procedures for spirometry in ACCESS are presented as follows:

I. Introduction

II. Volume-time and flow-volume tracings

III. Measurements obtained from spirometry

IV. BTPS correction factors

V. How a spirometer works

VI. Predicted or reference values

VII. Calibration and leak check (CAL)

VIII. The spirometry maneuver

- A. Withhold bronchodilator drugs
- B. Preparing the subject
- C. Explain and demonstrate the maneuver
- D. When is a session done?

IX. Post-bronchodilator testing

- A. Administration of the bronchodilator
- B. Post-Bronchodilator Spirometry (CLK, PFV)
- C. Printing results (DAT)

X. Examples of poor quality spirograms

XI. Quality Control

- A. Preventative maintenance

XII. Hygiene and infection control

XIII. Cleaning

XIV. Glossary

Table 3-1 BTPS conversion factors

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

I. Introduction

This manual is intended to serve as both a training document and a reference document for persons who perform spirometry for the Case Control Etiology of Sarcoid Study Research Network (ACCESS)It is written to be useful for people who have never performed pulmonary function testing before, as well as those who are experienced in performing these tests.

Spirometry is the timed-based measurement of the amount of air which can be forcefully exhaled from the lungs after a full inspiration. In this manual, we will use the term spirometry more specifically to refer to the measurement of the forced expiratory vital capacity (FVC) maneuver. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as as fast and as far as possible until no more air can leave the lungs. The volume of air leaving the lungs is recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function. This recording is called a spirogram.

When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. Indeed, in a highly trained, experienced subject a coefficient of variation of 2-3% is not unusual. The reason that spirometry is such a reproducible test is that people develop maximum flow rates of air leaving the lungs. Once this point is reached, no matter how hard the person tries to force air out of the lungs, the rate of flow of air cannot be increased. This phenomenon is called flow-limitation and is thought to be due to the fluid dynamics of flow through collapsible airways. Once a certain amount of effort has been exerted, the speed that air can be forced out of the lungs depends upon three factors: the elastic properties of the lung; the diameter of the airways; and the ease which airways tend to collapse. The elastic properties of the lungs are a major driving force for movement of air out of the lungs during a maximal expiration. The elastic recoil pressure of the lungs changes with the volume of air in the lung; ie it is greatest at full lung inflation and decreases at lower lung volumes. Therefore, there is greater flow out of the lung at higher lung volumes than at lower lung volumes.

In order to determine that all of the air has been blown out of the lungs, it is necessary that the participant continue to blow air out of the lungs until no more air can exit. As a rule of thumb, it takes about six seconds for a normal person to empty their lungs. In all cases the goal of testing is to continue effort until the flow of air out of the lungs falls to zero, i.e., no more air can leave the lungs. The duration of expiration should be adequate so that the final flows should be close to or zero.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

In order to obtain reproducible results, it is important to obtain maximum effort from the participant each time an FVC is performed. Determining whether a person is giving a maximum effort on a forced expiratory maneuver requires both experience and judgment. An important clue is whether the tests are reproducible, since less than maximum effort is difficult to reproduce.

In addition to the reproducibility of efforts, high peak flows, and long duration of expiration, it is important to observe the participant closely. The body language of the test subject is often a better guide to maximum effort than the recording of the maneuver. An experienced pulmonary function technician observes the test subject more closely than the spirometer or computer screen.

In ACCCESS, spirometry is not a primary outcome measure, but it is an important element in assessing disease severity and clinical course.Therefore, it is essential that this measurement be conducted with care, patience, enthusiasm and attention to detail.

II. Volume-time and flow-volume tracings

The forced expiratory maneuver measures the volume of air leaving the lung over time (Figure 2). The tracing inscribed is called the spirogram or the timed vital capacity or the volume-time tracing. When performed well, this tracing shows a steep initial slope, which smoothly and gradually becomes less steep until the slope is completely flat indicating that no further flow is leaving the lung. The slope of the volume-time tracing is equal to the flow which is leaving the lung. The flow leaving the lung is maximum during the early part of forced expiration (Peak Flow) and falls gradually to zero at the end of the effort. The advantage of the volume-time trace is that it emphasizes events at the end of the maneuver and it is easy to detect the end of test or zero flow point.

Assessment of Maximal Effort in a Forced Expiration

- **The maneuvers are reproducible**
- **The peak flows are high**
- **The onset of expiration is sudden and forceful**
- **The duration of expiration is ≥ 6 seconds**
- **The flow at the end of test is zero, even though the subject is still exerting effort**
- **The subject appears to be producing a maximal effort**

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

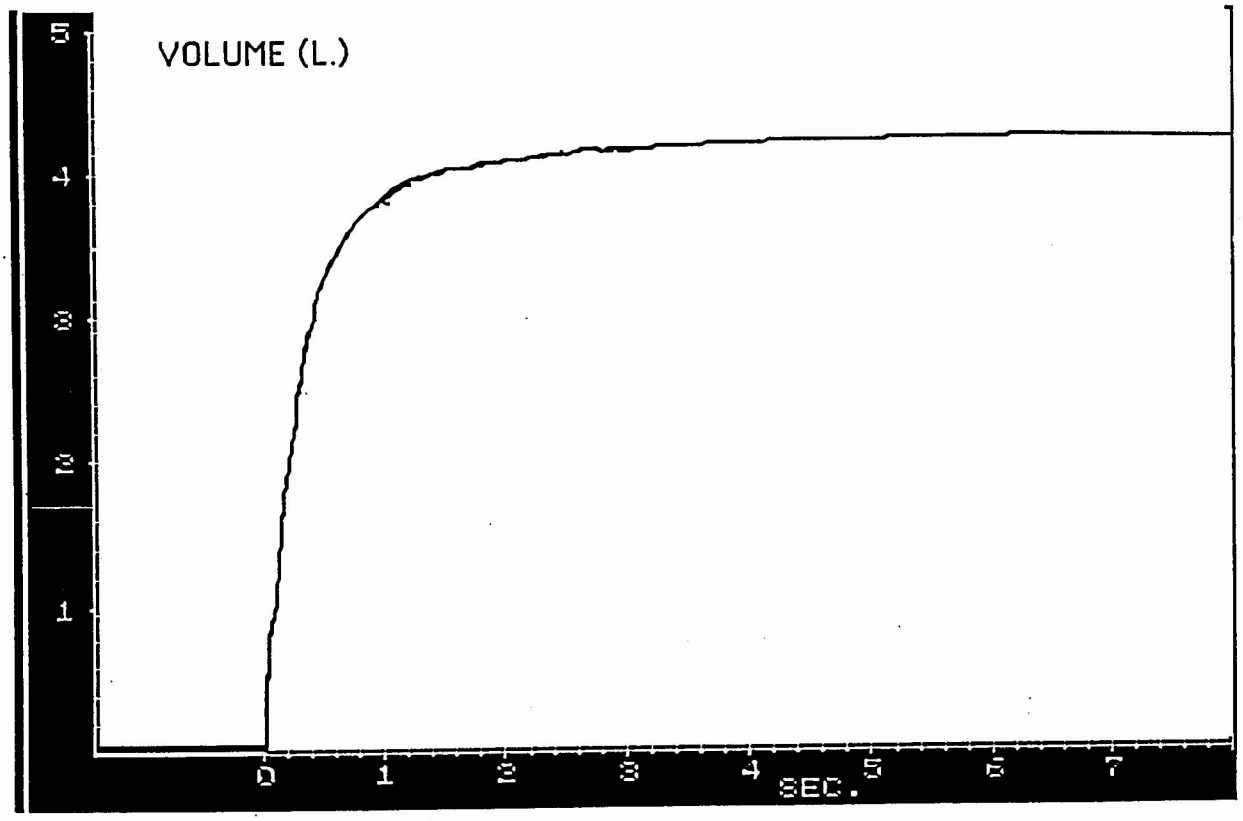


Figure 1. This is a volume-time tracing on a normal subject Note the clean start, and the clear end of test and zero flow point.

Another way to display the forced expiratory maneuver is to plot flow against volume. This is displayed as a flow-volume tracing or flow-volume curve. (Figure 2) Because it is easier to assess effort and reproducibility from a flow-volume tracing, this is the format that is often used to display the spirometry maneuvers. The FEV1 cannot be measured directly from the flow-volume curve, but it can be measured by a computer or by hand from the paper recording of the volume-time tracing.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

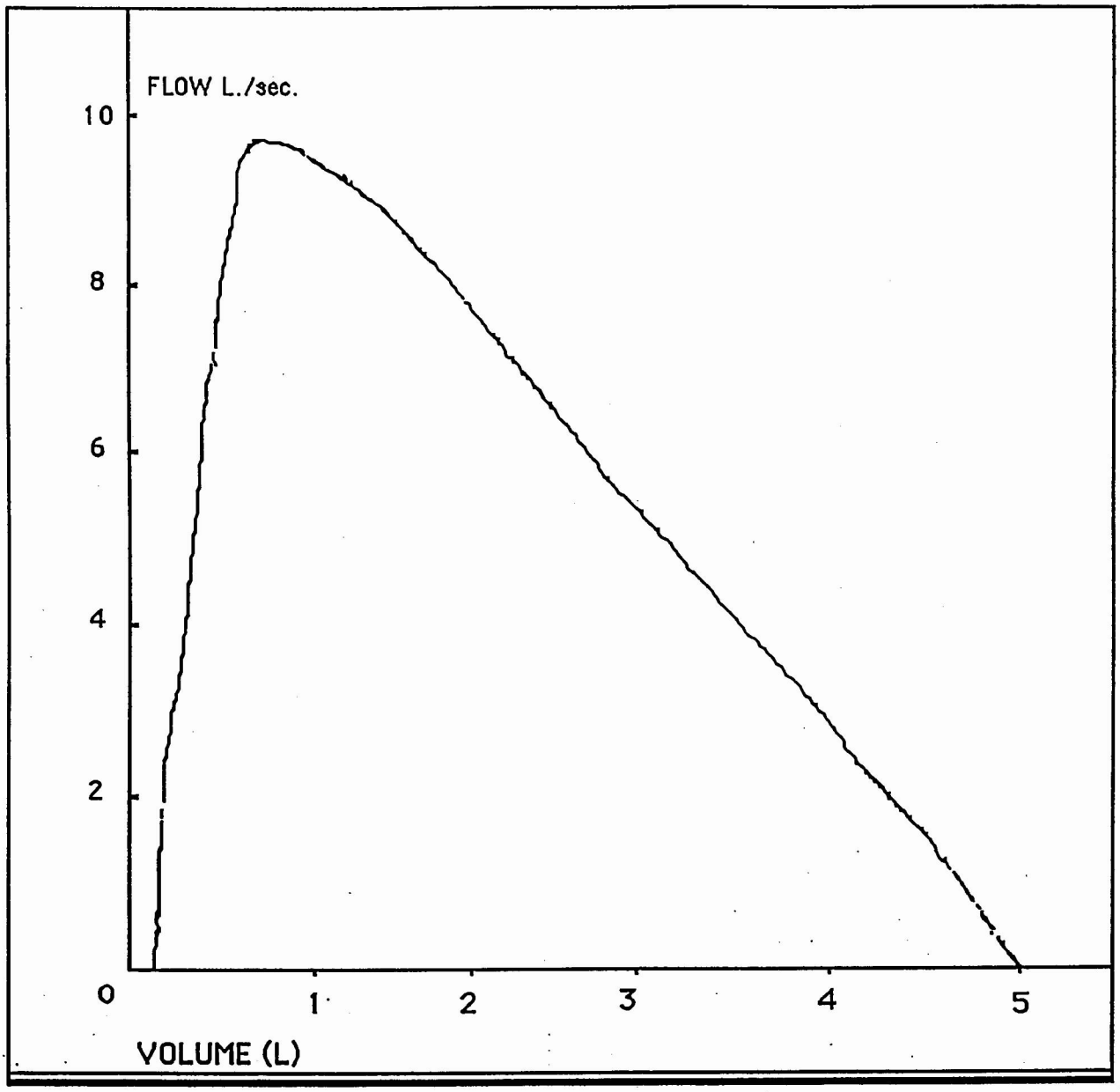


Figure 2. This is a normal good quality flow-volume tracing. There is an early and high peak flow ar continuous contour of the curve.

III. Measurements obtained from spirometry

The flow-volume curve and the spirogram provide many measures that are used by respiratory physiologists and physicians to measure lung function. In ACCESS , we are mostly concerned with two important measurements-- FEV1, and FVC. The FEV1 is the volume of air that is blown out during the first second of the maneuver. The FVC is the total amount of air that leaves the lung during the FVC maneuver. An additional useful calculation is the ratio of the FEV1 to FVC, which

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

expresses the fraction or percent of air that can be expired in one second. This is called the "FEV1-percent" (FEV1%) or more commonly, the FEV1/FVC ratio

In Sarcoidosis, the FEV1 and FVC are often reduced by about the same amount due to destruction or stiffening of the lung tissue. In this disorder, the FEV1/FVC ratio generally remains normal. normal (a restrictive ventilatory defect). However, the ratio is often reduced when there is airway involvement.

Basic Interpretation of Spirometry
- **Restrictive Ventilatory Defects**
  - **Reduced FEV1**
  - **Reduced FVC**
  - **Normal FEV1/FVC ratio**
- **Airflow Limitation (Obstructive) Defects**
  - **Reduced FEV1**
  - **Normal or reduced FVC**
  - **Reduced FEV1/FVC ratio**

V. BTPS correction factors

When the air is in the lung, it is warmed to body temperature which is 37° Celsius or 98.6° Fahrenheit. When the air leaves the lung and is collected in the spirometer, it cools off to room temperature and becomes about 10% smaller. This is described by Charles' Law which states that the volume of gas is directly proportional to its absolute temperature ($V/T = V'/T'$). The absolute temperature (Kelvin degrees) is equal to Celsius degrees + 273.

In order to make consistent measurements, we must always correct spirometry measurements to refer to the amount of air that would be in the lungs under conditions of normal body temperature. We also make a small correction that takes into account the barometric pressure (Boyle's Law : $PV = P'V'$) and humidity so that changes in the weather or altitude do not affect spirometry measurements. This standard method of expressing spirometry measurements is called BTPS meaning "Body Temperature and Pressure of Saturated gas". The standard body temperature is 37°, the standard pressure is barometric pressure at sea-level (760 mm Hg), and saturated gas means that it contains 100% humidity.

For average room temperature, the BTPS correction factor is about 1.07 to 1.08 meaning that one needs to increase the volumes measured in the spirometer by about 7 or 8%. In the some spirometers, this is taken care of automatically by an electronic thermometer (or thermistor) which measures the temperature in the spirometer, and a computer does the necessary calculations. The temperature

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

measuring device must be functioning properly or the computer will make wrong calculations, so comparison of the electronic thermistor to a standard thermometer is necessary.

If you have to make measurements by hand, then you will need to make this correction yourself. A table of BTPS correction factors can be found in Appendix A. The volume in BTPS conditions is equal to the volume of gas measured at ambient temperature and pressure saturated with water (ATPS) multiplied by the BTPS correction factor. For example, if you measure the FVC from the spirometer chart paper to be 2.35 Liters, and the spirometer temperature is 27o C, and your clinic is located at sea-level (Barometric pressure = 760) you would make the following calculation:

BTPS correction factor (27° C, 760 mm Hg) = 1.063

FVC (BTPS) = 2.350 x 1.063 = 2.498 L

V. How a spirometer works

A spirometer is a simple device that measures the volume of air blown into it by elevating a cylindrical bell. The bell is sealed so that it can move freely, and does not leak air. Two types of seals include water seals and dry seals. The change in volume of air contained in the spirometer for each centimeter elevation is fixed and is called the "bell factor". The bell factor is usually inscribed on a plate at the base of the spirometer. Because different models of spirometers from the same manufacturer may have different bell factors, one must use recording paper which is matched with the appropriate bell-factor to give correct measurements. Therefore, you should only use spirometry chart paper which is supplied for the spirometer to be used.

Other types of spirometers use a bellows or a horizontal cylinder to measure volume. Other common devices used for spirometry do not measure volume directly, but measure flow directly. These are called pneumotachometers, and they work by measuring a pressure drop across a fixed resistance of tubes or screens. The pressure drop increases in proportion to the flow. Still other devices depend upon the cooling of a heated wire. The greater the flow, the more the tendency of the wire to cool. These devices have the advantage of being less expensive and more portable than spirometers, but have the disadvantages that they require more frequent and careful calibration, and they often do not provide a direct paper tracing of the maneuver should the attached computer malfunction.

Since one goal of ACCESS will be to measure the change in lung function over time or to use data for other segments of the study, we must be certain that the

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

methods and equipment remain as stable as possible over time. Thus, frequent and stringent measures of the quality of the measurements and calibration of the instruments are required.

Spirometry testing involves considerable effort on the part of the participant, and sometimes they will experience some discomfort or dizziness during the test, or chest soreness for a day or two afterward. You need to balance the need to push the participant to maximum effort during the testing in order to acquire good test results, with the need to retain the participant's trust and continued voluntary participation in the study. Once a participant loses either their interest in the study or their trust that the study team has their welfare at heart, it is very difficult or impossible to regain their confidence.

For all subjects, demonstration of the spirometry maneuver is necessary since it is not a natural breathing behavior. This is best done using a demonstration mouthpiece and performing or simulating the maneuver in front of the subject. It is often helpful to compare the maneuver to "blowing out the candles on a birthday cake" which most people understand.

Because the rapid initiation of the forced expiration is important, a useful prompt for the start of the maneuver is to "BLAST out your air." At the end of the maneuver, a good prompt is to "PUSH, PUSH, PUSH, and KEEP PUSHING" out the air.

VI. Predicted or reference values

In order to compare one subject with others of the same age, height, race, and sex, we compare their tests to those measured on a large group of healthy people (ie no cardio-respiratory symptoms or disorders). In order to summarize these measurements, they are usually expressed as a mathematical formula, or regression equation that predicts the average value for a particular person, which is based on gender, age, and height and, where applicable, race.

Several sets of these prediction (better termed reference) equations are published, and, in some cases they indicate different predicted values for people of the same race, sex, age, and height. You should not, therefore, be surprised to find that the percent of predicted values displayed in reports from different laboratories are different and in certain circumstances the differences can be quite large.

If you discuss the testing results with participants, it is a good idea NOT to refer to the predicted values as "normal values" or percent predicted as "percent of normal". Some people take offense if they are not "normal". Since we feel that everyone should be above average, it is better to refer to these numbers as "reference values" or "normal range". There are several methods of calculating this, but, as a

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

simple rule, more than 80% predicted can be considered "normal" values for both FEV1 and FVC.

VII. Calibration and leak check

Each day, you must check the calibration on your spirometry system, and this should be recorded This is a safety feature to prevent a malfunctioning instrument from collecting incorrect and therefore useless data. The calibration check is performed by injecting and withdrawing 3 L of air from the spirometer using a carefully constructed calibration syringe (Hans-Rudolph, Kansas City). Because the air in the syringe and the spirometer should be of similar temperature, it is a good practice to store the calibration syringe right next to the spirometer at the same height in the room. You should ensure temperature equilibration between the calibration syringe and the spirometer by flushing the syringe into the spirometer three or four times before you do the actual calibration check.

You should also check the calibration of the spirometer every time you move it to a new area.

It is permissible, in accordance with ATS Standards, to have as much as a 3% error in the calibration of a spirometer. If you find that the calibration has changed by more it usually indicates that something is wrong.

Things to look for include:

Improper performance of the calibration check;
Unequal temperatures in the syringe and the spirometer;
A leak in the tubing or fitting of the syringe to the spirometer;
A leak in the bell of the spirometer

Calibration is then carried out by emptying the syringe into the spirometer three times. You should use three different speeds of emptying the syringe so that you will calibrate it over a range of flow-rates.

After the calibration is checked, it is necessary to perform a leak check on a spirometer. This is done by occluding the end of the breathing hose with a rubber stopper; putting a circular weight on the bell of the spirometer; and observing the change in volume over 30 seconds. The volume should not change at all over the 30 sec interval. If there is a leak, the leak test should be tried again. If still leaking, change or refit the breathing tube and stopper and test for leaks again. If this does not cure the problem, then it may be the result of a damaged spirometer bell. It is often difficult to detect a leak in the spirometer bell, but when it does occur it is most often at the seam where the clear plastic joins the top of the bell. The site of the leak

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

can be found by applying some soapy water or SNOOP™ (a commercially available expensive soapy water) to the seam while the bell is pressurized with a spirometer weight. Small leaks can be repaired with silicone adhesive. If the leaks are large or in the body of the bell, then the bell will need to be replaced. This costs far more than you would imagine, so please take care with all the parts of the spirometer.

Every week on a given day, you should perform a linearity check to test the integrity of the entire spirometer bell. The linearity check is done by injecting 1 liter increments of air into the spirometer with the smaller 1 liter calibration syringe and valve system (Vitalograph, Kansas City). If the linearity is not within acceptable tolerances, it most often means that there is a leak in the lower part of the bell, there is some dirt or water collected on the linear potentiometer, or it is time to fill the spirometer with water.

Once a week, when you perform your weekly quality control checks, you should document this.

VIII. The spirometry maneuver

Whenever possible, the same system should be used throughout for any particular subject, and the tests performed at the same time of day.

A. Withhold bronchodilator drugs

The subject should be told to avoid taking any bronchodilator medication for the specified time interval preceding the test.

Table 1. Examples of bronchodilators to withhold prior to spirometry

Withhold for 8 hr. before test	Withhold for 24 hr. before test
Alupent	Salmeterol
Berotec	
Brethaire	
Bronkometer	
Maxair	
Proventil	
Theolair	
Tornolate	
Ventolin	
Atrovent	

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

B. Preparing the subject

The testing can be performed with the subject standing or sitting, but which ever you use, be sure to be consistent for that participant. If you use the standing posture, a chair without wheels should be placed behind the test subject so that if they feel light-headed or dizzy during the testing they may sit down, unless there is a good reason not to have the subject sit.

The breathing tube of the spirometer should comfortably fit in the mouth of the test subject without undue effort. Place the spirometer on a platform about six inches above normal desk height.

Tight fitting belts or garments should be loosened, and loose fitting dentures, oral appliances, chewing gum, candy, and other foreign bodies should be removed from the test subject's mouth.

The subject's shoeless height should be measured or obtained prior to test session. It is necessary to know this information for the predicted values for lung function.

Place a nose clip on the test subject's nose just before each maneuver. Although it is nearly impossible to blow air out of both the mouth and the nose simultaneously , it is possible to take an extra breath of air in through the nose and blow it out at the end of the maneuver. This leads to an erroneously large FVC. Therefore it is good technique to clip the nose. If the nose clip slides off the nose, it can be often held in place with a piece of tissue paper. An acceptable alternative for persons who cannot tolerate the nose clip is to allow them to pinch their nose with their free hand.

C. Explain and Demonstrate the Maneuver

The maneuver should be briefly explained to the participant in words that he/she will understand: "I want you to take a breath in as far as you can and then blast it out as fast and as hard as possible until no more air comes out. It is like trying to blow out all of the birthday candles" Remember that many of the people you will test will be performing spirometry for the first time, so they may be frightened.

Effort and time can be saved, however, by giving a demonstration of the maneuver using a cardboard mouthpiece. **This should be done in all cases.** To demonstrate, take a deep breath with your mouth wide open, elevate your shoulders, stick out your tongue, lay the mouthpiece on it, close your mouth around the mouthpiece, and forcefully blast out through the mouthpiece, continuing to blow for

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

10 seconds. Use enough body language to demonstrate that it must be a forceful and prolonged effort. You will also enlist better cooperation from the participant if they see you sweat a little.

D. When is a session done?

The goal of the testing session is to obtain three good quality or "acceptable" maneuvers (according to ATS standards) and two "reproducible" maneuvers.

Acceptable maneuvers are those that have a rapid onset of maximum or peak flow, have an extrapolated volume less than 5% FVC, that are smooth without hesitation or coughing, and that continue until the flow rate is zero and have a minimum expiratory time of 6 seconds.

Reproducible maneuvers are those that have an FEV1 and FVC within 5% of the highest acceptable maneuver, and that have a Peak flow within 15% of the highest acceptable value.

No less than three and no more than eight maneuvers are allowed in a single session, since experience has shown that the likelihood of improving the quality of the session is slight and the likelihood of fatiguing and frustrating the test subject (and the technician!) increases with the more maneuvers that are performed.

Goals of Spirometry Test Session

- **At least three acceptable maneuvers**
  - **Rapid onset of expiration**
  - **High initial peak flow**
  - **Extrapolated volume less than 5% FVC**
  - **No hesitation or coughing**
  - **Prolonged until no flow**
  - **At least 6 seconds effort**
  - **Terminal flows of zero**
- **At least two "reproducible" maneuvers**

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

FEV1 and FVC within 5% of best

Peak flow within 15% of best

- **No more than eight attempts**

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

Key Points in Performing Spirometry

- **Always demonstrate the maneuver**
- **Prompt the subject to BLAST out the air**
- **Continue by having the subject PUSH out the air**
- **Continue until the flow falls to zero or at least six seconds**

A measure of the rapid onset of effort is the extrapolated volume. It should be less than 100 ml or 5% of the FVC to indicate a good quality test. If this value is high, it means that the subject needs to start blowing out harder. Make certain that the subject is not putting their tongue into the mouthpiece, something they seem to like to do.

VIII. Post-bronchodilator testing

After the initial measurements of forced expiratory maneuvers, the test is repeated after an inhaled bronchodilator. Albuterol (Ventolin™ or Proventil™ brand name) is the bronchodilator selected for use in many labs. This allows the investigators to determine how much the participant's lung function can be quickly "reversed" or returned toward normal.

A. Administration of the bronchodilator

1. Administer two(2) puffs of Albuterol, using the standard metered dose inhaler (MDI) technique with the patient standing, as follows:

a) Shake the MDI* several times and trigger it once to prime it. Hand the MDI to the subject.

b) The subject should exhale

c) The mouthpiece should be inserted fully into the mouth, holding the MDI in its upright position and close his/her lips around it

d) As the subject begins to breathe in very slowly the MDI should be triggered

e) The subject should continue to breathe in slowly and deeply to TLC.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

f) The breath should be held for 10 seconds at the end of a full inspiration

g) Instruct the subject to shake the MDI and repeat steps b - f for a second puff. Although there may be a small benefit to waiting 5 minutes between inhalations of a bronchodilator, it is more practical and satisfactory to administer the second inhalation (2 puffs) about 30-60 seconds after the first.

2. **Wait 15 minutes before performing post-bronchodilator spirometry.** After administration of albuterol, the maximum bronchodilation may take 30 minutes to take place, but sufficient bronchodilation occurs within 15 minutes

If the test subject is answering questionnaires or doing other activities while the bronchodilator is taking effect, the testing should be performed within 45 minutes after taking the medication.

B. Post-Bronchodilator Spirometry

The testing procedure is the same as baseline spirometry.

C. Printing results

After the test session is completed, you will print out a copy of the report, if you are using a system with an attached printer.

IX. Examples of poor quality spirograms

If you have the ability of obtaining flow-volume curves one can recognize some common problems as shown on the following pages.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

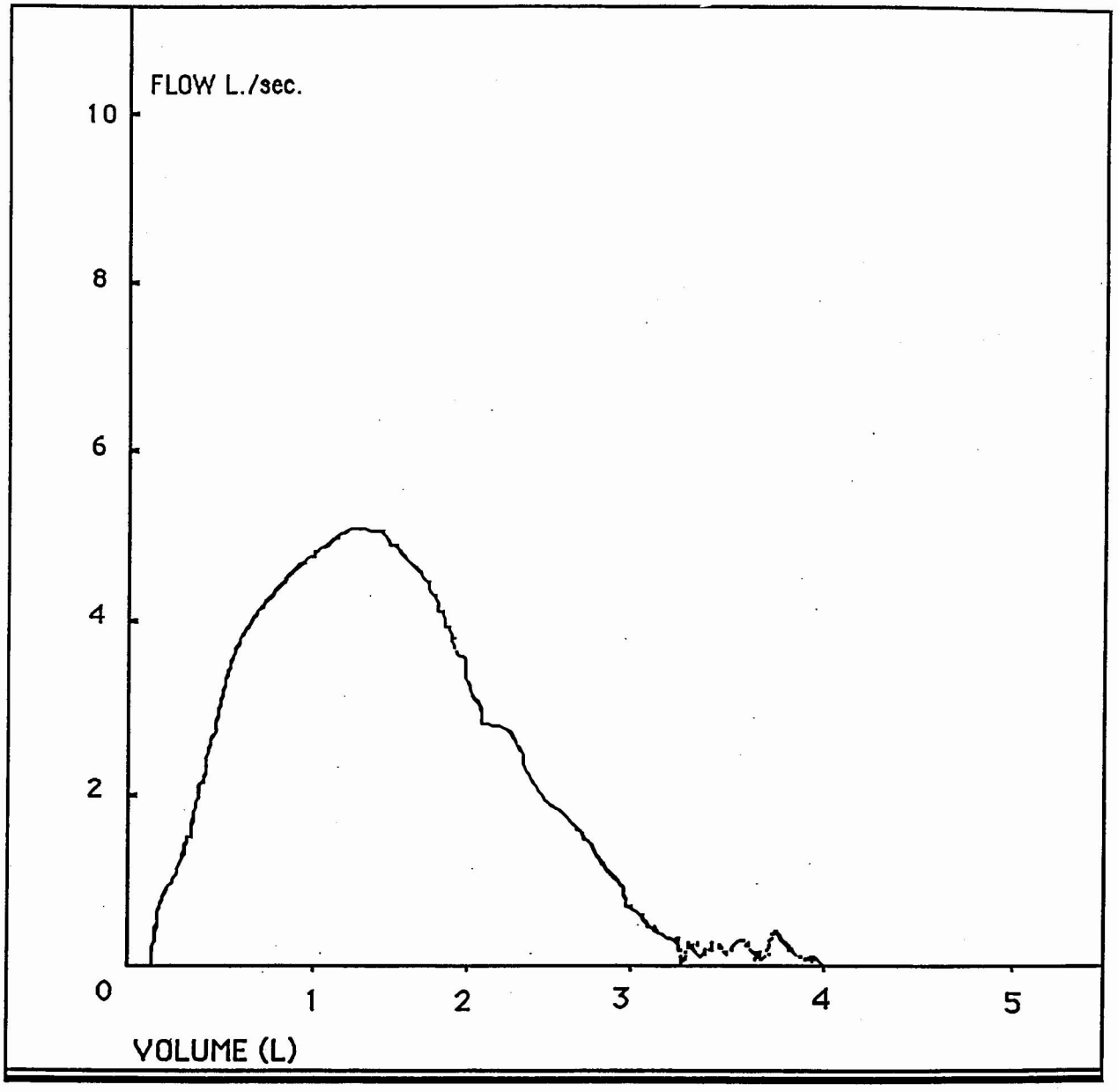


Figure 3. This is a smooth tracing, but the initial peak flow is delayed and not as high as it should be. The subject should be instructed to start blowing out faster.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

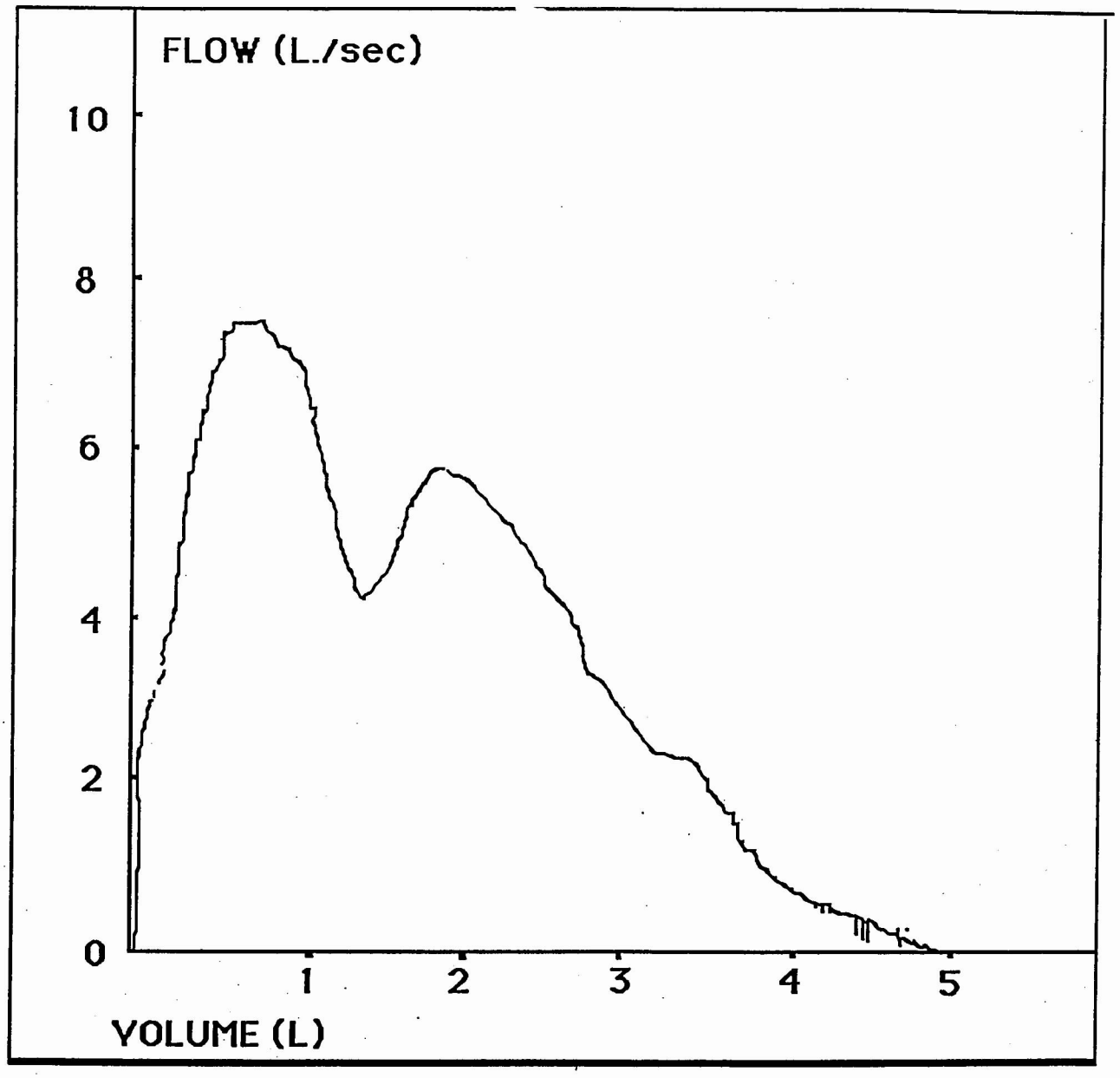


Figure 4. This flow-volume tracing starts off with a good flow, but there is a sudden reduction in flow. This is most often caused by coughing, although occlusion of the mouthpiece by the tongue can also produce type of trace.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

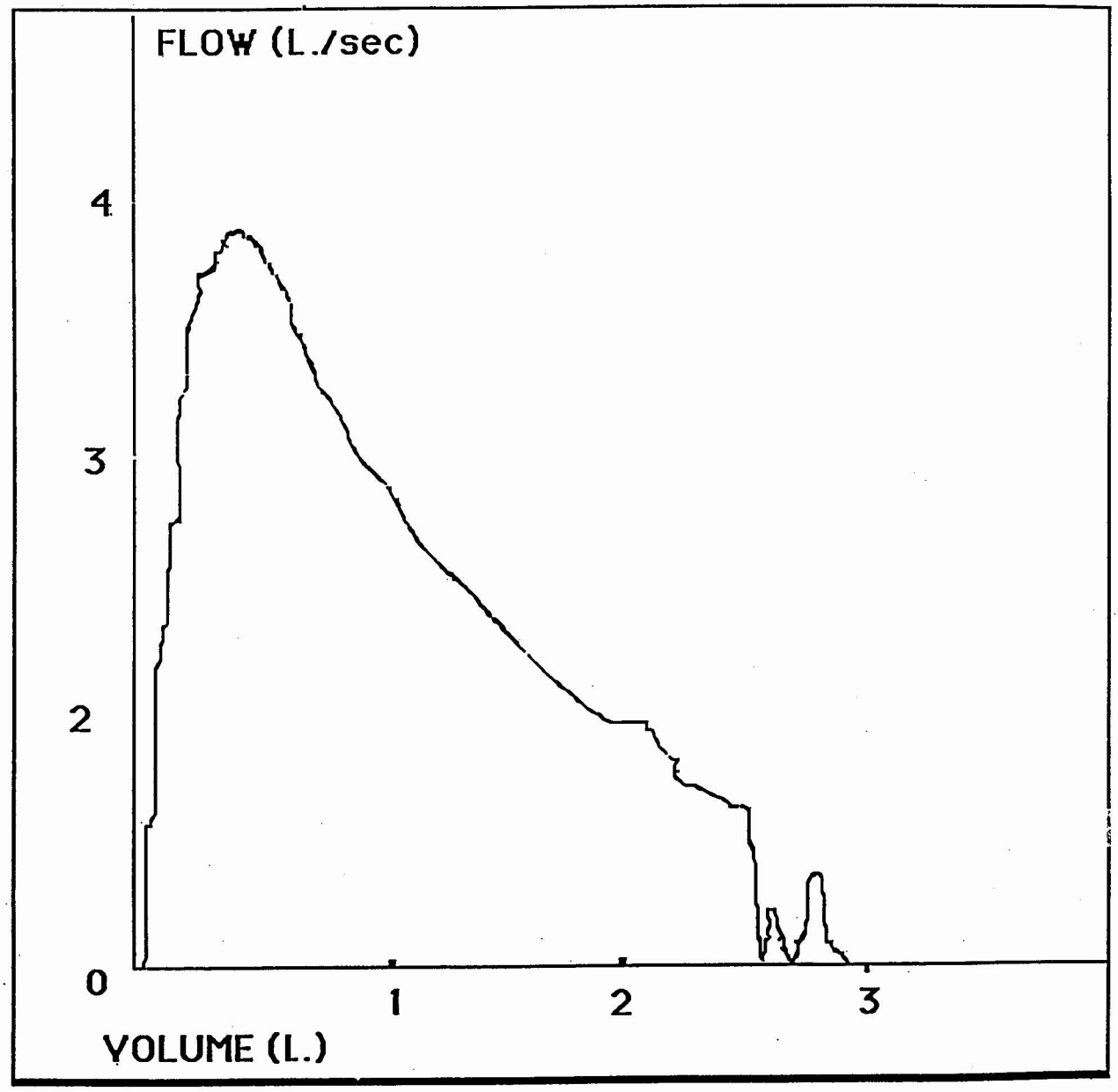


Figure 5 This maneuver has a good start and good peak flow, but it is stopped too soon, causing the drop in flow at the end. Instruct the subject to continue blowing out longer. This is one of the most common problems you will encounter

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

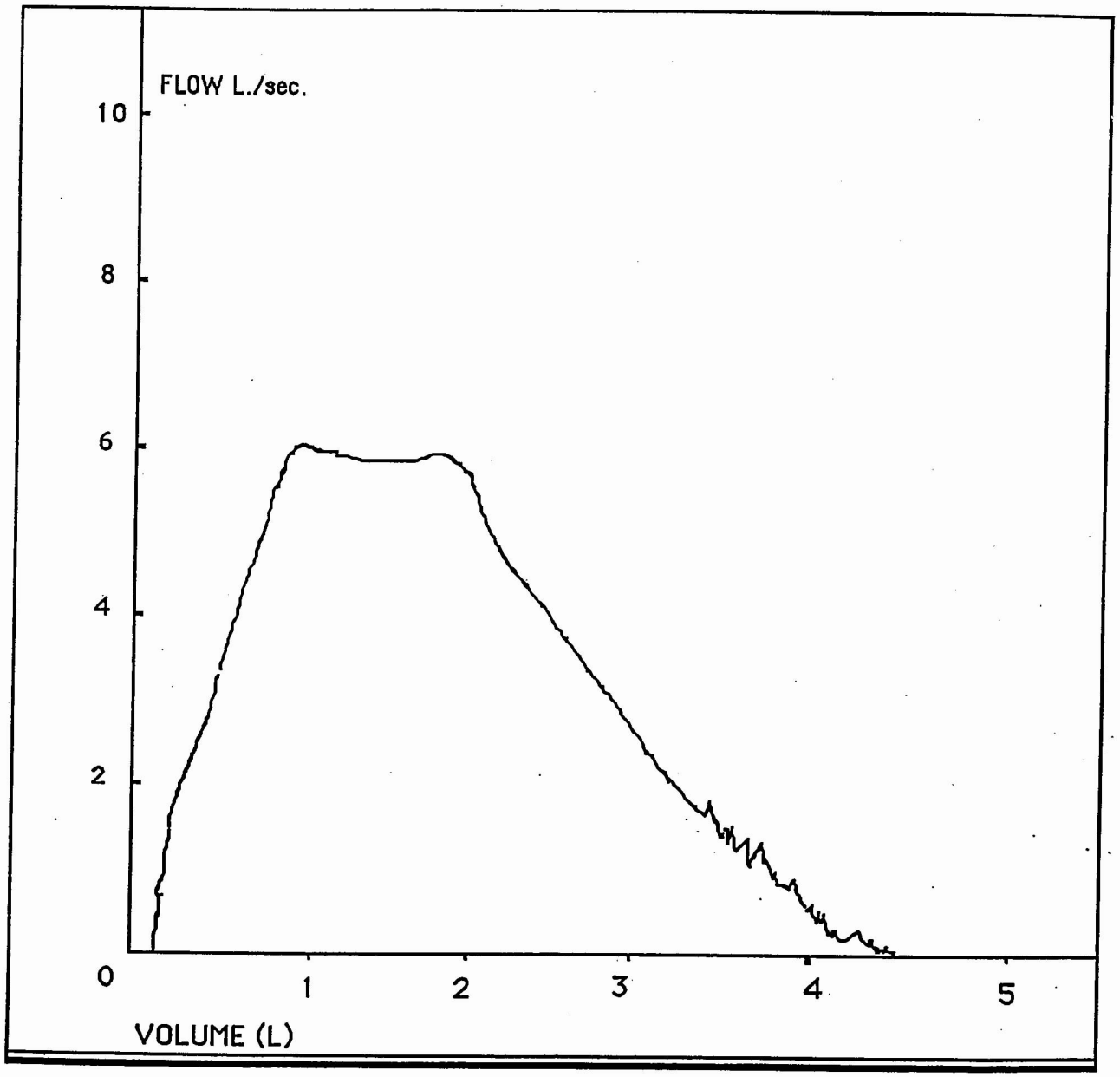


Figure 6 The tracing shows both a delayed start and poor peak flow. Instruct the subject to start blowing out faster and harder.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

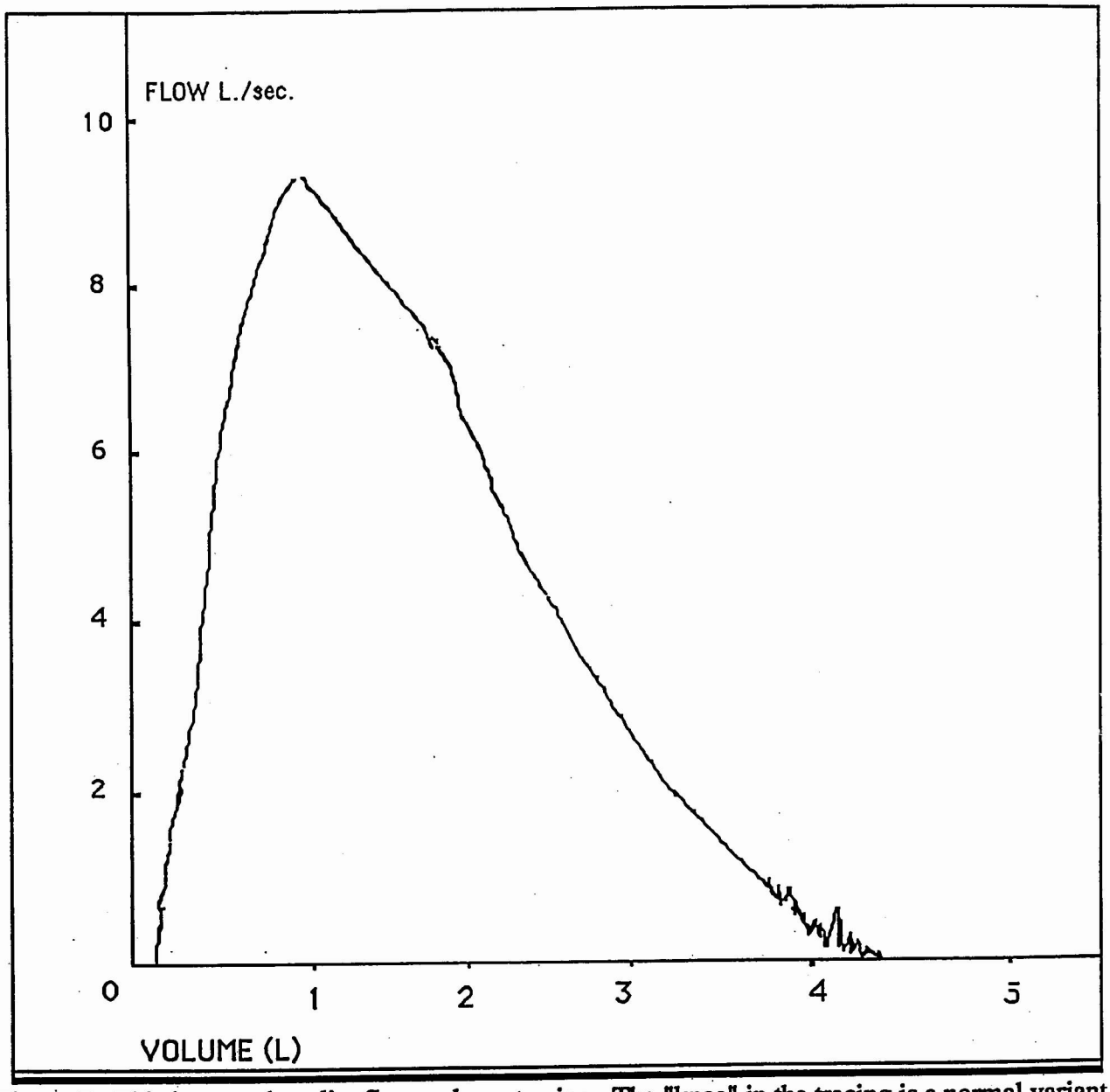


Figure 7. This is a good quality flow-volume tracing. The "knee" in the tracing is a normal variant. It should be distinguished from a plateau which indicates poor effort or upper airway obstruction

X. Quality control

A. Preventive maintenance

In addition to the daily 3-Liter syringe calibration check, and the daily leak check, there are several tasks that should be completed each week. The first of these is the 1-L syringe linearity check. This will test the full range excursion of the spirometer bell. It also tests to see if the water level in the spirometer is high enough in water sealed spirometers.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

Another important weekly test of preventive maintenance is to have a healthy individual perform a weekly spirometry test on the spirometer.

If appropriate, the third weekly preventive maintenance procedure is to check that the calibration of the thermistor in a spirometer is accurate by comparing the temperature value with that of an accurate mercury or electronic reference thermometer. The reference thermometer and the thermistor should agree within 0.5° C.

Quality Control Schedule

- **Daily**
  3-Liter Calibration Check (CAL)
  Leak test (LEA)
- **Weekly**
  Linearity check (LIN)
  Healthy subject (Laboratory standard) check
  Thermometer check

XI. Hygiene and infection control

Recent events have heightened the concern by the general public concerning the transmission of infectious disease (i.e., AIDS). **Attention to the following recommendations can not be under emphasized.**

You should also be aware that many viral respiratory infections are thought to be transmitted by hand contact. Since it is important for you to avoid these illnesses, you should try to avoid handling equipment that may have respiratory secretions with bare hands. You should use a tissue to pick up mouthpieces, use examination gloves, and wash your hands as needed.

Attach a clean breathing tube and mouthpiece to the spirometer for each new test subject. As a matter of hygiene, do not touch the mouthpiece directly with your hands. You may pick it out of the sterile box with a piece of tissue paper. Another method that can be used is to store the mouthpieces in a medical bandage jar, using tongs to remove them. Participants can be able to pick out their own mouthpiece from a dispenser. You will find it most useful to keep the mouthpieces and nose clips in individual ziplock plastic bags or in Seal-a-Meal bags. You can then use the plastic bag to remove the mouthpiece and discard it hygienically.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

Use a clean nose clip for each participant.

Although the risk of transmitting infection through spirometry is small or nil, any respiratory infections that occur after a testing session may be blamed by the participant on the test. This is particularly apt to occur if there is a sense that there is not careful attention to cleanliness in all aspects of the procedure.

The testing room should be clean, neatly organized, and well lighted and ventilated. A view of the ocean, lake or mountains may also help!

You should also be careful to flush the stale air out of a spirometer several times between patients. This will clean out the air from the spirometer and minimize any chance of spreading airborne infections. Be careful, however, that you do not allow the stale air to blow directly in either your face or the face of one of the participants.

XII. Cleaning

The breathing tubes, nose clips, nebulizers, an MDI spacers should be cleaned and disinfected after each participant. The cardboard mouthpieces are disposable and should be discarded after each patient. The tubing should be cleaned out with a long brush with water and detergent to remove any debris that may have collected. It should then be rinsed in tap water and allowed to soak for at least 20 minutes in a disinfectant solution containing glutaraldehyde. Manufacturers of this solution include Cidex, Sporocidin, Wipe-Out and Procide. Please observe your insitution's guideline for using these products. If you are sterilizing tubes, nebulizers , etc. in the laboratory be sure to use gloves and perform these tasks in a fume hood or similar setting. Other disinfectants such as alcohol, bleach solution, or benzalkonium are not as effective in killing spores, and should **not** be substituted. Gas sterilization with ethylene chloride is an acceptable alternative, but is not as readily available and tends to deteriorate plastic. Some clear plastic items may become discolored after repeated disinfection. This does not cause any health problem, but they appear unsightly to participants and should be discarded.

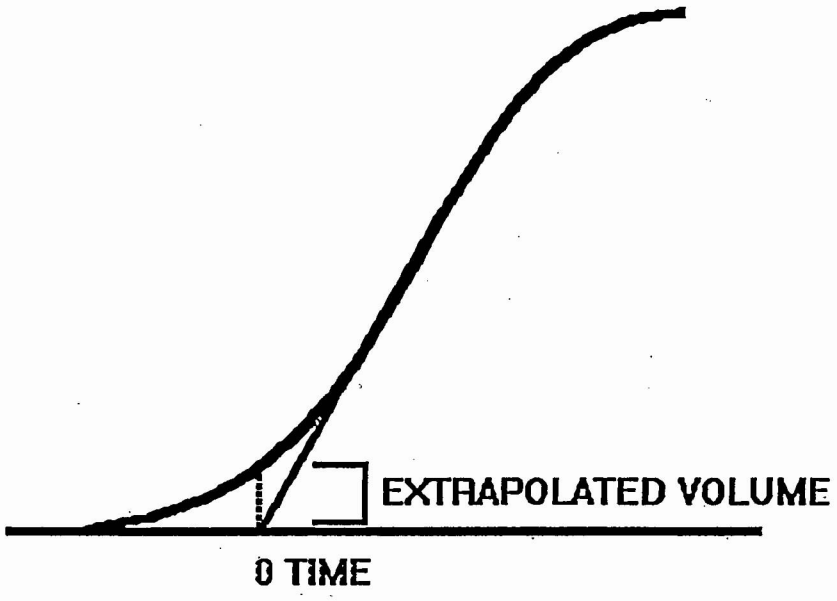
EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

XIII. Glossary

ATPS - Ambient Temperature and Pressure of Saturated Gas. This is the condition of the expired gas when it is collected into the spirometer.

ATS - American Thoracic Society. This is the organization that promotes standards for spirometry testing.

Back-Extrapolation



In order to calculate the FEV1, it is necessary to measure the time that the spirogram began ("Zero time"). Since the maximum flow may take a fraction of a second to take place, this is corrected by using "Back-extrapolation". Essentially, this means drawing a line from the steepest portion of the volume-time curve and extending it back to the baseline on the volume axis. Where these two lines intersect is the zero time used for measurement of FEV1. The volume that has left the lung at this zero time is called the "Extrapolated Volume". A good maneuver has an extrapolated volume that is less than either 5% of the FVC or less than 100 ml. If the extrapolated volume is too large, the QC prompt will suggest that the patient start the maneuver more rapidly.

Bell - This is the light plastic bucket-shaped transparent object that collects the air in the spirometer. It is also a device that makes a pleasant ringing sound and calls you to dinner.

Bell Factor - This is the factor that one must multiply the height excursion of the spirometer in order to convert it to volume.

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

BTPS - Body Temperature and Pressure of Saturated Gas. This is the condition that gas is in when it is in your lungs. For consistency, all lung volume measurements are "corrected" to the volume that would exist in the lungs in this condition.

Calibration syringe - For ACCESS, a 1-Liter and a 3-Liter calibration syringe should be used. Although they are quite rugged, they should not be dropped from any great heights as they may lose their accuracy if they are damaged. If you are concerned that a calibration syringe is inaccurate, a quick check is to compare it to another calibration syringe on the same spirometer.

DEC Computer Corporation - This is the company that manufactures the computers attached to the spirometer.

Dry-seal - This is the opposite of a wet-seal.

Extrapolated volume - See Back extrapolation.

Expire - This means to breathe out. It also means to die. Please do not tell the participants to expire. They may not understand what you mean.

FEV1 - The amount of air expired in the first second during a forced expiratory maneuver.

FVC - Forced vital capacity. The maximum amount of air that can be expelled from the lung during a forced expiration. The volume of air left in the lung is called the Residual Volume (RV). The maximum amount of air that can be taken into the lungs is called the TLC or Total Lung Capacity. Thus, FVC = TLC - RV.

Glutaraldehyde - This is the material contained in disinfectants such as Cidex and Sporocidin that is used to disinfect spirometry tubing and nebulizers. It is very effective in killing bacteria and molds. It is also very irritating, and should be used in a well-ventilated area or in an exhaust hood. You should wear gloves when handling this material. Check with your local safety office regarding safe handling of these materials.

Inspire - This means to breath in. It also means to motivate. You should inspire your test subjects to inspire deeply.

Leak test - This is a test where the spirometer is pressurized with a circular weight placed on the top. No air should leave the spirometer.

Linearity check - This is a test to determine that the spirometer rises an equal amount for each increment in volume. Usually when there is a problem with

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

linearity, it means that there is a problem with the potentiometer or there is a leak near the bottom of the spirometer bell.

NHLBI - The National Heart Lung and Blood Institute. This is the section of the government that is organizing and paying for ACCESS.

Obstruction or Obstructive ventilatory defect - This is the condition in which it takes longer than normal to empty the lungs during a forced expiration. It is used in contrast to restriction which means that the lungs are too small. Asthma is a condition characterized by an obstructive ventilatory defect. Other conditions include emphysema and chronic bronchitis. In some cases, asthma may appear to be a restrictive condition because air is trapped in the lungs, and the vital capacity is disproportionately reduced. You can also use the term "airflow limitation".

Pneumotachometer - This is a device that measures air flow directly.

Potentiometer- A device that changes its resistance. A rotary potentiometer is used to control the volume of a radio. A linear potentiometer is used to measure the excursion of a spirometer.

Reference (Prediction) equations - Equations used to predict the average value of lung function measures for a person of a certain age, sex, height, and race.

Restriction or Restrictive ventilatory defect - A disease process of the respiratory system which causes a reduction in lung volumes..

Spirometer - A device that measures gas volume expired from the lungs as a function of time.

Spirometry - The measurement of the volume of gas entering and leaving the lung. In the context of this manual it refers only to the forced expiratory maneuver.

Thermistor - A device that measures temperature by changing its resistance.

Water-seal or wet-seal - This is the type of spirometer we are using for this trial. It uses water to seal the bell, but still allows the bell to move. Be sure to keep the spirometer filled with water. Use distilled water to keep the crud down

EXHIBIT 3-1
ACCESS SPIROMETRY MANUAL (Continued)

Appendix A

BTPS Conversion Factors

Temp. Centigrade	Temp. Fahrenheit	Water Vapor Pressure (mm Hg)	Barometric Pressure (mm Hg) 760	730	700	670
18.0	64.4	15.611	1.112	1.114	1.116	1.119
18.5	65.3	16.039	1.110	1.112	1.114	1.116
19.0	66.2	16.488	1.107	1.109	1.111	1.114
19.5	67.1	16.958	1.104	1.106	1.109	1.111
20.0	68.0	17.450	1.102	1.104	1.106	1.108
20.5	68.9	17.963	1.099	1.101	1.103	1.105
21.0	69.8	18.498	1.097	1.098	1.100	1.103
21.5	70.7	19.054	1.094	1.096	1.098	1.100
22.0	71.6	19.631	1.091	1.093	1.095	1.097
22.5	72.5	20.230	1.088	1.090	1.092	1.094
23.0	73.4	20.850	1.086	1.087	1.089	1.091
23.5	74.3	21.492	1.083	1.085	1.086	1.088
24.0	75.2	22.155	1.080	1.082	1.083	1.085
24.5	76.1	22.839	1.077	1.079	1.081	1.082
25.0	77.0	23.545	1.074	1.076	1.078	1.079
25.5	77.9	24.272	1.072	1.073	1.075	1.076
26.0	78.8	25.021	1.069	1.070	1.072	1.073
26.5	79.7	25.791	1.066	1.067	1.069	1.070
27.0	80.6	26.582	1.063	1.064	1.066	1.067
27.5	81.5	27.395	1.060	1.061	1.063	1.064
28.0	82.4	28.229	1.057	1.058	1.060	1.061
28.5	83.3	29.085	1.054	1.055	1.056	1.058
29.0	84.2	29.962	1.051	1.052	1.053	1.055
29.5	85.1	30.860	1.048	1.049	1.050	1.051
30.0	86.0	31.780	1.045	1.046	1.047	1.048
30.5	86.9	32.721	1.042	1.043	1.044	1.045

CHAPTER 4

SCHEDULE AND DESCRIPTION OF CASE AND CONTROL EVALUATIONS

4.1 INTRODUCTION

ACCESS consists of two components: a case control study to investigate the etiology of sarcoidosis, and a prospective cohort study to investigate the clinical course of sarcoidosis. In the etiology study, sarcoidosis patients (cases) and controls are interviewed by ACCESS Clinical Center staff, asked to fill out questionnaires, and asked to provide specimens for subsequent laboratory analyses. The first 252 cases were asked to participate in the ACCESS Clinical Course Study; the recruitment goal was 240 cases with a minimum of 20 cases from each Clinical Center. For the Clinical Course Study, Clinical Center staff contact enrolled cases by telephone at 6, 12 and 18 months after study entry. These cases are also asked to return for an examination approximately 24 months after the baseline evaluation. For cases enrolled after June 1997, the examination may be performed earlier than 24 months after entry. Data to be collected as part of the baseline evaluations and the follow-up visits are described in this chapter.

4.2 ETIOLOGY STUDY

Sarcoidosis patients (cases) and an age-race-gender matched control for each case participate in the etiology study. This part of ACCESS requires cases and controls to complete a baseline evaluation.

When conducting the interviews for the etiology study, it is very important that the interview locations and the approach to asking questions on the study forms be as similar as possible for the cases and the controls. Any deviation in the type of surroundings or in the way the questions are asked may affect an individual's recall so the procedures for administering the questionnaires should be the same for all cases and all controls in each Clinical Center. For this reason it is recommended that cases and controls be interviewed in the same location to the extent that is possible. In some circumstances it will not be possible to bring a case or a control to the primary interview location. In that situation, the interviewer should take care to create an atmosphere as

similar as possible to that of the primary interview site. For instance, performing an interview in a person's living room that is filled with pictures of the person's relatives may change the way the person answers questions about his/her relatives.

It is also possible that the order that the questions are asked could affect the individual's recall of events and associations. For this reason, is requested that the order of administration of the questionnaires not be changed. For cases and controls, the order of administration of the questionnaires should begin with Form 10 and end with Form 23. The order of administration is sequential. At any point during the administration of these questionnaires the case or control is allowed to take breaks. When the respondent is ready to continue, he/she should resume taking the questionnaire at the point where he/she left off. Since the physical examination may include questions about the case's medical history, the physical examination and the laboratory tests should be postponed until the core set of forms (Forms 10 through 23) have been administered. If it is necessary to obtain the blood specimens before conducting the interview for a case, the blood specimens for the matched control should be taken before conducting the interview; the Form 10 for the case and the Form 10 for the control should be completed noting that the blood specimens were taken before the interview. Once the cases have finished with Form 23, they should be asked the questions in Form 26.

Both cases and controls complete a baseline evaluation for the collection of required data and biological specimens for future evaluation (see Table 4-1). The baseline evaluation includes collection of demographic information (age, race, gender, residence, marital status, etc.), medical history, environmental and occupational exposure history, questions about the individual's family (first degree relatives), standardized psychosocial data on health related quality of life, and medical care usage. These data are collected by administration of ACCESS Forms 10-23 (see Table 4-1). In addition, cases complete a baseline questionnaire (Form 26) to collect data on matters pertaining specifically to sarcoidosis.

To assist in making edit corrections to the forms, and for the purpose of quality control evaluations, the interviews in which the above information is collected are tape recorded. The tape recording is erased within six months of the interview.

In addition to answering the questions on the forms, both cases and controls undergo phlebotomy for specific tests and for specimens to be stored in an NHLBI repository. (See Chapter 6.) ACCESS cases have the following required procedures besides the questionnaires and phlebotomy already mentioned: physical examination, tissue biopsy (which will be reviewed by a pathologist), chest X-ray, spirometry with pre- and post-bronchodialators, standard biochemistry, and a complete blood count (CBC) with differential. Bronchoalveolar lavage (BAL) specimens are collected, if available from clinically indicated bronchoscopies. Forms 24 and 25 are completed to record the physical examination and laboratory test data. The required laboratory test data may have been collected on different dates prior to study entry; whenever this is the case the date of the test results that is farthest from the date of entry should be recorded as the "date of the tests." The chest X-ray, spirometry, complete blood count, and other biochemical tests are expected to be within six months prior to date of entry. If a test was performed more than six months prior to the actual date of entry, the Request to Extend Time Window Form (Form 70) is completed and sent to the CCC. CCC staff forward the completed Form 70 to the Study Chairman or Vice Chairman (depending on who is available) for review. The decision for each request is reviewed with the Executive Committee on scheduled conference calls.

Table 4-1 lists the ACCESS data and specimen collection activities scheduled for the baseline evaluation for all cases and controls and the 24-month follow-up evaluation for the cases enrolled in the Clinical Course Study.

4.3 CLINICAL COURSE STUDY

The process of recruitment for the follow-up study started with the first case enrolled in the etiology study and continued until the end of September 1997 after 252 cases were enrolled in the study. Clinical Center staff contact these ACCESS cases by telephone at 6, 12 and 18 months after

entry. The telephone call is designed to maintain contact with the patient and to ask about the patient's general well being. A Telephone Contact Summary (Form 28) is completed for each case at each telephone contact. If Clinical Center staff are unable to contact the case, the Missed Contact/Visit Form (Form 33) is completed and sent to the CCC.

A clinic visit is scheduled approximately 24 months after the patient's baseline evaluation. Cases enrolled after June 1997 may be seen in the interval 21 to 24 months after entry. At the 18-month telephone contact, the Research Coordinator discusses the timing of the follow-up evaluation. The case is reminded by telephone or mail of his/her follow-up evaluation closer to the time of the appointment. The follow-up evaluation includes a medical history, physical examination, chest X-ray, spirometry, routine biochemistry, complete blood count and differential, and additional tests as clinically indicated. A complete job history is obtained for a sample of cases selected by the CCC; for all other cases, the job history between the baseline interview and the follow-up interview is obtained. A follow-up blood specimen is collected. The chest X-ray, spirometry and other required tests are to be within the period defined by three months before and ending six months after the 24-month anniversary of the baseline interview. The Follow-Up Questionnaire for Cases Only, Parts I and II (Forms 35 and 36) are administered. These questionnaires are designed to collect information specifically relating to sarcoidosis. In addition, a study physician completes the Change in Organ Involvement Since Initial Examination Form (Form 37); this form is completed for each case using the Physician Examination Forms (Form 24) completed at baseline and at the Follow-up Visit. The procedures and forms required at the two-year follow-up visit are summarized in Table 4-2, and a time line for data collection is presented in Figure 4-1.

TABLE 4-1

ACCESS STUDY FORMS AND DATA AND SPECIMEN COLLECTION

Activity (Form)	CASES		CONTROLS
	Baseline Evaluation	24-Month Follow-up	Baseline Evaluation
Participant Information (Form 01)	R		R
Confirmation of Eligibility (Cases) (Form 02)	R		
Case Registration Worksheet (ATRS) (Form 03)	R		
Case Enrollment/Non-Enrollment Worksheet (ATRS) (Form 04)	R		
Confirmation of Eligibility (Controls) (Form 05)			R
Control Status Worksheet (ATRS) (Form 06)			R
Enrollment Confirmation Form (from ATRS) (Form 09)	R		R
Demographics and Medical History Questionnaire (Form 10)	R		R
Blood Specimen Collection	R		R
Occupational History Worksheet (Form 11)	R		R
Occupational and Recreational Questionnaire (Form 12)	R		R
Environmental Questionnaire (Form 13)	R		R
Medications Questionnaire (Form 14)	R		R
Questionnaires 15-19	R		R
Relationship Questionnaire A (Form 20)	R		R
Relationship Questionnaire B (Form 21)	CR1		CR1
Family History Questionnaire (Form 22)	R		R
Family History Supplement (Form 23)	CR2		CR2
Physical Examination Form (Form 24)	R	R	

R = Required
R* = Required at 6, 12 and 18 months after enrollment.
R+ = Required if available from clinically indicated evaluations.
R++ = Required if initial diagnosis of sarcoidosis is probable or possible.
CR1 = Required if participant has biological children.
CR2 = Required if participant has more than nine siblings.

TABLE 4-1

ACCESS STUDY FORMS AND DATA AND SPECIMEN COLLECTION (Continued)

Activity (Form)	CASES		CONTROLS
	Baseline Evaluation	24-Month Follow-up	Baseline Evaluation
Laboratory Data Form (Form 25)	R	R	
Spirometry with Pre- & Post-Bronchodilators	R	R	
Complete Blood Count and Differential	R	R	
Biochemistry	R	R	
Baseline Questionnaire for Cases Only (Form 26)	R		
Chest Radiography Interpretation Form (Form 30)	R	R	
Chest X-Ray	R	R	
Diagnostic Specimen Report (Form 31)	R		
Tissue Biopsy	R		
Bronchoalveolar Lavage (BAL) Form (Form 32)	R+		
Tissue Sample Shipping Form (Form 40)	R++		
Telephone Contact Summary (Form 28)		R*	
Follow-up Questionnaire for Cases Only (Parts I and II) (Forms 35 and 36)		R	
Change in Organ Involvement Since Initial Examination (Form 37)		R	

R = Required
R* = Required at 6, 12 and 18 months after enrollment.
R+ = Required if available from clinically indicated evaluations.
R++ = Required if initial diagnosis of sarcoidosis is probable or possible.
CR1 = Required if participant has biological children.
CR2 = Required if participant has more than nine siblings.

TABLE 4-2

PROCEDURES AND FORMS REQUIRED AT TWO-YEAR FOLLOW-UP VISIT

Procedures:

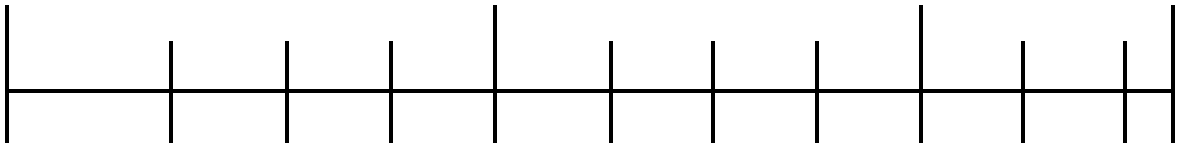
1. Physical Examination and Medical History
2. Chest X-ray
3. Spirometry (Pre- and Post-Bronchodilator)
4. Laboratory Tests (Biochemistry, CBC)
5. Job History (between baseline interview and follow-up interview for most cases; complete job history for sample of cases selected by the ACCESS Clinical Coordinating Center)

Forms:

1. Occupational History Worksheet (Form 11)
2. Physical Examination Form (Form 24)
3. Laboratory Data Form (Form 25)
4. Chest Roentgenography Interpretation Form (Form 30)
5. Follow-up Questionnaire for Cases Only (Part I) (Form 35)
6. Follow-up Questionnaire for Cases Only (Part II) Form 36
7. Change in Organ Involvement Since Initial Examination (Form 37)

FIGURE 4-1

CLINICAL COURSE STUDY:
SCHEDULE FOR SARCOIDOSIS SUBJECT ASSESSMENT (IN MONTHS)*



0 months	3	6	9	12	15	18	21	24	27	30
1a		1b		1b		1b		1c		
2								2		
3								3		
4								4		
5								5		
6								6		
7										

1a) Entry evaluation (questionnaires)
1b) Telephone contact
1c) Follow-up questionnaires
2) Medical history and physical examination
3) Chest X-ray (posteroanterior view only)
4) Spirometry (Pre- and Post-Bronchodilator)
5) Laboratory: Biochemistry, complete blood count
6) Optional: Testing of other organs as indicated by clinical symptoms/signs
7) Biological specimen collection (see Chapter 6).

* The following intervals will be used to bracket data collection for each time period: ± 1 month for entry evaluation and for telephone contacts scheduled at 6, 12 and 18 months. For the 24-month follow-up visit, the interval of data collection may extend to 30 months after enrollment, but should be as close to 24 months from enrollment as possible and should not be less than 21 months from enrollment. Data obtained outside of these windows are to be collected, although centers will emphasize the need to maintain maximum data collection within the bracketed windows.

CHAPTER 5

GUIDELINES FOR THERAPY OF SARCOIDOSIS

5.1 INTRODUCTION

Treatment guidelines are based on conservative therapy for patients who are asymptomatic or have mild clinical abnormalities and steroid therapy for patients whose symptoms and abnormalities indicate therapy. The guidelines outlined below are applied in all Clinical Centers to the extent feasible for a referral patient population. It is expected that these guidelines will reduce variability among Clinical Centers in the assessment of clinical course.

5.2 INDICATIONS FOR TREATMENT OF PULMONARY SARCOIDOSIS

The following is a suggested plan for treatment of patients participating in ACCESS.

Indications for treatment of pulmonary sarcoidosis: Include considerations of symptoms, pulmonary function tests, radiographic abnormalities and presence of extrathoracic disease.

1) Symptoms

   Progressive disabling dyspnea and/or cough is the major treatable symptom based on an acceptable modified scale (e.g., Borg). Among the treatable symptoms are severe fatigue and weight loss.

2) Chest radiographs

   No chest X-ray findings would of themselves warrant systemic therapy for sarcoidosis

3) Pulmonary function

   One or more of the following:

   1) Vital capacity less than 70% of predicted.
   2) FEV_1 (Forced Expired Volume in One Second, which is the amount of air expired in first second during a forced expiratory maneuver) less than 70% of predicted.
   3) $DLCO_{SB}$ (diffusing capacity of the lungs for carbon monoxide, single breath) less than 70% of predicted.
   4) A decrement of 15% or more in any of the above parameters.

5.3 EXTRATHORACIC SARCOIDOSIS (SIGNIFICANT ORGAN DYSFUNCTION OR THREATENING ORGAN FAILURE)

Systemic therapy may be appropriate for extrathoracic sarcoidosis with organ dysfunction or threatening organ failure of the following:

1) Ocular.
2) Neuromuscular.
3) Pituitary.
4) Cardiac.
5) Hypercalcemia.
6) Hypersplenism.
7) Hepatic.
8) Dermatologic.
9) Osseous.
10) Nasal/sinuses.

5.4 MEDICATIONS

1) Prednisone 30-40 mgm qd as initial dose. Taper monthly or bi-weekly to maintenance dose of 10-15 mg daily. (Higher doses rarely necessary.)
    a) Monitor closely for the following steroid side effects:
        (1) Obesity.
        (2) Hypertension.
        (3) Hyperglycemia.
        (4) Hypopotassemia.
        (5) Osteoporosis.
        (6) Cataracts.
        (7) Glaucoma.
        (8) Upper gastrointestinal symptoms.
        (9) Aseptic necrosis of bone.

b) Isoniazid 300 mgm qd prophylaxis if $PPD5_{TU}$ (purified protein derivative, five tuberculin units) is positive should be considered.

2) Anti-malarials -- Consider hydroxychloroquine (200 mg daily) or chloroquine in six-month courses as the treatment of choice for dermatologic lesions and hypercalcemia. A six-month interval off treatment between courses is recommended. These treatments require ophthalmologic examinations before the start of new or repeat courses and every four months.

3) Special circumstances:

a) Erythema nodosum -- Non-steroidal antiinflammatory drugs.

b) Anterior uveitis -- Ophthalmologic steroid drops.

c) Skin and hypercalcemia -- See above.

d) Abnormal liver chemistries alone are not an indication for prednisone therapy. Progressive elevations of liver enzymes to levels greater than 3 times the upper level of normal, especially for alkaline phosphates, would be treated at the attending physician's discretion.

e) Suggested indications for treatment of hypersplenism include a palpable spleen and one or more of the following: Hemoglobin < 9.0 gm %; Hematocrit < 28%; White Blood Cell Count < 1500; Platelets < 90,000.

4) Other medications and the ultimate decision to treat, not to treat and to alter therapy are left to the discretion of the treating physician.

CHAPTER 6

BIOLOGICAL SPECIMENS

6.1 OVERVIEW

The purpose of this chapter is to provide guidelines for the collection and disposition of biological specimens (blood, bronchoalveolar lavage, and biopsy slides) in ACCESS. Bronchoalveolar lavage (BAL) specimens are collected as residual specimens from clinically indicated bronchoscopy procedures.

A summary of blood samples required from cases and controls in ACCESS follows:

Whole blood: 54 ml in EDTA; and

40 mlin heparin only for those Clinical Centers providing cell pellets for RNA analysis by differential display polymerase chain reaction (DD-PCR) as part of the special laboratory study at the Beth Israel Hospital; unless specifically notified by the Executive Committee ACCESS Clinical Centers other than the Beth Israel Hospital do not collect these specimens.

Study forms and data files are used to track processing, shipment and receipt of biological specimens from Clinical Centers to Core Laboratories, Special Study Laboratories and the Central Repository. All specimens collected and shipped including (blood and bronchoalveolar lavage) must be handled according to universal precautions including double-bagging of mailed specimens. **6.2**

BLOOD SAMPLE COLLECTION

6.2.1 Phlebotomy

Phlebotomy should be performed by venipuncture using a large enough needle (size #19 or lower) to avoid hemolysis and trauma whenever possible, and limited use of the tourniquet. Polyvinylpropyleneiodine (PVP) must be used to clean the subject's skin and the rubber stopper of the vacutainer tube.

Sterile vacutainers should be used. The vacutainer tubes to use are: 5 large (10 cc) purple top (EDTA), 4 large (10 cc) green top (heparin [selected Clinical Centers only]) and 1 small (4 cc) purple top (EDTA) tubes.

Phlebotomy should be timed so that specimens can be received at the core facilities (see below) between Tuesday and Friday. Clinical Center staff should send e-mail notification to core facilities the same day shipments are being made to assist core facility staff preparation for specimen receipt. By special arrangement the DNA Core Laboratory and Dr. Lesser's laboratory* ("Role of Mycobacterial Cell Wall Deficient Forms in Sarcoidosis,") will receive specimens on Saturday; Clinical Center investigators must contact Dr. Iannuzzi and Dr. Lesser before noon on Friday to determine whether or not a specimen can be received on Saturday.

6.2.2 Processing Blood Samples

All five large (10 cc) purple top tubes should be labeled and shipped by overnight mail at ambient temperature to the core facility for processing of samples for DNA and plasma.

Address: Dr. Mary Maliarik
Pulmonary & Critical Care, Internal Medicine
Henry Ford Hospital
1 Ford Place, 5D
Detroit, Michigan 48202

One small (4 cc) purple top tube should be labeled and shipped by overnight mail at ambient temperature for special cultures to:

Address: Dr. Marvin Lesser*
Bronx VA Medical Center
130 West Kingsbridge Road
Bronx, New York 10468

Initially only Beth Israel Hospital will collect specimens from cases and controls for the DD-PCR special laboratory study. For Clinical Centers providing blood cells for RNA analysis, all four

*Dr. Peter Almenoff was Director of the Special Study Laboratory for Role of Mycobacterial Cell Wall Deficient forms in Sarcoidosis" from September 1996 through July 1997.

large green top tubes should be used to isolate peripheral blood mononuclear cells (PBMC) using a standard ficoll-hypaque separation technique. The PBMC should be centrifuged into a cell pellet, resuspended in solution D (guanidinium based solution) and stored at -70°C; shipping of these samples on dry ice should occur within one month to the following address:

Dr. Patricia Finn
Respiratory Division
Brigham & Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

6.3 KVEIM BIOPSIES

Tissue diagnosis may be established with a Kveim skin test biopsy for patients who have Löfgren's syndrome (as defined by erythema nodosum). The use of the Kveim skin test in ACCESS is permitted under an investigational new drug (IND) exemption awarded to Dr. Alvin Teirstein by the U.S. Food and Drug Administration (FDA). All physicians using the Kveim skin test in ACCESS must adhere to the procedures described in Dr. Teirstein's IND proposal, obtain the patient's informed consent for use of Kveim, and report adverse reactions (see Exhibit 6-1). Tissue specimens may be sent to Dr. Teirstein for all histopathology processing.

For patients whose diagnosis is made locally with Kveim biopsy tissue confirmation, one pathology slide stained with hematoxylin and eosin should be sent to:

Dr. Alvin S. Teirstein
Mount Sinai Medical Center
1 Gustave L. Levy Place
Box 1232
New York, New York 10029

6.4 BRONCHOALVEOLAR LAVAGE (BAL) SPECIMENS

The recommended systematic approach to the collection, handling, and interpretation of bronchoalveolar lavage fluid for patients in ACCESS is based on the collective experience of the groups involved. Final details of the techniques have been developed as the result of a questionnaire that established that each Clinical Center uses BAL techniques that are sufficiently comparable to allow for standardized specimen collection. Patient samples are routinely cultured

in Clinical Centers for mycobacteria and fungi. Either bronchial wash or BAL samples may be sent for culture. It is not required that both be sent unless it is the standard procedure of that institution. Sampling for cytology and bacterial cultures is done only if clinically indicated. Residual BAL specimens available following clinically indicated bronchoscopy procedures are stored in ACCESS Clinical Centers at -80^{o} C and transported, frozen in batches (once every six months) to the Central Repository operated by BBI - Biotech Research Laboratories* under contract with the NHLBI.

Standardized procedures recommended for BAL are:

1. BAL should be performed in the areas of the middle lobe or lingula in patients with diffuse disease and in the area of most disease in those patients with local disease.
2. The lavage volume should be 240 ml.
3. The fluid should be collected either by hand-held syringe or low-pressure suction.
4. For the purpose of the study, only one area should be analyzed and collected.
5. The gauze technique should not be used.
6. The initial 20 ml aliquots should not be discarded, but be part of the preparation.
7. From the cell count, determine the amount or dilution of neat fluid to use. The concentration should be about 0.2×10^6 cells/ml. The following are some rough pre-determined dilutions:

   $\leq 30 \times 10^5$ cells, use 200 µl neat fluid;

   $30\text{-}69 \times 10^5$ cells, use 100 µl neat fluid;

   $\geq 60 \times 10^5$ cells, use 1:2 dilution, 100 µl neat fluid and 100 µl Roswell Park Memorial Institute (RPMI) solution or normal saline; and

   $> 150 \times 10^5$ cells, use 1:3 dilution.

   Assemble slide, gasket, holder, and plastic well: 200 µl of pre-determined cell dilution to the well. Place in the cytospin.

*McKesson Biosciences served as the Central Repository from March 1996 through November 1998.

8. Unstained slides and Wright-Giemsa stained slides are made available to a central laboratory for cell counts.
9. Cell counts as well as lymphocyte subpopulations using flow activated cell sorting are performed at the local laboratory. Use of additional markers beyond those to determine general T cell population, including CD4 and CD8 subpopulations, are obtained as clinically indicated.
10. In addition to the stained and unstained slides that are sent to the BAL Core Laboratory, BAL samples are held for aliquots for shipment to the Central Repository. In particular, four 2 ml aliquots are held at -80^{o} C, and the cell button is prepared and stored at -80^{o} C for shipment to the Central Repository.

Each center prepares three sets of slides (six slides in three pairs of one Wright-Giemsa stained and one air dried slide). One set is kept at the Clinical Center; one set is sent to the Central Repository; and one set is sent for differential cell counts in the BAL Core Laboratory.

Pairs of BAL slides for differential cell count in the BAL Core Laboratory are labeled and stored in the Clinical Center. These slides are shipped to the BAL Core Laboratory once every two months or earlier if six or more pairs are ready for shipment. Shipment to the BAL Core Laboratory should be accompanied by the ACCESS Bronchoalveolar Slide Transmittal List (Form 65). Pairs of slides should be sent in standard slide transport packaging (e.g., cardboard slide holders) labeled with each patient's ACCESS specimen number label, secured for transport (i.e., so that slides do not fall out of holders), and packed appropriately (i.e., well protected in an envelope or package marked fragile). Batches of pairs of slides should be sent to:

Dr. Robert Baughman
University of Cincinnati Medical Center
231 Bethesda Avenue, Room 6004
Cincinnati, Ohio 45267-0564

BAL specimens are stored, frozen at the Clinical Center. These specimens are shipped to the Central Repository once every six months or more frequently if six or more patients' specimens are ready for shipment. Shipments to the Central Repository should be accompanied by the

ACCESS Bronchoalveolar Lavage Transmittal List (Form 30). Shipping materials are provided by the Central Repository. The following shipment procedures should be used:

1. Specimens are shipped to the Central Repository on a Monday, Tuesday, or Wednesday. Do not ship on a Thursday or Friday. Ship all specimens by Federal Express.
2. Place 2 vials in each ziplock bag. Cotton balls are used as absorbent material in case of leakage. Squeeze the air out of the bags and then close.
3. Place the ziplock bags into the aluminum can and then place the top on the can.
4. Place a layer of dry ice on the bottom of the shipping box. Place the aluminum cans into the shipping box. A minimum of 7 pounds of dry ice per shipping day is required. It is recommended that the box be filled with dry ice to ensure the samples remain frozen in the event the shipment is delayed in transit.
5. Replace the styrofoam cover on the box and place the shipping paperwork on top.
6. Seal the cardboard container on the top and corners with packing tape.
7. Place the shipping labels on the box. Do not allow any labels to overlap! The placement of the shipping labels is as follows.

Return Address Label	placed on top in upper left corner
Consignee Address Label	placed on top in lower right corner
Dry Ice “9" Label	placed on top under Return Address Label
Diagnostic Specimens Label	placed anywhere on top
Keep Frozen Label (optional)	placed anywhere on top

8. Enter the weight of dry ice (in kilograms) on the dry ice “9" label.

Pounds	Kilograms
7	3.1
8	3.5
9	4.0
10	4.4
11	4.8
12	5.3
13	5.7
14	6.2
15	6.6

9. Place the Federal Express airbill holder on the front of the package.

10. A partially completed Federal Express airbill is included in your supplies. Complete the following sections of the airbill:

    Section 1: Type in the date, your Federal Express account number, and your phone number.

    Section 5: Record the weight (in kilograms) of dry ice in the package (e.g., 1 package x 6 kg)

    Section 6: Record the weight (in pounds) of the package

    Total the Packages and Weight columns

11. Fax the shipping information (date of shipment and airbill number) to the Clinical Coordinating Center: Attention Martha Canner.

6.5 LABELING OF BIOLOGICAL SPECIMENS

The ACCESS Clinical Coordinating Center provides each Clinical Center with pre-printed labels for blood specimens and bronchoalveolar lavage specimens and slides. The ACCESS label sheets use randomized sample collection numbers in order to ensure the processing laboratories remain “blind” to patient identification. There is one label sheet for blood samples, one label sheet for BAL fluids and BAL slides, and one label sheet for pathology and Kveim slides. Figure 6-1 is a flow diagram for the shipment of specimens.

6.5.1 Blood Samples

From the supply of labels for blood specimens, select the next sheet of labels which is identified by “ACCESS BLOOD SPECIMENS” and by “SHEET XXXX”, the first and second labels in the left hand column (see Exhibit 6-2). Record the label sheet number on ACCESS Form 10, Item 32. Record the case or control ID number on the label sheet in the space provided on Form 10. For each type of label, there are extra labels to be used if needed. Each label type has a unique specimen number and can be used only for the specified specimen type. In Columns Two and Three there are twelve (12) labels for the five large (10cc) purple top (EDTA) vacutainer tubes that are used for DNA processing. In Column Four, there are six (6) labels for the one (1) small (4cc) purple top (EDTA) vacutainer tube. In Columns Five and Six, there are twelve (12) labels - eight (8) labels for the four large (10cc) green top (Heparin) vacutainer tubes and two (2) for the guanidinium cell pellet. Labels are to be securely affixed to the specified tubes.

Place the last thirteen (13) rows (Rows 9 to 21) of labels on the sheet in an envelope and ship with the specimens to the DNA Core Laboratory.

After all blood specimens are labeled, the Sheet Number Label, the second label in the left hand column with the case or control ID number should be affixed to the appropriate page of the Form 10. The top half of the label sheet should be attached to the completed Form 10.

All blood specimens are processed and shipped according to the instructions in Section 6.2.

6.5.2 Bronchoalveolar Lavage (BAL) Fluid and Slides

From the supply of BAL fluid and slide labels, select the next sheet of labels which is identified by “ACCESS BAL Aliquots & Slides”, “SHEET XXXX”, the first and second labels in the left hand column (See Exhibit 6-3). Record the label sheet number on ACCESS Form 32, Item 18. Record the case ID number on the label sheet in the space provided. There are 58 labels with the same specimen number to be used for the BAL fluids, aliquots, and slides. Process the BAL fluids as stated in Section 6.4. For the air dried slides, affix the labels in an unobtrusive location on the slides. Process and ship the slides according to the instructions in Section 6.4. After all BAL fluids

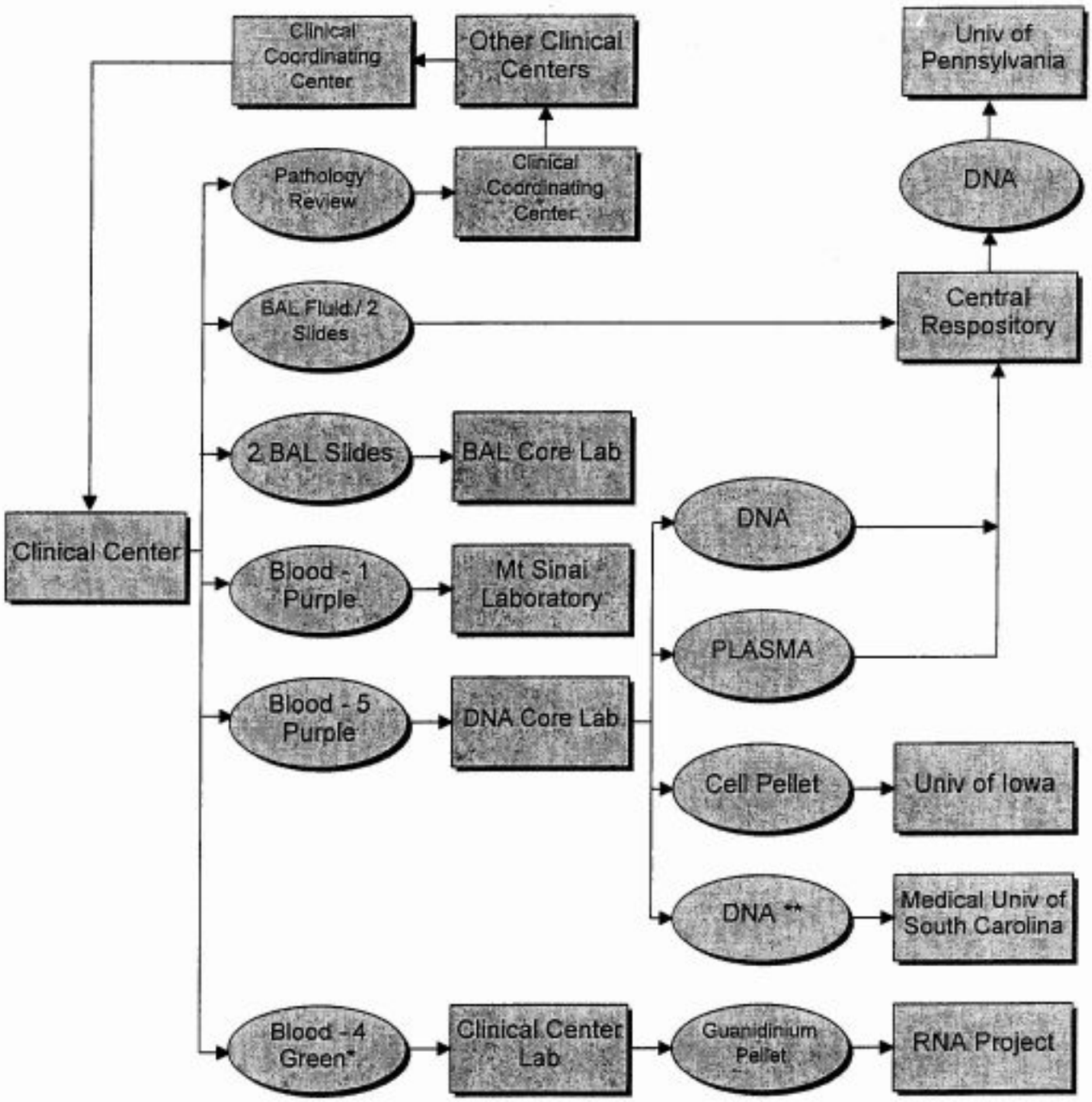
and slides are labeled, the second label in the left hand column with the case ID number should be affixed to the appropriate page of Form 32.

6.5.3 Pathology and Kveim Slides

From the supply of ACCESS ID Labels, select the sheet of labels which matches the assigned case or control study identification number. Each sheet of labels are identified by "ACCESS ID XXX-XXXX Pathology and Kveim Slides" (Exhibit 6-4). Each sheet has thirty (30) ACCESS ID number labels. Affix the labels in an unobtrusive location on the slides.

FIGURE 6-1

BIOLOGICAL SPECIMEN PROCESSING



* Heparinized (green top) tubes to be collected in the Beth Israel Hospital, Boston, Massachusetts only (until further notice).

** 2 Micrograms

EXHIBIT 6-1

ACCESS KVEIM SKIN TEST DOCUMENTS

ADVERSE REACTION CASE REPORT FORM

ID: ____ ____ ____ - ____ ____ ____ ____ Form Type: A R 0 1

Initials: ___ ___ ___

Date of Kveim Skin Test: __ __ __- __ __- __ __ __ __
Month Day Year

Reaction	Time 0	4 Weeks	12 Weeks
Pain			
Inflammation			
Fever			
Miscellaneous			

Noted by Physician:

Reaction	Time 0	4 Weeks	12 Weeks
Inflammation			
Fever			
Miscellaneous			

EXHIBIT 6-1 (Continued)

ACCESS KVEIM SKIN TEST DOCUMENTS

PATIENT'S NAME:_____

PERMISSION FOR KVEIM TEST FOR SARCOIDOSIS PROCEDURE

1. I hereby authorize Dr. _____ or associates or assistants of his/her choice at the (Clinical Center) to perform upon me or the above-named patient a Kveim skin test.

2. I understand that the Kveim test is performed by injection of a 0.15 cc (a few drops) of fluid into my skin similar to a tuberculosis skin test.

3. I understand that the Kveim test is made from human tissue. There is considerable experience with this test. The material has processed to minimize risks or harmful substances, however, the possibility of unforseen events cannot be eliminated.

4. In four weeks, if a nodule appears in your skin, a small biopsy will be performed (about 1/3 of an inch) under local anesthesia. You will feel the prick of the local anesthesia needle.

5. You will have a small scar at the site of the Kveim test biopsy.

6. I understand that there are other ways of making the diagnosis of sarcoidosis. They include bronchoscopy, lymph node biopsy and other surgical procedures.

7. For the purpose of advancing medical knowledge and education, I consent to the photographing, videotaping or televising of the procedure to be performed, provided my/the patient's identity is not disclosed. I also consent to the admission of observers to the treatment room.

8. Any tissues or parts surgically removed may be examined and retained by the Hospital for medical, scientific or educational purposes and such tissues or parts may be disposed of in accordance with accustomed practice.

9. I acknowledge that no guarantees or assurances have been made to me concerning the results intended from the procedure.

10. I understand that I may refuse the Kveim test and I will still receive optimal standard care for my illness.

Witness (Optional): _____ Patient/Relative or Guardian: _____

_____ (Print Name)

_____ (Print Name)

Date: _____

_____ (Relationship, if signed by person other than patient)

I hereby certify that I have explained the nature, purpose, benefits, risks of, and alternatives to, the proposed procedure, have offered to answer any questions and have fully answered all such questions. I believe that the patient/relative/guardian fully understands what I have explained and answered.

Date:_____ Physician:_____ (Signature)

The signature of the patient must be obtained unless the patient is under the age of 18 or incompetent.
NOTE: THIS DOCUMENT MUST BE MADE PART OF THE PATIENT'S MEDICAL RECORD.

EXHIBIT 6-2
SAMPLE ACCESS LABEL SHEETS
BLOOD SPECIMENS

ACCESS BLOOD SPECIMENS	Send specimens to the DNA Core Lab for DNA/Plasma Processing	Send specimens to the DNA Core Lab for DNA/Plasma Processing	Send specimens to Mt Sinai **SHEET 1935**	Send specimens to the local lab for RNA processing	Send specimens to the local lab for RNA processing
SHEET 1935 **ID**____________	ACCESS **05257** 10ml EDTA Purple	ACCESS **05257** 10ml EDTA Purple	ACCESS **06453** 4ml EDTA Purple	ACCESS **03874** 10ml HEPARIN Green	ACCESS **03874** 10ml HEPARIN Green
Leave the above label on sheet. Staple top half of label sheet to Form10.	ACCESS **05257** 10ml EDTA Purple	ACCESS **05257** 10ml EDTA Purple	ACCESS **06453** 4ml EDTA Purple	ACCESS **03874** 10ml HEPARIN Green	ACCESS **03874** 10ml HEPARIN Green
	ACCESS **05257** 10ml EDTA Purple	ACCESS **05257** 10ml EDTA Purple	ACCESS **06453** 4ml EDTA Purple	ACCESS **03874** 10ml HEPARIN Green	ACCESS **03874** Guanidinium Solution Cell Pellet
SHEET 1935 **ID**____________	ACCESS **05257** 10ml EDTA Purple	ACCESS **05257** 10ml EDTA Purple	ACCESS **06453** 4ml EDTA Purple	ACCESS **03874** 10ml HEPARIN Green	ACCESS **03874** Guanidinium Solution Cell Pellet
Affix the above label to Patient's Form 10, ITEM 32.	ACCESS **05257** 10ml EDTA Purple	ACCESS **05257** 10ml EDTA Purple	ACCESS **06453** 4ml EDTA Purple	ACCESS **03874** 10ml HEPARIN Green	ACCESS **03874** Guanidinium Solution Cell Pellet
	ACCESS **05257** 10ml EDTA Purple	ACCESS **05257** 10ml EDTA Purple	ACCESS **06453** 4ml EDTA Purple	ACCESS **03874** 10ml HEPARIN Green	ACCESS **03874** Guanidinium Solution Cell Pellet

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA	ACCESS **05257** DNA
ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**
ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**
ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**	ACCESS **05257**
ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA
ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA
ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA	ACCESS **05257** Iowa DNA

EXHIBIT 6-3

SAMPLE ACCESS LABEL SHEETS

BAL FLUID AND SLIDES

ACCESS BAL Aliquots & Slides	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
SHEET 9001 ID___________	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765
ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765	ACCESS BAL 98765

EXHIBIT 6-4

SAMPLE ACCESS LABELS FOR PATHOLOGY AND KVEIM SLIDES

ACCESS	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**
~~999-0006~~	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**
ACCESS	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**
~~999-0006~~	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**
ACCESS	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**	**ACCESS**
~~999-0006~~	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**	**~~999-0006~~**

CHAPTER 7

CLINICAL CENTER PROCEDURES

7.1 INTRODUCTION

The Research Coordinator plays an important role in each Clinical Center participating in ACCESS. This individual is usually the Clinical Center staff member who has the largest time commitment to the study and who is most familiar with study procedures and operations. Thus, with the Principal Investigator, this person shares responsibility for the efficient, enthusiastic operation of the Clinical Center, quality of the data collected and transmitted to the Clinical Coordinating Center (CCC), and adherence of all Clinical Center staff to the study protocol. Standardization of procedures is necessary if pooling of findings across Clinical Centers is to be valid. The procedures described in this chapter are those which are followed in all Clinical Centers and which the Research Coordinators and Principal Investigators are responsible for implementing and maintaining.

7.2 MATERIALS SENT FROM THE CLINICAL COORDINATING CENTER

Each Clinical Center receives from the CCC data collection forms to be used for recording study data.

A microcomputer and printer for ACCESS functions were provided by the CCC to each Clinical Center prior to the initiation of case and control recruitment. The microcomputer is used for data entry and initial editing of the data, and for electronic mail communications (see Volume III of ACCESS Procedures Manual for details).

7.3 CASE/CONTROL SELECTION AND ENROLLMENT

Cases and controls must fulfill certain eligibility requirements in ACCESS. The procedures required as part of the screening process are described in Chapter 1 (Recruitment Procedures and Information Flow Charts) of this volume of the Procedures Manual. The following sections describe Clinical Center procedures for facilitating completion of these examinations and procedures.

7.3.1 Case Selection

Potential ACCESS cases may be admitted to the Clinical Center for diagnosis or treatment or referred to the Clinical Center by their personal physicians for participation in the study. A Case Screening Log is used by Clinical Center staff to record preliminary assessment of eligibility determined by review of medical records. Completion of the Screening Log for Cases was discontinued in October 1997. Each case is assigned a study ID (identification) number (from a list provided by the CCC). Potential new cases who are identified as ineligible for ACCESS by this assessment are not contacted for possible participation in ACCESS. If the information from the medical record indicates that a potential new case may be eligible for ACCESS, Clinical Center staff arranges an interview with the potential new case.

7.3.2 Initial Interviews with Potential New Cases

Advance work by the Clinical Center staff facilitates completion of interviews and reduces waiting time. To be properly prepared for the patient's visit, it is suggested that the Clinical Center staff follow the procedures described below.

The Research Coordinator in each Clinical Center assembles screening packets so that forms and other materials are readily available. These packets should include a consent form for the potential case to sign, a Form 01 (Participant Information), a Form 02 (Confirmation of Eligibility - Cases), and a Form 03 (Case Registration Worksheet - ATRS). The ID number assigned to the potential case should be written on the Form 02 and Form 03 in the spaces provided.

During the interview, the interviewer determines the potential case's willingness to participate in the study and, if willing, obtains informed consent, completes Form 01 and begins completion of Form 02 and the process of tissue collection for diagnosis of sarcoidosis, if the potential case has not already had tissue collected and examined. If the potential case is willing to participate in the study and fulfills eligibility criteria, Form 03 is completed and the potential case is registered on the Automated Telephone Response System (ATRS). However, the potential case cannot be enrolled in the study until a positive diagnosis of sarcoidosis is obtained by examination of tissue specimens

(see Chapter 3). When a potential case is officially enrolled, the Form 02 is completed and the data on the form entered into the database. The Form 31 (Diagnostic Specimen Report) is completed for each enrolled case and entered in the database. Whatever the outcome of the tissue pathology report, the status of the case is updated on the ATRS by transferring the information on the completed Form 04 (Case Enrollment/Non-Enrollment Worksheet) by telephone. If the case is enrolled, a facsimile transmission is sent by the ATRS to the Clinical Center as Form 09, Enrollment Confirmation Form. This form should be checked and entered into the local database within 24 hours of case enrollment. As soon as the case is officially enrolled, the Research Coordinator schedules an appointment with the case for the extended interview, physical examination, and blood drawing.

7.3.3 Control Selection

As soon as a case is enrolled using the ATRS, the Clinical Center is sent Form 09, Enrollment Confirmation Form; this form must be entered into the local database to confirm the age, gender and ethnic origin of the case. After receipt of the Form 09 data, the CCC staff and the RDD (Random Digit Dialing) Interview Group begin the procedures (described in Chapters 1 and 9) to select a control who will match the case in age, gender and race (ethnic origin). When the RDD Interview Group has identified a potential control, the RDD Interview Group sends the name and telephone number of the individual to the Clinical Center by facsimile transmission. The Research Coordinator attempts to call the potential control and sends a letter (see Exhibit 1-1 in Chapter 1) as soon as possible. This letter provides an explanation of the study and thanks the potential control for his/her interest in ACCESS. The telephone call should be timed so that it is made very soon after receipt of the RDD notification of a potential control. During the telephone call, the Research Coordinator arranges a visit with the potential control, preferably at the Clinical Center. (The visit may take place at the potential control's home or workplace, if necessary.) Clinical Center staff make every effort to schedule appointments with the potential controls within two weeks of receiving the notification of the potential control. If a potential control does not complete an appointment after

five separate discussions on scheduling an interview with Clinical Center staff or could not be contacted after at least five attempts at different times, the control should be considered a refusal. If the potential control refuses to participate, does not complete the visit or is determined to be ineligible, the CCC is notified by transferring, by telephone, the information on the completed Form 06 to the ATRS.

The packet prepared for the visit of each control contains an informed consent form, a Form 01 (Participant Information), a Form 05 (Confirmation of Eligibility - Controls) and a Form 06 (Control Status Worksheet - ATRS). The potential control is assigned an ID number from the list provided by the CCC and the number recorded on the forms in the spaces provided. If the potential control is eligible at the visit, the control signs the consent form, is interviewed, and is enrolled. The CCC is notified by transferring, by telephone, the information on the completed Form 06 to the ATRS. The Form 05 is completed and entered into the database within a day or two of receipt. A facsimile transmission of Form 09, Enrollment Conformation Form for this control is sent by the ATRS to the Clinical Center. This form should be checked and entered into the local database within a day or two of receipt.

7.4 BASELINE EVALUATION AND INTERVIEW

7.4.1 Baseline Evaluation for Cases

The Research Coordinator prepares a packet of forms prior to the scheduled visit for the baseline evaluation for each case. The packet should contain a Form 10 (Demographics and Medical History Questionnaire), Form 11 (Occupational History Worksheet), Form 12 (Occupational and Recreational Questionnaire), Form 13 (Environmental Questionnaire), Form 14 (Medications Questionnaire), Forms 15 - 19 (Scales A - E), Form 20 (Relationship Questionnaire A), Form 21 (Relationship Questionnaire B), Form 22 (Family History Questionnaire), Form 23 (Family History Supplement [to be used only if needed]), Form 24 (Baseline Physical Examination Form), Form 25 (Laboratory Data Form), Form 26 (Baseline Questionnaire for Cases Only), Form 30 (Chest Radiograph Interpretation Form), and Form 32 (Bronchoalveolar Lavage Form). The Research

Coordinator makes prior arrangements with the Clinical Center Physician, the Interviewer (if the Research Coordinator does not do the interviewing), the Spirometry Technician, and the phlebotomist to be available for the baseline evaluation of the case.

All scripts, anchor date cards and response cards should be readily available. All forms are completed using the guidelines provided in Section 7.6 and the scripts and instructions for each form (see Volume II, Part B of the ACCESS Procedures Manual).

When the evaluation is completed, all forms are data entered using the dedicated Clinical Center microcomputer. (See Volume III of the ACCESS Procedures Manual for data management procedures). Only pages 1 and 4 of Form 11 are entered in the local database. The entire Form 11 is copied and the copy kept at the Clinical Center. The original is forwarded to the CCC for Standard Industrial Classification/Standard Occupational Classification(SIC/SOC) Coding. Blood specimens and bronchoalveolar lavage (BAL) specimens are processed according to procedures described in Chapter 6, Procedures for Biological Specimen Collection, Processing and Shipping. Chest X-rays are processed using the procedures described in Chapter 3, Diagnosis and Assessment.

7.4.2 Baseline Evaluation for Controls

The baseline evaluation of an eligible control can be scheduled to follow the initial interview for determining eligibility or completed at a separate visit performed within one month of enrollment. The packet for the control baseline evaluation contains all the forms listed in Section 7.4.1 with the exception of Forms 24, 25, 26, 30, 31 and 32. All forms and materials are processed using the procedures described in Section 7.4.1.

7.5 TELEPHONE CONTACTS AND FOLLOW-UP EVALUATION FOR CASES

The first 252 (goal was 240) ACCESS cases were enrolled in the Clinical Course Study. The Research Coordinator or Interviewer contacts these cases by telephone at 6, 12, and 18 months after baseline. Form 28 (Telephone Contact Summary) is used to record information obtained during these telephone contacts. Each case who participates in the Clinical Course Study is

scheduled for a follow-up evaluation between 24 and 30 months after the baseline evaluations. Cases enrolled after June 1997 may be seen in the interval 21 to 24 months after entry. Form 24 (Physical Examination Form), Form 25 (Laboratory Data Form), Forms 35 and 36 (Follow-up Questionnaire for Cases Only, Part I and Part II, respectively) and Form 37 (Change in Organ Involvement Since Initial Evaluation) are completed at the follow-up evaluation. A chest X-ray is obtained and processed as described in Chapter 3, Diagnosis and Assessment. If the Clinical Center staff cannot locate a case for a telephone contact or the case does not come to the Clinical Center for his/her two-year follow-up visit, the Missed Contact/Visit Form (Form 33) is completed. All data collected are entered into the database using data entry procedures described in Volume III of the ACCESS Procedures Manual.

7.6 COMPLETING AND REVIEWING STUDY FORMS

Black ink should be used for completing the forms. This facilitates the photocopying of a sample of forms selected for data entry at the Clinical Coordinating Center. For items which cannot be answered by a check mark (**T**) or an "X," the response should be printed clearly in the space provided. Abbreviations should not be used unless necessary and then should be only widely-recognized abbreviations. The first items to be completed on any study data form are the participant's ID number and Form Type, if the Form Type is not already printed in the upper right-hand corner of the first page. The initials and other information requested in the "Visit Identification" section of the form are completed next. The remaining sections of the form are completed by appropriately trained and certified ACCESS staff members.

When the form is returned to the Research Coordinator at the end of the interview, examination or procedure, the Research Coordinator should review it, preferably while the participant is still in the Clinical Center, to assure that all required information has been recorded in a legible, unambiguous fashion. Missing and/or inconsistent items are reviewed with the individual staff members who completed that section of the form. Any administrative information requested at the end of the form is supplied by the Research Coordinator.

Since data entry staff are to enter the data exactly the way the forms are completed, the providers of the data are requested to complete the forms as clearly and as legibly as possible, and to follow certain conventions in reporting data to minimize the possibility of errors in processing the data collection forms.

I. Responses Answered by a Check Mark (**T**) or an "X"

If a response is to be answered by a check mark (**T**) or an "X," then only a check mark or an "X" within the parentheses is an acceptable response.

II. Numeric Responses

For items which require a numeric response, the exact number of spaces is indicated. Answers to integer items which require less than the number of spaces provided must be right justified. For example, 3 spaces are provided for diastolic blood pressure; if the participant's diastolic blood pressure is 80 mm Hg, it may be recorded as _ 8 0 or 0 8 0.

Answers to items calling for responses with decimal places must have all the decimal places completed and filled with trailing zeros if necessary. For example, four spaces, including one decimal place, are provided for height in centimeters. If the height is exactly 153 centimeters, it should be recorded as 1 5 3.0.

III. Overwritten Responses

A. If the response has been written over to carefully delineate the existing mark, the response is acceptable. The tracing of the existing mark(s) should be done in black ink.

B. If the response has been written over to change the response, the response is considered illegible unless the

desired response is clearly designated, initialed and dated. The desired check mark or "X" must be clearly and neatly circled, initialed and dated by the individual designating the correct response.

C. An incorrect numeric or alphabetic response is completely crossed out and the correct numeric or alphabetic response written clearly and neatly above or below the original response. The correct response is circled, initialed and dated by the individual making the correction. An incorrect response should never be circled or initialed.

IV. Completion of Dates

The dates on ACCESS data collection forms are written month, day, and year using alphabetic abbreviations for the month and numbers for the day and year. For example, October 21, 1996 is written OCT-21-1996.

7.7 EDIT STATEMENTS

In spite of earnest attempts by all members of the Clinical Center staff, items on the data collection forms are sometimes overlooked, information is sometimes recorded in the wrong format, or items are answered inconsistently. In order to identify such problems as well as errors that may have occurred during data entry and to retrieve as much information as possible, all data are subjected to a local computer edit to detect missing or improbable answers to each and every item. The data transmitted to the CCC are also subjected to a computer edit.

Problems detected by the special computerized edit procedures trigger "edit messages" or statements which are printed at the Clinical Center for staff resolution immediately after data entry. Thus, data entry of forms soon after form completion is highly desirable so that edit queries can be processed while Clinical Center staff can still recall the details of the data collection interview. The data transmitted to the CCC are edited within one week of receipt and any edit messages are sent

to the appropriate Clinical Center for resolution. The format of edit statements generated by the local edit and central edit is identical and the same procedures are used to respond to both types of edit queries.

7.7.1 Types of Problems Listed on Edit Statements

1. Inconsistencies

   a. Within a form, the responses to different parts of an item are checked for consistency. For example, if certain parts of the item are to be answered only if the first part of the item is answered "YES," a message is generated for each item that is answered if the first part is answered "NO."

   b. Within a form, responses to different items are checked for consistency. For example, if the response to the question asking if the case has non-thoracic involvement is “YES,” involvement of at least one organ system must be indicated.

2. Out-of-Range Checks

   Values that are outside specified limits are identified.

3. Unanswered Items

   All non-valid unanswered items are identified. An unanswered item is indicated on the edit statement by an asterisk(*) under the old value column (Exhibit 7-1).

An edit message is printed for each error identified by the computer edit. The list of edit messages for a specific form is referred to as an Edit Statement.

7.7.2 Format of Edit Statements

The format of the Edit Statement is designed to limit the work required to "correct" the item in question, as well as to limit the possibility of additional "errors" in processing the corrections at the Clinical Centers. The Edit Statement consists of basic identifying information, the edit messages and the general instructions for correcting edit messages. An illustration of a typical statement is presented in Exhibit 7-1.

The top left side of the edit statement identifies the form number and revision number, the Clinical Center Number, and participant ID number. The top right side identifies the participant initials, the visit, and the date of visit for the form edited. The date the edit was printed appears in the title of the edit statement.

The edit statement consists of the following information:

The type of error detected.

The number of the item in question.

The name of the item in question, if applicable.

Original or old value.

The value given in this column is:

a. The value or date recorded on the form, for write-in responses, or

b. The precoded number printed within parentheses on the form for checked answers, or

c. An (*) if the answer is missing.

Edit messages for unanswered items and for out-of-range items are printed first, followed by the edit messages for the inconsistencies and date checks.

7.7.3 Specific Procedures for Correcting Edit Statements

Time should be set aside during at least one day a week to respond to edit statements. Each form failing edit is checked against the edit statement. The particular item failing is located on the form, corrected on the form, and the correction is circled, initialed and dated. If an item is listed as out-of-range but is correct, the value on the form is noted as correct by circling, initialing and dating the item. Edit statements are filed with the forms to which they refer so that they are available for audits. The database is be corrected using the procedures described in Chapter 8, Volume III of the ACCESS Procedures Manual.

If Clinical Center staff identify an item or subitem that requires correction that is not listed on the edit statement, an unsolicited correction is made to the form and the correction entered into the database using the same procedures as those for forms failing edit.

7.8 PROCEDURES FOR USING THE AUTOMATED TELEPHONE RESPONSE SYSTEM (ATRS)

When using the Automated Telephone Response System (ATRS), authorized personnel can only register cases and controls for the Clinical Center in which they are working. Access to the system is gained by calling the telephone number listed at the top of the ATRS Worksheet and logging into the system by entering the appropriate Personal Identification Number (PIN) and Clinical Center Password on request. These numbers should be kept secure (either on your person, or in a secure location not accessible to others). ATRS certified staff should not disclose his/her PIN to others at the Clinical Center. The Clinic Password (CP) is common to all personnel eligible to register cases and controls at a Clinical Center, but should not be disclosed to persons other than those authorized to use the system.

The steps in the process are as follows. First, enter the case's (or control's) Identification Number (ID) and initials in the appropriate spaces on the worksheet. Next, using the coding chart located above the spaces for the initials, numerically transcribe the case's (or control's) initials into a series of 6 numbers, and place these numbers in the spaces provided for Character Codes.

Second, call the number for the ATRS. The call can be initiated from any telephone with a touch-tone dial. Third, follow the verbal instructions. As the verbal instructions request numerical information to be entered, push the necessary numbers on the touch-tone phone pad to enter the numbers. The system does not accept voice input; only the touch-tone sounds are recognized by the system. If there is a problem, the Clinical Coordinating Center Coordinator (410-435-0663) should be called to provide assistance. At the conclusion of the call to the ATRS, the individual placing the call is given the current status for the case or control. ATRS Worksheets are to assist Clinical Center staff in registering cases and controls and reporting on the status of each registered case and control until the case or control is enrolled or declared ineligible.

To use the ATRS, the user must have:

1. A Personal Identification Number (PIN);
2. A Clinical Center Password; and
3. The appropriate completed ATRS Worksheet (Forms 03, 04 and 06).

7.9 QUALITY CONTROL

7.9.1 Audits

Periodically, staff from the CCC visit each Clinical Center to compare the data submitted electronically to the CCC with the paper forms and edit statements on file in the Clinical Center. The Research Coordinator is responsible for providing the paper forms requested in advance for audit. Additional information on audits is provided in Chapter 8.

7.9.2 Data Entry Comparisons

Several times a year each Clinical Center is requested to send copies of a sample of data collection forms to the CCC. These forms are entered at the CCC by an experienced data entry operator. The data entered at the Clinical Center are compared with the data entered at the CCC and discrepancies reported to the Clinical Center. (See Chapter 8.)

7.10 OTHER DUTIES OF THE RESEARCH COORDINATOR

7.10.1 Supply Orders

The Research Coordinator is responsible for keeping the Clinical Center stocked with supplies of materials needed for ACCESS.

Forms and copies of manuals and reports are ordered from the CCC. A Form Requisition Sheet is shown in Exhibit 7-2.

Materials for submitting specimens to the Core Laboratories are obtained from the Core Laboratories (see Volume IV of the ACCESS Procedures Manual). Other supplies are ordered from the appropriate local or national suppliers.

7.10.2 Certification of Clinical Center Staff

Certification is required for each Clinical Center member who performs one or more of the various tasks involved in patient examination or evaluation and data collection and handling. The procedures for training and certification are described in Chapter 10.

7.10.3 Other Procedures

CCC staff are to be notified promptly of changes in Clinical Center personnel, Clinical Center address, or telephone numbers so that the ACCESS Address Directory can be maintained correctly. Changes are reported by sending an updated copy of the Address Directory page to the CCC.

It is recommended that an individual in each ACCESS Clinical Center, usually the Research Coordinator, maintain a calendar of ACCESS meetings and training sessions, deadlines for special projects, dates for submission of budgets, etc.

All ACCESS memoranda, summary notes and reports are issued unique numbers, designating the type of document, e.g., memoranda, summary notes or reports. Beginning May 1998, all numbered memoranda are sent by e-mail. All numbered ACCESS documents should be printed and filed for easy reference. Research Coordinators are expected to read and understand

all numbered memoranda. Any questions concerning ACCESS memoranda or other documents are referred to the CCC as soon as possible.

The ACCESS Protocol, Procedures Manual, and Address Directory are kept up-to-date by inserting revised pages as they are distributed by the CCC. Volume IIA of the Procedures Manual contains a copy of the latest revision of each ACCESS form and should be available to the Clinical Center staff for reference. The forms in Volume IIA are not to be used for data collection.

Information requested by the CCC or other groups should be provided promptly. If an immediate response is not possible, the appropriate individual should be notified.

EXHIBIT 7-1

ACCESS Edit Query
Feb-12-1997

Form/Rev:	**02 /0**	**Initials:**	**FFF**
Clinic:	**999**	**Visit:**	**CA01**
ID:	**9992345**	**Visit Date:**	**Feb-11-1997**

ITEM		OLD VALUE
	This response is out of range.	
5	Age	72
PLEASE VERIFY THIS RESPONSE.		
	This (These) response(s)	
5	Age	72
	is (are) inconsistent with some or all of the following responses	
5A	Less than 18 yrs old	1
	This (These) response(s)	
10D	Other biopsy	2
	is (are) inconsistent with some or all of the following responses	
10D_rk	Specify other biopsy	Missing

EXHIBIT 7-1 (Continued)

ACCESS Edit Query
Feb-12-1997

Form/Rev:	**02 /0**	**Initials:**	**FFF**
Clinic:	**999**	**Visit:**	**CA01**
ID:	**9992345**	**Visit Date:**	**Feb-11-1997**

ITEM		OLD VALUE
	This (These) response(s)	
14	Any stops	2
is (are) consistent with some or all of the following responses		
5A	Less than 18 yrs old	1
8A	Tuberculosis	2
8B	MD-sarcoid 6 mo ago	2
8C	Billiary cirrhosis	2
8D	Crohns disease	2
8	Histoplasmosis RX	2
8F	Beryllium	2
9	Specimen obtained	1
11B	Path rpt-sarcoidosis	2
11C	Any path exclusion	2
13	Culture positive	2

EXHIBIT 7-2

ACCESS Form 51
Rev. 0 1/26/99
Page 1 of 2

FORMS REQUISITION SHEET FOR CLINICAL CENTER USE

Clinical Unit No. _____

Date of Requisition: - ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

Requested by: _____

Telephone Request: ---------- ( )

QUANTITY	FORM NUMBER	FORM
_____	01	Participant Information
_____	02	Confirmation of Eligibility (Cases)
_____	03	Case Registration Worksheet (ATRS)
_____	04	Case Enrollment/Non-Enrollment Worksheet (ATRS)
_____	05	Confirmation of Eligibility (Controls)
_____	06	Control Status Worksheet (ATRS)
_____	10	Demographics and Medical History Questionnaire
_____	11	Occupational History Worksheet
_____	12	Occupational and Recreational Questionnaire
_____	13	Environmental Questionnaire
_____	14	Medications Questionnaire
_____	15	Questionnaire 15
_____	16	Questionnaire 16
_____	17	Questionnaire 17
_____	18	Questionnaire 18
_____	19	Questionnaire 19
_____	20	Relationship Questionnaire A
_____	21	Relationship Questionnaire B
_____	22	Family History Questionnaire
_____	23	Family History Supplement
_____	24	Physical Examination Form
_____	25	Laboratory Data Form
_____	26	Baseline Questionnaire for Cases Only

EXHIBIT 7-2 (Continued)
REQUISITION SHEET FOR CLINICAL CENTER USE

QUANTITY	FORM NUMBER	FORM
____	28	Telephone Contact Summary
____	29	Affected Relative Report Form
____	30	Chest Roentgenography Interpretation Form
____	31	Diagnostic Specimen Report
____	32	Bronchoalveolar Lavage Form
____	33	Missed Contact/Visit Form
____	35	Follow-up Questionnaire for Cases Only (Part I)
____	36	Follow-up Questionnaire for Cases Only (Part II)
____	37	Change in Organ Involvement since Initial Examination
____	40	Tissue Sample Shipping Form
____	51	Forms Requisition Sheet
____	60	Bronchoalveolar Lavage Transmittal List
____	61	DNA Blood Specimen Shipping Form
____	62	L-Forms Blood Specimen Shipping Form
____	65	Bronchoalveolar Lavage Slide Transmittal List
____		Screening Log for Cases
____		Log for RDD Controls

QUANTITY	MATERIALS
____	Clinical Coordinating Center Address Labels
____	Blood Specimen Label Sheets

FOR CLINICAL COORDINATING CENTER USE ONLY

Date Received at Clinical Coordinating Center: ____ ____ ____ -____ ____-____ ____ ____ ____
Month Day Year

Date Forms/Materials Mailed: ____ ____ ____ -____ ____-____ ____ ____ ____
Month Day Year

CHAPTER 8

CLINICAL COORDINATING CENTER PROCEDURES

8.1 INTRODUCTION

The Clinical Coordinating Center (CCC) is organized and staffed as part of Clinical Trials & Surveys Corp. (C-TASC) to serve the needs of ACCESS. The CCC staff fulfill key roles in developing and implementing the study's statistical design, data collection and management, and analysis of study results. The major responsibilities of the CCC, which serves as the central data repository for the information collected under the study protocols, are: (1) serve as communication center for the study; (2) provide and maintain a distributed data management system for each Clinical Center; (3) work with the RDD (Random Digit Dialing) Interview Group to establish procedures for selecting controls; (4) maintain a central database of data integrated from all Clinical Centers and the Core and Special Study Laboratories; (5) generate analyses to monitor for evidence of the etiology of sarcoidosis and for adherence to the study protocol; and (6) generate analyses to meet the goals of the study. The objectives and procedures designed to achieve these obligations are presented in this chapter.

8.2 OBJECTIVES OF THE CLINICAL COORDINATING CENTER

The general aims of the ACCESS CCC are to:

- Serve as a collaborating partner with the other investigators in the organization, design, conduct, and analysis of the study.
- Provide biostatistical and epidemiologic expertise to the study in the area of design and operation of this multicenter study.
- Work with the other investigators to draft and revise as necessary the Protocol, Procedures Manual, and study forms.
- Provide expertise in the area of data management systems and statistical analysis.
- Develop and implement the required data processing procedures for handling all study forms and materials.

- Develop, implement and maintain quality control procedures to detect and correct deficiencies in data collection, processing or analyses.
- Provide facilities and staff to carry out appropriate analyses to monitor the study for evidence of the etiology of sarcoidosis and other study goals.
- Serve as the communication center for the study.
- Prepare progress reports and assist in preparation of publications.

8.3 ORGANIZATION OF MEETINGS AND CONFERENCE CALLS

The members of the ACCESS CCC play a major role in the organization and conduct of investigator meetings, subcommittee meetings, and conference calls held during all phases of the study. The ACCESS CCC staff provide training to ACCESS Clinical Center staff in the collection and processing of data, as necessary. In addition, the ACCESS CCC staff provide logistical support for orientation and training sessions.

During participant recruitment and follow-up, it is anticipated that a number of aspects of the protocol will require clarification, certain procedures will require revision as a result of the Clinical Center experience, and specifications for other procedures will require development. ACCESS CCC staff periodically review current procedures and develop additional procedures as needed throughout the course of the study.

8.4 DATA COLLECTION AND STORAGE

8.4.1 ACCESS Procedures Manual

The ACCESS Procedures Manual provides a detailed description of study design, organization, methods, definitions, and procedures used in data collection and processing. The professional staff of the CCC in conjunction with Clinical Center investigators are responsible for the coordination of the preparation of this document for approval by the Executive Committee, Steering Committee, and Data Safety and Monitoring Board. This Manual will be revised as necessary during the course of the study. The CCC staff prepare and supply all ACCESS forms to the ACCESS Clinical Centers.

8.4.2 Data from the Clinical Centers

The CCC staff receive recruitment information on cases and controls by telephone by means of the Automated Telephone Response System (ATRS). Data for cases and controls are received by electronic transmission from the Clinical Centers' distributed data management systems (see Volume III of the ACCESS Procedures Manual). Some forms are sent by mail for central processing.

8.4.3 Data from the Core and Special Study Laboratories

Specimens are sent directly to the DNA Core Laboratory from the Clinical Centers, and specimen transmittal information is contained in forms entered into the Clinical Center data management system. CCC staff use these data to generate an electronic log of all specimens. The DNA Core Laboratory staff complete a report about the condition of the specimen received, (e.g., frozen or thawed), and the number of aliquots made from each specimen. The electronic log is used to identify as delinquent any reports not received from the DNA Core Laboratory two weeks after a Clinical Center shipped the specimen. These procedures are also used to track the specimens shipped from the DNA Core Laboratory to the Central Repository, the Medical University of South Carolina and the University of Iowa. Similar procedures are used to track the specimens sent from the Clinical Centers directly to the RNA Core Laboratory or directly to the Central Repository. At regular intervals, CCC staff prepare lists of specimens to be shipped to the University of Pennsylvania from the Central Repository. The use of the remaining specimens will be determined by the Executive and Steering Committees as outlined in Chapter 5 of the Protocol.

The CCC staff are also responsible for the receipt and storage of data from the ACCESS Core and Special Study Laboratories. A regular schedule for transmission of this information has been established. All data are transmitted electronically. Detailed descriptions of each Core and Special Study Laboratory's methods are given in Volume IV of the Procedures Manual.

8.4.4 Storage System for Study Reports, Minutes, and Important Documents

A storage system for study reports, minutes of meetings, and important documents has been designed and implemented and is updated regularly.

8.4.5 Biopsy Specimens

The CCC staff track the biopsy specimens submitted for the Tissue Sample Reading Program (see Chapter 3).

8.4.6 Chest X-Rays

The CCC staff identify chest X-ray films for review at study meetings, and notify the appropriate Clinical Center Investigators in advance of the study meetings concerning which films to bring to the meeting (see Chapter 3).

8.5 CLINIC MONITORING AND COMMUNICATIONS

CCC staff are responsible for monitoring for protocol violations and for notifying all appropriate ACCESS personnel or appropriate committees of any violations when they occur. To minimize the number of protocol violations, CCC staff have included certain protocol adherence aids in the distributed data management system for the Clinical Centers. These include case appointment schedules and monthly lists of cases due for telephone contact or two-year follow-up in a specified time period. The distributed data system also includes a display of all forms entered for each enrolled case and control.

Labels for blood samples and tissue specimens are generated and distributed to the Clinical Center by the CCC. The procedures for labeling specimens are described in Chapter 6.

The CCC staff provide logistical support for meetings and training sessions. They are responsible for preparing handouts and other materials for meeting participants as well as for preparing and distributing the minutes of these meetings.

The CCC staff are a resource for the numerous telephone inquires and written inquiries concerning the study procedures from study investigators and Clinical Center personnel.

CCC staff maintain and distribute an ACCESS Address Directory. This directory contains a listing of study personnel from each Clinical Center and each Core and Special Study Laboratory as well as personnel from the Program Office at the National Heart, Lung and Blood Institute (NHLBI), Clinical Coordinating Center, and RDD Interview Group. A list of the membership of all study committees is included. This directory is updated periodically and revised pages are distributed to all centers.

8.5.1 Certification

In cooperation with the Steering Committee, the CCC staff has developed and implemented the ACCESS staff certification program outlined in Chapter 10. The CCC staff maintain a roster of certified staff for each Clinical Center and monitor the completed data records to verify the study procedures are completed by certified staff.

8.5.2 Automated Telephone Response System (ATRS)

An Automated Telephone Response System (ATRS) allows Clinical Center staff to report the enrollment status of cases and controls quickly and at any time of day (see Chapter 7). This system is used to prepare the weekly recruitment reports.

8.5.3 Recruitment Reports

Weekly reports on the status of recruitment are prepared by the CCC staff and circulated to the ACCESS Executive Committee and each Clinical Center. These reports include the number of cases and controls enrolled to date and ratio of this number to the number who should have been enrolled to date given the scheduled recruitment period already completed. Each matched control is to be recruited into the study shortly after the corresponding case.

8.6 DATA MANAGEMENT AND MAINTENANCE

The CCC data management staff have designed and implemented the distributed data management system to be used in the Clinical Center as well as the data management system for the CCC. The Clinical Center staff are responsible for data entry, data editing, and corrections, if

necessary, of all case and control study forms. These procedures are described in Volume III of the ACCESS Procedures Manual.

The CCC staff are responsible for retrieving the data, and storing and analyzing all received study data. CCC staff use microcomputers and a central workstation on a local area network for the study.

8.6.1 Data Management Staff

CCC staff collaborate with Clinical Center staff in the operation of a distributed data management system dedicated to ACCESS. Designated CCC staff interact with Clinical Center staff to maintain the operations of the distributed system. Since the CCC has microcomputers identical to the Clinical Center machines, the CCC staff are able to "walk through" Clinical Center problems. In the event Clinical Center staff report a hardware failure (e.g., damage to a hard drive), steps are taken immediately to provide a loaner machine and replace the damaged hardware to avoid interruption to Clinical Center activities. A software package allowing remote access to the microcomputers in the Clinical Center is used by CCC staff for resolution of problems and to poll Clinical Center microcomputers for transmission of accumulated and corrected data.

8.6.2 Form Editing

Forms are edited for acceptable codes, valid ranges and logical consistency by electronic checks during data entry at the Clinical Center and after the completion of data entry. Additional information on these procedures is given in Chapter 7. A form is available for transmission to the CCC only after completion of data entry. Forms are transmitted to the CCC on a regular schedule. Once the form is received in the CCC, the data are edited more extensively.

Study data are edited in the CCC for completeness, consistency with previous and concurrent data from the same patient, and numerical values outside of specified limits. Edit queries for a given form are printed and sent to the appropriate Clinical Center. Clinical Center staff correct the forms using screen images of the data form. All corrections made are electronically audited. The audit file includes the old and new values for the field, date of the correction and who

soon as responses to edits have been made and accepted. Next, the form is subjected to the local edit and then transmitted again to the CCC.

8.6.3 Protocol Adherence Aids from Data Management System

The CCC staff prepare and distribute protocol adherence aids using the central data management system. These protocol adherence aids include lists of cases and controls enrolled in the study on a biweekly basis with dates of next expected visit or contact for cases, notation of cases for whom controls must still be recruited and notation of specific data forms not yet entered for each case and control. Clinical Centers are notified weekly of delinquent data entry of Form 09s.

8.7 DATA ANALYSES

Details of the data analysis plan are contained in Chapter 11.

8.8 DATA REPORTING

CCC staff will assist, if requested, the participating Clinical Center staff in the preparation of publications which have received prior approval according to study procedures (see Chapter 5 of the ACCESS Protocol). Upon request of the National Institutes of Health (NIH) any and all of the above data are made available to the NIH to access and utilize at any time after the completion of the ACCESS investigation. At that time any and all data requested by the NIH are transferred to the National Heart, Lung and Blood Institute (NHLBI).

8.9 PATIENT PRIVACY, CONFIDENTIALITY OF DATA, AND DATA SECURITY

Because of the importance of protecting study data at the CCC from theft or unauthorized perusal or alteration, access to computer files is restricted through the use of passwords. Protection of the computer files from catastrophic loss is accomplished by a backup system.

To maintain patient privacy, the study records submitted to the CCC do not contain participants' names, addresses or other identifying information. Each participant record is identified by a unique ID (identification) number and participant's initials. Names and addresses

corresponding to the identifying codes are kept on file at the Clinical Center on a special form (ACCESS Form 01, Participant Information).

CCC staff utilize a variety of safeguards to protect the study from catastrophic loss of data. There is routine back-up of all ACCESS files in the Clinical Centers. In the CCC, the databases are archived on a daily basis. Other files including programs used for all data management functions are fully archived once every week with an "incremental" back-up daily. An incremental back-up is one in which only files that have been modified are archived. The back-up system is designed to permit the restoration of the system with a minimum expenditure of time and money should any file be destroyed by a man-made or natural disaster. Prior to any major change in the operating system, back-up tapes of the main database are created and saved for a minimum of six months.

Copies of analysis files and programs used in the preparation of scientific presentations and publications are retained for the duration of the contract and stored off site. The analysis files include the programs and procedures that are utilized to extract the data from the database. CCC staff provide a computer program on the distributed data management system for routine use by Clinical Center staff to archive locally the database and programs and copy them to tape.

8.10 QUALITY CONTROL

8.10.1 Quality Assurance of Clinical Center Data

Clinical Center personnel are trained at a central location or are instructed by a certified staff member on the methods to use the ACCESS distributed database. As part of the certification process, they enter the data for selected forms (see Chapter 10), using completed forms provided by the Clinical Coordinating Center. The data records from these forms are compared to the master file at the Clinical Coordinating Center and discrepancies noted.

Verification of Demographic Characteristics of Cases and Controls

Before a search for a potential control for a given cases is initiated, Clinical Center staff must confirm the age, gender, and ethnic origin for the case by data entry of the Form 09. The Form 09 contains the demographic characteristics sent to the CCC by means of the ATRS as well as on the Case Eligibility Form (Form 02). The request for the search begins only after appropriate Clinical Center staff confirm the demographic characteristics of the case as reported on the Form 09. After enrollment of a control the age, gender, and ethnic origin of the control are confirmed and compared with the characteristics of the matching case to verify that there have been no errors in the selection of the control. Any discrepancies are brought to the attention of the appropriate Clinical Center to ascertain whether the error was a result of a data entry error or whether some other mistake has been made.

Data Entry

A randomly selected sample of all data collection forms are requested periodically from the Clinical Centers to be sent to the CCC for independent data entry. Data items from the sample forms and the corresponding information entered into the local database are compared to those keyed at the CCC. Discrepancies are resolved with the data entry personnel at the Clinical Centers. Error rates for the various data items are tabulated by type of form, by Clinical Center, and by CCC staff. These tabulations are included in the Quarterly Performance Reports. Initially, a sample of forms was selected each week to obtain a 20% sample but this was reduced to a selection of forms once a month to collect a 10% sample after the percent of discrepancies was approximately 0.5%.

Interviews

Once each quarter the CCC staff randomly select one case and one control from each Clinical Center for review. The Principal Investigator and Research Coordinator at each Clinical Center are requested to review selected items from selected forms on the interview tapes and compare the information on the tapes with the information on the completed study forms and entered into the local data management system. CCC staff provide a computer printout of the

information in the local data management system for the items being reviewed. Any discrepancies are noted on the computer printout. The Principal Investigator and Research Coordinator also assess the overall quality of the interview and record their assessment on a Review of Tape Recorded Interview Form (Form 41). The annotated computer printout and the completed Form 41s are returned to the CCC for evaluation. Site (or Audit) visit teams during the visits reviewed tapes for selected cases and controls and compared the interview data with data on the study forms and in the database as described above (see Section 8.10.4 below).

8.10.2 Quality Assurance of Information Stored in Computer Database

All forms are extensively edited at the Clinical Center, and all corrections made at the Clinical Center in response to edit messages are recorded. The central edit at the CCC provides a more extensive check of the data submitted by the Clinical Center. To test edit programs, a mock set of study forms which contain errors and inconsistences are used. The edit program is also run on a few forms received from the Clinical Centers and the edit output is carefully checked. If that test indicates no problem, the edit program becomes part of the usual maintenance procedure, but the edit output continues to be checked for a period of time before deciding the program has been adequately tested.

The validity of information on the computer master file is ascertained by means of a form audit. This is a structured procedure to compare (for a sample of each type of study form) the information on actual patient records with a printout of the record as entered on the computer master file. If master file problems are identified as a result of the audit, required corrective action is taken. Any major discrepancies are discussed with the staff and appropriate changes are made to resolve these problems.

Printouts listing baseline and follow-up values for important study variables of individual patients are generated. These printouts are prepared so that site visitors to a Clinical Center may compare the printouts for selected patients against the original Clinical Center records. All discrepancies are noted and appropriate steps taken to resolve and rectify these problems.

8.10.3 Performance Reports

Performance of the Clinical Centers with respect to case and control recruitment is assessed in weekly reports. These reports include the number of cases and controls enrolled to date and ratio of this number to the number who should have been enrolled to date given the scheduled recruitment period already completed. Each matched control is to be recruited into the study shortly after the corresponding case. The CCC each month provides information about the number of women and minority cases being recruited into the study. Performance in other areas are assessed by consideration of the following at quarterly intervals:

1. Average differences and ranges in time between identification of cases and matched controls are presented for each Clinical Center.
2. Number of study forms for cases and matched controls for which the data are past due at the CCC, based on each case's date of enrollment.
3. Number of study forms for cases and controls that have passed the first edit and that have passed current edit.
4. Specimens which are past due at the Central Repository.
5. Studies (e.g., pulmonary function tests or chest X-rays) which are required in the Protocol but were not performed.
6. Number of Protocol violations.
7. Percentage of cases with missed visits and percentage of cases who are inactive, i.e., no longer willing or able to have their regular examinations or visits.

The CCC staff compare performance and quality of submitted materials for items such as forms past due, studies not performed, or specimens improperly prepared or labeled, etc. among Clinical Centers. The CCC staff also compare each Clinical Center's quarterly performance to its own past performance and to agreed upon study standards which determines whether the Clinical Center's performance is outside study standards or whether the level of performance has worsened substantially compared to its previous record. Study standards have been set by weighing how

crucial an item is to the study Protocol and the levels of performance which past experience has shown to be attainable.

In addition to the above analyses, quarterly reports include summary statistics for each Clinical Center. Large changes in these statistics from quarter-to-quarter within a Clinical Center may indicate changes in the way data are being collected. Comparison of these statistics across Clinical Centers could suggest either differences in how data are collected or differences in the patient population, and may prompt further investigation.

8.10.4 Site (or Audit) Visits

In addition to preparing the Clinical Center performance monitoring reports, the CCC staff insure data quality by conducting periodic site visits (or audit visits) to the Clinical Centers. The data on cases' (or controls') records are compared against listings of data residing on the main database at the CCC as of the date of the request for a site visit. Using the data as of the site visit request should prevent any audit-prompted revisions of the data form(s). Plans for site visits and site visit requests are provided to the Study Chairperson and NHLBI Project Office on a schedule agreed to with the NHLBI Project Office. Recertification of Clinical Center personnel responsible for key areas of data collection may also be performed during site visits.

Each ACCESS Clinical Center and the Clinical Coordinating Center were site visited during the first year of patient recruitment. The Site Visit Team included the Study Chairman or Vice Chairman, the NHLBI Project Officer, a Principal Investigator from another Clinical Center, a Research Coordinator from another Clinical Center, CCC staff, and for some visits the NHLBI Contract Officer. Some Clinical Centers were site visited a second time. An Audit Visit to each Clinical Center that did not have a second Site Visit was conducted by CCC staff approximately one year after the Site Visit to that center. Site (Audit) Visit reports were submitted to the Principal Investigator of the Center, the Executive Committee and the Data and Safety Monitoring Board.

During the Site (or Audit) Visits, the team conducted an audit of the accuracy of data reported from the medical record for a random sample of cases. For this purpose, the chest X-ray

reports, pathology reports, and pulmonary function tests for all enrolled cases were reviewed and compared with the data recorded in the database. The consent forms for cases and controls were also reviewed. The tapes for the interviews of two cases and two controls were reviewed to compare the interviewer's responses to the data recorded on the study forms and on the computer printout from the database for each case or control. The Clinical Center staff were notified prior to the visit what information should be available (e.g., forms, medical records, tapes, etc.). Differences between the data items in the forms or medical records and the database were brought to the attention of the Clinical Center staff and resolved. The results of the audit were submitted to the Principal Investigator of the Clinical Center, the Executive Committee and the Data and Safety Monitoring Board.

8.10.5 Quality Control for Core and Special Study Laboratories

The CCC uses submission of duplicate, blinded specimens to monitor the reliability of test results from each Core and Special Study Laboratory. Results from the duplicate sample submissions are compared to assess reliability using the Kappa statistic for categorical data; and Spearman's or Pearson's correlation coefficient for ordinal or continuous data. The intra-class correlation coefficients are calculated for continuous and ordinal measures.

As part of the site visit to each Clinical Center with a Special Study Laboratory that uses PCR technology, the visitors reviewed the Laboratory's methods for minimizing contamination of specimens since this assay is noted for widely varying results if exact sterile techniques are not used. The Laboratory provides documentation of appropriate methods to verify that each sample is analyzed with a minimum chance of contamination.

The CCC staff in collaboration with the DNA Core Laboratory staff developed the procedures for preparing duplicate specimens of plasma and DNA for a quality control program to monitor the performance at ACCESS Special Study Laboratories at the University of Pennsylvania, the University of Iowa, and the University of South Carolina. These procedures also prepare specimens for quality control of any other laboratories designated to process specimens which are stored at

the Central Repository. The procedures are similar to the usual procedures for preparation of ACCESS samples except that one half of the prepared aliquots is labeled with a quality control specimen number rather than the specimen number assigned in the ACCESS Clinical Center. With an odd number of aliquots the lesser number of aliquots is given quality control numbers. The sample selected for the quality control program are all specimens received in the DNA Core Laboratory on randomly selected dates as directed by the CCC. On the dates designated by the CCC staff for preparation of quality control specimens, all purple tubes (for a given case or control) labeled for DNA plasma processing have half the prepared aliquots labeled with a specimen number assigned at the Clinical Center and the other half of the plasma aliquots labeled with the quality control specimen number. Similarly, half the aliquots of DNA are labeled with the assigned specimen number and half are labeled with the same quality control number as designated for the plasma quality control specimen. The DNA cell pellets prepared for the University of Iowa are prepared in a similar fashion. On the designated quality control days, two specimens are prepared for the University of South Carolina (one usual specimen and one quality control specimen). The two specimens prepared for the University of South Carolina each have two micrograms of DNA. After 20 pairs (usual and duplicate quality control specimens) have been processed, the results for the usual specimen and the duplicate quality control specimen are compared and a summary of the differences sent to the appropriate Core Laboratory Director for review and any other action appropriate based on the results of this program.

8.10.6 Quality Control of the Clinical Coordinating Center

CCC staff perform the following activities to insure the quality of the data and analyses.

1. Persons (such as the Principal Investigator and Co-Investigator) not involved in the development of the data management system complete a few study data forms, making deliberate errors. These forms are keyed and processed through the data editing system to see if all of the errors are detected by the data management system.

2. A sample of original data forms are compared against the data on the CCC computer (as part of the site (or audit) visit procedures described in Section 8.10.4). This procedure is used not only to detect data entry errors, but also to detect problems with the editing software developed and implemented by the CCC.

3. For each continuous variable on the database, a point frequency distribution (i.e., a tabulation of the frequency of occurrence of every distinct value) is obtained. This helps to identify many types of abnormalities in continuous data such as: (a) digit preferences; (b) bi-modality or other distinctive shapes of the distribution; and (c) outliers (i.e., extreme values distinctly separate from the rest of the distribution).

   Once an observation is identified as an outlier, the first step is to go back to the original records and determine whether a recording or keying error was made. If such a value has been verified as correct through the distributed data system, the CCC Co-Investigator inquires as to the reasons an outlier exists. The question of whether or not to include the value in the data analysis depends upon the nature of the analysis. There is no reason to exclude the value if the analysis is a count of the number of participants having a value exceeding a given cut-point. However, if measures of central tendency and variability are being computed, or if correlation or regression analyses are being carried out, non-parametric statistics may be preferable.

4. New analysis programs (including those that utilize standard statistical packages such as SAS) are tested by running these programs on a small subfile of 10 or 20 participants and independently reproducing the tabulations and statistical calculations from the original data. These procedures help to assure that the correct variables have been selected from the analysis file, the variables and cut-points have been defined properly, and that transformations of the original variables on the analysis file have been formulated correctly.

5. When preparing data reports, different tables which may have resulted from a variety of analysis programs, are checked for consistency of denominators.

8.11 CLINICAL COORDINATING CENTER CONTACTS

CCC staff serve as a resource for all ACCESS Clinical Center staff and Core (Special Study) Laboratory staff. We recommend that questions concerning the Protocol and study procedures be sent to the CCC by e-mail (see ACCESS Address Directory) and CCC staff will return a response by e-mail within one working day of receipt of the query. Procedures for submitting e-mail requests for Protocol clarifications are described in Volume III of the ACCESS Procedures Manual. Questions on other study issues may be directed to appropriate CCC staff (Director, Deputy Director, Coordinator or Data Management staff). Names and telephone numbers of current CCC staff are given in the ACCESS Address Directory.

CHAPTER 9

PROCEDURES FOR IDENTIFICATION AND ENROLLMENT OF CONTROLS

9.1 INTRODUCTION

The Random Digit Dialing (RDD) Interview Group at Telesurveys Research Associates in Houston, Texas is responsible for making calls to designated telephone numbers to identify individuals who match specific cases on age (no more than five years older or younger), gender, and self-designated race (black, white, other) and who are willing to be considered for the study by agreeing to be interviewed by the appropriate Clinical Center staff. The procedures for generating the lists of telephone numbers to be called, the schedule and number of calls made to each number on the list, the interviewing scripts used for the calls, the procedures for transferring information between the RDD Interview Group and the Clinical Coordinating Center (CCC), and the information sent to the Clinical Centers by the RDD Interview Group are described in this chapter. An overview of these procedures is given in Figure 9-1.

9.2 PROCEDURES FOR INITIATING SEARCH FOR POTENTIAL CONTROL

9.2.1 Generation of Telephone Lists

Each week on Thursday the CCC staff request a list of 200 telephone numbers from a subcontractor (Survey Sampling, Inc.) for each confirmed case enrolled during the past week, that is, each case for whom the Form 09 was entered into the Clinical Center database during the past week (see Exhibit 9-1). The subcontractor is given the ten-digit telephone number of the case (identified only by the case's identification (ID) number concatenated to a sequence number). The last part of each request includes incremental updates of case telephone numbers, control telephone numbers and telephone numbers of individuals who should not be called. These numbers are to be added to a roster of numbers maintained by the subcontractor (and at the CCC); this roster is used to exclude numbers from the lists to be used by the RDD Interview Group as described below. The weekly notice also contains a list of cases for whom controls have been enrolled and the files can be closed.

The subcontractor generates batches of telephone numbers using the following procedures. The first six digits of the case's ten-digit telephone number are fixed (made constant). A random sample of 1000 numbers between 0000 and 9999 are generated. These numbers are concatenated with the fixed leading six digits to yield 1000 telephone numbers. The numbers are systematically divided into batches of 200 numbers. The first 200 numbers are compared to a roster of telephone numbers for currently enrolled cases and controls and individuals who have been contacted previously and have stated that they do not want to be called again by ACCESS staff as well as a national listing of business numbers. Any telephone numbers on the list of permuted numbers that match telephone numbers on the above rosters are deleted. The remaining numbers are stored in a special file which may be accessed electronically by the RDD Interview Group and the CCC via computer modem accounts. This file of numbers for the first batch (or the next batch if the RDD Interview Group requires more than one batch to identify a control) is placed in the special file no later than Monday morning of the week after the request was sent.

If a potential control is not identified by the RDD Interview Group during a call to the numbers in the first batch, another batch of numbers is requested for this case by CCC staff. The next 200 numbers for this case are screened (as described above) and the remaining numbers are stored in the file which may be accessed electronically.

In some situations, a case is recruited from a rural setting and the exchange number for the case does not have many active telephone numbers from which to select a control. This is detected in processing the first batch of numbers. RDD Interview Group staff notify the CCC of the low density exchange and CCC staff request that the subcontractor make available all remaining numbers for this case; that is, the batch size is increased to a maximum of 800. If the RDD Interview Group staff use all of the numbers in that batch, an additional sample of 1000 numbers will be requested, and all 1000 numbers are made available to the RDD Interview Group.

9.2.2 Use of ZIP Code to Generate Additional Telephone Numbers

If at least 1,000 numbers from the case's exchange have been exhausted in a search for a potential control, a second sample of random digit dialing numbers will be generated using a ZIP Code analysis. In this analysis, CCC staff notify the subcontractor that a ZIP Code analysis for a case should be performed. This notification is part of the regular weekly contact. The procedures for the ZIP Code analysis are as follows.

1. The subcontractor generates a ZIP Code analysis sheet for each listed case. A copy of the ZIP Code analysis sheet is sent by facsimile transmission (FAX) to the CCC.
2. The ZIP Code analysis sheet is a list of exchanges that cover the ZIP Code. The list is sorted in descending order by percentage of listed numbers in the exchange that are in the ZIP Code. The first k (e.g., 10) exchanges that cover 90% of the listed numbers in the ZIP Code are selected for use in the ZIP Code analysis sample.
3. The percent of listed numbers from the k exchanges that are in the ZIP Code is used to calculate a multiplier for the number of random digit dialing (RDD) telephone numbers to generate. This multiplier is the reciprocal of the proportion of telephone numbers from the k exchanges that are in the ZIP Code. For instance, when considering all of the listed numbers from 10 exchanges, 25% of the numbers are in the ZIP Code and 75% outside the ZIP Code. In this case the multiplier is 4. The multiplier is applied to the number 2000 to determine the total number of RDD numbers to generate. In the example, 8000 RDD numbers are generated.
4. A random number generator is used to create a sample of the last four digits of each RDD number to be generated.
5. The resulting sample is divided into k groups of equal size. The first group has the highest ranking area code and exchange (in terms of ZIP Code coverage)

appended to the front of the four-digit numbers. The next group of four-digit numbers has the next highest ranking area code and exchange appended to the front of the RDD four-digit numbers for the group. This proceeds until the total number of RDD four-digit numbers generated are ten-digit telephone numbers.

6. Any number from this sample that is known to be outside of the ZIP Code is deleted from the list.
7. The remaining numbers are sorted into a random order and divided into batches of 1,000 numbers.
8. The first 1,000 numbers are compared to the list of business numbers and any matches are deleted from the list. If the process of business number comparison places the numbers in a deterministic order, the list is re-sorted to a random order.
9. The batch (<1,000 numbers) is sent to the RDD Interview Group for processing.
10. If the RDD Interview Group exhausts the first batch of ZIP Code numbers, a request is made to the CCC for the next batch from the file. This request is passed along to the subcontractor as part of the regular weekly contact between the CCC and the subcontractor. The subcontractor staff compare the next 1,000 numbers (nth from the list) to the business numbers, matches are deleted from the list, and the remaining numbers in that batch are sent to the RDD Interview Group.

9.3 IDENTIFICATION OF POTENTIAL CONTROLS BY THE RDD INTERVIEW GROUP

Each week on Friday (or Monday of the next week) the CCC staff send by facsimile transmission to the RDD Interview Group a notice of the cases for whom telephone numbers have been requested from the subcontractor that week. This notice (see Exhibit 9-2) contains the following information.

1. The name of the Clinical Center in which the case was recruited.
2. The special case identifier.

3. A lower age limit.

4. An upper age limit.

5. The gender of the case.

6. The self-designated race of the case.

The RDD Interview staff retrieve the stored batch of numbers for each designated case using the case identifier on the CCC notification. The information from the CCC on the demographic characteristics of the case and the telephone numbers are loaded into the computer assisted telephone interview (CATI) system. The first two digits of the case identifier are used to identify the script for the appropriate Clinical Center to be used for the search for a control for a given case. The RDD Interview Group uses a structured interview (see Exhibit 9-3 for model script) for each telephone call and records the outcome of each of these telephone contacts. The numbers are called in the order provided to determine whether there is an individual in the household for a given telephone number who matches the age, gender and self-designated race characteristics of a specific enrolled case. If there is a potential control candidate, the individual is apprized of the purpose of the study, sponsorship and given a brief explanation of what is required of the participant and the individual is asked whether he/she will consider being interviewed by the appropriate Clinical Center staff. The RDD Interview Group notifies, by facsimile transmission, the appropriate Clinical Center and the CCC of each potential control who agrees to be interviewed (see Exhibit 9-4). Copies of these notices are destroyed by the CCC staff after the Clinical Center staff notify the CCC that a potential candidate is enrolled, and the Clinical Center staff have submitted data for this control or have notified the CCC that the potential candidate is ineligible or refused to participate. At the end of each day, CCC staff send by e-mail to each Clinical Center a list of notices of potential controls sent that day to the Clinical Center by the RDD Interview Group.

At least five calls are made to each telephone number if the first attempt results in no answer or a telephone answering machine. The timing is:

1. Weekday evening between 7:00 and 9:00 PM (local time);

2. Weekday day time between 9:00 and 5:00 PM (local time);
3. Weekday evening between 5:00 and 7:00 PM (local time);
4. Saturday between 10:00 AM and 5:00 PM (local time); and
5. Sunday between 1:00 and 6:00 PM (local time).

The RDD Interview Group staff process the batches of numbers prepared by the subcontractor according to the order in which they are listed. However, some of the calls are not answered by the appropriate person, and some are not answered the first time. In these situations, the CATI system establishes a time to call the number again, and the number is placed in a waiting list as the system moves to the next number. As the process of calling the numbers in a batch proceeds, the rate of dialing new numbers or redialing numbers on the waiting list is higher than the rate of numbers that are closed-out (ineligible person, business number, or phone not answered after five tries) of the system. As the process of dialing the numbers nears the end of the batch, the rate of dialing new and wait-list numbers is reduced and there are not sufficient calls to keep the operators fully occupied. This inactivity becomes more pronounced as the end of the batch is neared. RDD Interview Group staff have determined that the idle time is too great when 72% of the numbers in a batch have been closed-out. At this point a new batch of numbers is requested. The outcome of each telephone call and each batch of telephone numbers is transmitted to the Clinical Coordinating Center on a floppy disk.

On a weekly basis, the Clinical Coordinating Center notifies the RDD Interview Group of the status of each potential control who has been enrolled or deemed to be ineligible or refused to participate. If a potential control is enrolled, the RDD Interview Group closes out the appropriate batch of telephone numbers. If the potential control has refused or was ineligible, the RDD Interview Group resumes the search for a potential control with the first unused number of the last batch of telephone numbers for the unmatched case.

9.4 CLINICAL CENTER PROCEDURES FOR CONTACTING AND ENROLLING POTENTIAL CONTROLS

As soon as possible after receiving notification that the RDD Interview Group has

identified a potential control, Clinical Center staff attempt to contact the potential control by telephone and also send a letter to the potential control (see Chapter 1). The letter provides an explanation of the study and informs the potential control that someone will be calling him/her. It is important to make contact with the control quickly (within two days is preferable, but for all controls the period between identification and Clinical Center contact should be no more than seven days). When telephone contact is made, the interviewer identifies himself/herself and states the purpose of ACCESS. The interviewer verifies that the potential control matches the case for age (± 5 years), gender and self-designated race (white, black, other). The interviewer gives the potential control a brief description of the information that will be collected from the individual and explains that blood specimens will also be collected. The individual is given an explanation of the costs that will be defrayed by the study. If the control expresses interest in ACCESS, a visit is scheduled so that the informed consent can be signed by the control and a witness. If the potential control is determined to be eligible at the visit, the control is enrolled and interviewed by Clinical Center staff, and they notify the Clinical Coordinating Center of the enrollment of a control using the ATRS. If the potential control does not complete the visit, or is determined to be ineligible, the Clinical Center staff notify the CCC of the refusal or ineligibility status of this candidate using the ATRS, and CCC staff initiate the procedures to resume the search for a control.

FIGURE 9-1

Overview of Procedures for Identification and Enrollment of Controls

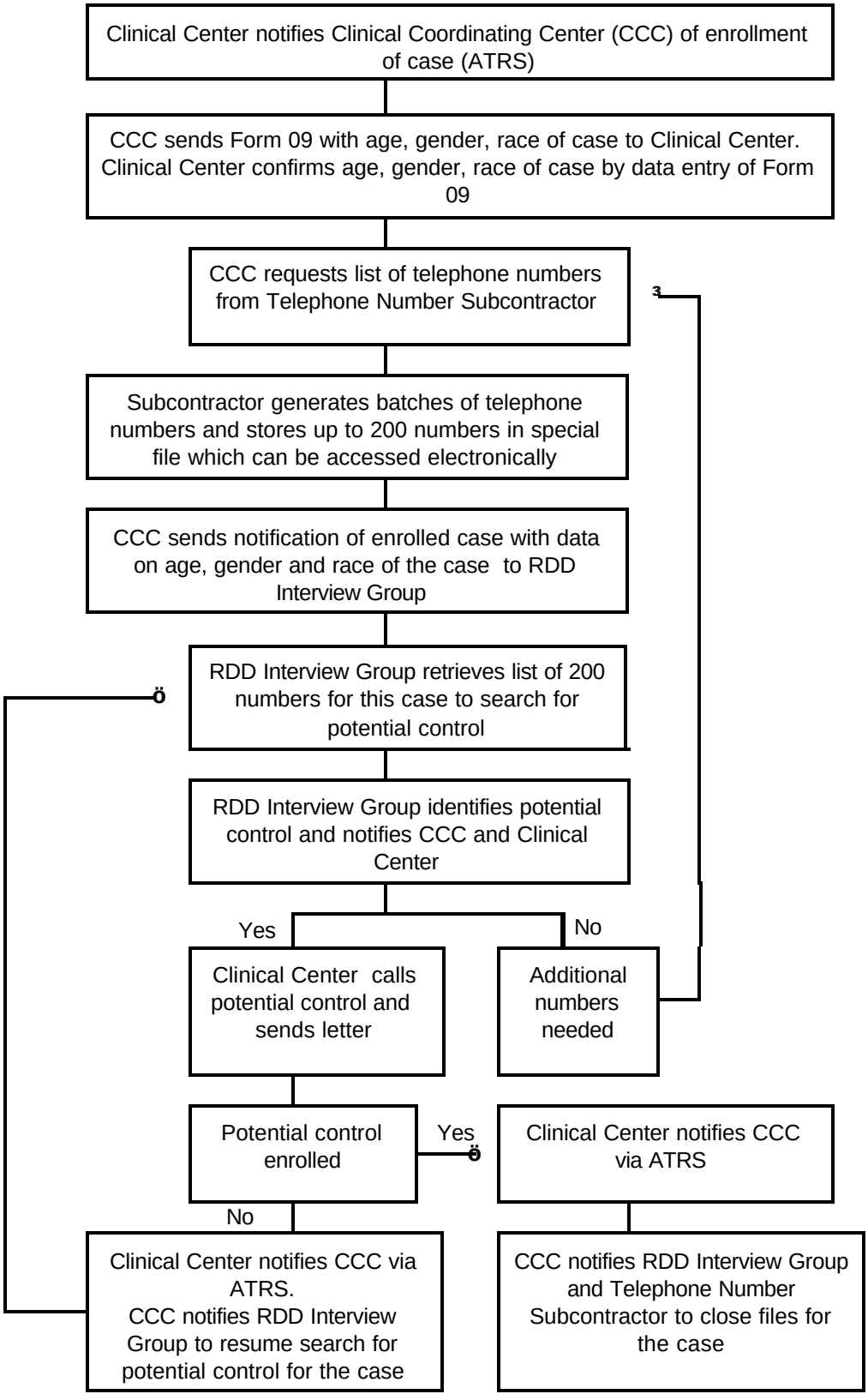


EXHIBIT 9-1 January 27, 1997

SAMPLE TELEPHONE BATCH REQUEST

Ms. Lisa Christiansen
Survey Sampling, Inc.
One Post Road
Fairfield, CT 06430

FAX NO.: (203)254-0372
TEL. NO.: (203)255-4200

RE: Telephone Batch Requests as of December 17, 1996

A. **Initial** batches are requested for the following 1 telephone numbers:

Case Identifier (Constant)	Case Telephone No.
1. 04000020010	1. 410XXXXXXX

B. **Additional** batches are requested for the following 2 telephone numbers (**n**th from balance file):

Case Identifier (Constant)	Case Telephone No.
1. 05000030003	1. 803XXXXXXX
2. 09000040004	1. 515XXXXXXX

C. The following 0 telephone numbers should be purged from all future control batches:

None

As agreed, these numbers should be available by 8:00 a.m. Monday morning following this request.

Problems or questions should be directed to Pat Wilkins at (410)435-0663.

cc: Martha Canner
Christopher Donhauser
Genell Knatterud, Ph.D.
Donna Stevens
Michael Terrin, M.D.
Bruce Thompson, Ph.D.

CLINICAL TRIALS & SURVEYS CORP.

EXHIBIT 9-2

SAMPLE NOTIFICATION OF CASE ENROLLMENT

January 17, 1997

M E M O R A N D U M

TO: Richard D. Jaffe, M.A.
Telesurveys Research Associates

FROM: Bruce Thompson, Ph.D. and Patricia Wilkins
ACCESS Clinical Coordinating Center

SUBJECT: Notification of Case Enrollment for Week Ending January 14, 1997

Attached please find age, race and gender information for __1__ new case enrolled during the period referenced above.

If you have questions relating to any information provided herein, please call Martha Canner at (410) 435-0663.

cc: Martha Canner
Christopher Donhauser
Genell Knatterud, Ph.D.
Michael Terrin, M.D.

EXHIBIT 9-2 (Continued)

SAMPLE NOTIFICATION OF CASE ENROLLMENT

12/03/96

A CASE CONTROL ETIOLOGIC STUDY OF SARCOIDOSIS

ENROLLED CASE PROFILE

Clinic Name:	CLINICAL TRIALS & SURVEYS CORP.
Case Identifier:	99900020010
Age Range:	56 to 66
Gender:	FEMALE
Self Designated Race:	WHITE

EXHIBIT 9-3

MODEL TELEPHONE INTERVIEW SCRIPT

Hello, my name is _____. I am calling for the University of _____ to collect information for the National Institutes of Health. We are trying to learn the cause of a disease that has afflicted someone in your community. The University of _____ and the National Institutes of Health want to find out about the general health and exposures of people in your community to be able to see what is different from you about the person in your community who has the disease that we are studying. People who complete the interview and give a blood sample will be paid __ dollars.

Are there any (white, black, minority other than black), (men, women), between the ages of ___ and ___ in your household?

[If Yes: continue with question 2.]

[If No: skip to question 6.]

2. How many are there?
3. Could you please give me the current age and name each of the (white, black, minority other than black), (men, women), between the ages of ___ and ___?

   [Enter age(s) and name(s).]

   [Enter name.]
4. [If more than one household member matches, follow sampling procedure.]

   [Is there a match in this household?]

   [If Yes: circle the individual's name and skip to question 6.]

   [If No: continue with step 5.]
5. Not eligible statement: As it turns out, there are no individuals eligible for this study in the household.

   [Ask questions 6-8 and end the interview.]

EXHIBIT 9-3 (Continued)

MODEL TELEPHONE INTERVIEW SCRIPT

6. Just for my records, I need to verify that the number I dialed is (read number). Is this correct?
7. And is this number for home use only -- or for home and business use? [If business only, end with notation that this is not a residential number.]
8. And is this household located in (eligible geographic area)? (Make sure household is in eligible area.) If eligible, go to Item 10.
9. End the phone call: These are all the questions that I have. Thank you very much.

   Wrong phone number: I am sorry. I dialed the wrong number. Thank you very much.

   Wrong geographic area: Your household is just outside of our survey area and too far away for individuals to join in the study. These are all the questions I have. Thank you very much.
10. [If an individual is sampled: continue with the enrollment script.]

    Enrollment Script

If an eligible individual is identified in the household ask to speak to the individual then. If the individual is not available arrange a call back time. Note the best times for the call back on the log sheet.

When speaking to the individual to be recruited: Hello, my name is _____. I am calling for the University of _____ to collect information for the National Institutes of Health. We are trying to learn the cause of a disease that has afflicted someone in your community. I am calling to let you know that you have been randomly selected for our study. We are trying to find out the differences in general

EXHIBIT 9-3 (Continued)

MODEL TELEPHONE INTERVIEW SCRIPT

health and exposures between this person and other people in your community that explain why another (white, black, minority other than black), (man, woman), about your age in your community has a disease called sarcoidosis. If you agree, a researcher from the University of _____ will call you to set up an appointment for an interview. At the end of the interview (he, she) will ask for a blood sample to send to the National Institutes of Health. The entire interview should take about two hours. We will give you ____ dollars after you complete the interview and the blood sample has been collected.

If questions asked on how selected: For our study, we needed to select a sample of people from the population at large who are like the person who has the disease in age, race, and gender. Your phone number was picked randomly by a computer. We did not have your name. We were able to contact you by calling this telephone number.

At this time, I am just calling to arrange for the researcher at the University of _____ to contact you directly. (He, she, name) will have more details about the interview. I can tell you that we are flexible about the time and location of the interview.

1. Note comments/questions/other helpful observations.
2. _____ enrollment status.
3. Obtain contact information: I need to get some basic information so that University of _____ researcher can call you.

   After obtaining address: the University of _____ researchers are going to send you a letter which provides more information about the study.
4. If refusal, find out why. Always leave door open for re-contact.

EXHIBIT 9-4

ACCESS POTENTIAL CONTROL NOTIFICATION

TO: ACCESS Clinical Coordinating Center FAX No. (410)435-0689

ACCESS Clinical Center _____ FAX No. _____

FROM: Telesurveys Research Associates

DATE: _____

SUBJECT: NOTIFICATION OF POTENTIAL CONTROL

Notification is made of the location of a potential control for the following case:

Case Identifier No. _____

The potential control is:

Name _____

Address _____

_____

Telephone No. _____

Date of RDD contact _____

Time of RDD contact _____

Any questions related to information provided on this sheet should be addressed to Martha Canner at 410-435-0663

CHAPTER 10

TRAINING AND CERTIFICATION PROCEDURES

10.1 INTRODUCTION

Each ACCESS Clinical Center must be certified for screening patients and performing physical examinations and spirometry in order to recruit and examine cases and controls for ACCESS. The staff who will be performing ACCESS test procedures, interviewing ACCESS cases and controls, and completing ACCESS data collection forms and performing data entry must attend a training session or be trained by a certified person and demonstrate proficiency in the procedures they will perform during the study in order to be certified.

10.2 CLINICAL CENTER CERTIFICATION

In order for an ACCESS Clinical Center to be certified to screen cases, the Clinical Center must submit to the Clinical Coordinating Center (CCC) documentation of Institutional Review Board (IRB) approval of the ACCESS Protocol and Consent Forms. Copies of the Consent Forms were submitted to the Clinical Coordinating Center for review before recruitment was started and are sent to the Clinical Coordinating Center whenever the forms are revised. Notification of IRB approval is also required annually. Conflict of Interest Statements (Appendix A) for appropriate ACCESS staff members are required for certification and these forms are to be submitted annually. In addition, the ACCESS Clinical Center must have at least one certified research coordinator, one physician certified to perform physical examinations, one individual certified to use the Automated Telephone Response System (ATRS), and a certified Spirometry Laboratory.

In order to be certified to enroll cases and controls into ACCESS, the Clinical Center must have the facilities and staff to collect, analyze and ship blood specimens, certified staff to interview cases and controls, and the facilities for the distributed data management system at the Clinical Center. When all requirements have been completed, the Principal Investigator of the Clinical Center notifies the Clinical Coordinating Center by submitting a completed Request for Clinical Center Certification for Participation in ACCESS (Form 120 - see Exhibit 10-1).

10.2.1 Spirometry Laboratory

The Spirometry Laboratory in the Clinical Center Pulmonary Function Laboratory should adhere to the American Thoracic Society standards (Crapo et al, 1995) for performance and quality control of spirometry. The Principal Investigator of the Clinical Center notifies the Clinical Coordinating Center that the designated Spirometry Laboratory meets ACCESS requirements by submitting a completed Request for Certification, ACCESS Spirometry Laboratory Form (Form 103 - see Exhibit 10-2). The quality control procedures for performing spirometry in the local Pulmonary Function Laboratory should be documented in a log as follows:

a) 3L calibration syringe check daily;

b) Leak check daily;

c) Linearity check weekly;

d) Repeat spirometry performed on healthy laboratory staff member(s) or other volunteer(s) to check for consistency monthly; and

e) Spirometry thermistor compared to a reference thermometer monthly.

This log must be available for review during site (or audit) visits.

10.3 CERTIFICATION OF INDIVIDUAL ACCESS STAFF MEMBERS

10.3.1 Research Coordinator / Interviewer

In order for a person to be certified as a Research Coordinator / Interviewer in ACCESS, the person must attend a training session, or be trained and tested by a certified Research Coordinator/Interviewer. The certification process includes a test on the methods and procedures of ACCESS and knowledge of the ACCESS interviewing procedures. The person completes one successful practice session registering a case or control using the Automated Telephone Response System (ATRS). The person completes and submits to the CCC two copies each of the ACCESS Demographics and Medical History Questionnaire (Form 10), Family History Questionnaire (Form 22), and the Occupational and Recreational Questionnaire (Form 12) using data from sarcoidosis patients already known at the Clinical Center. The completed forms are submitted with a completed

Request for Certification, Research Coordinator/Interviewer Form (Form 101 - see Exhibit 10-3). The forms are reviewed at the CCC for correctness and attention to study guidelines; a call is placed to the applicant to discuss any problems. Once the problems are resolved, the Clinical Center Principal Investigator is notified by mail that the Research Coordinator/ Interviewer has been certified.

10.3.2 Physical Examination Physician

The Principal Investigator of an ACCESS Clinical Center notifies the Clinical Coordinating Center that an ACCESS physician is certified to perform physical examinations on ACCESS patients by signifying that the physician understands the ACCESS protocol, including the procedures that he/she is to perform and has taken a test on the methods and procedures associated with the ACCESS protocol. A completed Request for Certification, ACCESS Physician Form (Form 102 - see Exhibit 10-4) is submitted to the Clinical Coordinating Center for each physician.

10.3.3 Data Entry Personnel

The individuals certified to enter data using the distributed data management system may be research coordinators or other designated Clinical Center staff. It is the responsibility of the Clinical Center Principal Investigator to determine who is responsible for collecting data, and who is responsible for entering data into the ACCESS database.

The person responsible for entering data must attend a training session or be trained by a certified data entry person. Once trained, the candidate must enter data for two forms each of the: Demographics and Medical History Questionnaire (Form 10), the Family History Questionnaire (Form 22), and the Occupational and Recreational Questionnaire (Form 12) using completed forms from the CCC that are sent to the Data Entry Applicant. The applicant notifies CCC staff that the form data have been entered, and these data are electronically transferred to the CCC database for further analysis. The records generated from the practice forms are compared to the study standard forms at the CCC, and the applicant is notified of any discrepancies. Once the material

has been received in a satisfactory format, the Clinical Center Principal Investigator is notified that the Data Entry Applicant has been certified and assigned a permanent certification number.

10.3.4 ATRS Staff

C-TASC staff have established a system to allow authorized personnel to practice a few registrations without actually entering a case. The same procedures are used for this practice session as for an actual registration except that: when requested to enter the Clinic Password, 9999 is to be entered rather than the Clinic Password that has been assigned to the Clinical Center. The ATRS identifies this call as a practice session. The instructions are the same as if a case were actually being registered or enrolled. The practice case ID (identification) number is 999-9999. Each individual authorized to register or enroll patients practices at least once to be certified to use the system for cases and controls. The practice session is to be performed during working hours, weekdays 9:00 a.m. - 4:00 p.m. so that problems can be resolved if they occur. At the end of the practice session, the system indicates the status of the practice session. The Principal Investigator of the Clinical Center notifies the Clinical Coordinating Center that an individual is eligible to be certified to use the ATRS by submitting a completed Request for Certification ACCESS ATRS Staff Form (Form 104 - see Exhibit 10-5).

The practice system will remain in place for the duration of the study. If Clinical Center staff periodically think they need some practice using the system after certification, or if new personnel are assigned to register cases and controls, the practice system can be used for this purpose.

10.4 RESPONSIBILITIES OF THE CLINICAL COORDINATING CENTER IN TRAINING AND CERTIFICATION

The responsibilities of the Clinical Coordinating Center in training and certification are as follows:

1. Assist in organization and presentation of training sessions.
2. Review of forms submitted by ACCESS personnel as part of certification requirements and communication of concerns to those personnel.

3. Coordinate results of review of certification materials submitted by personnel at Clinical Centers.
4. Maintain documentation of the various aspects of certification requirements which have been completed or need to be completed by Clinical Centers and individual staff.
5. Issue certification numbers to certified individuals.

EXHIBIT 10-1

**REQUEST FOR CLINICAL CENTER CERTIFICATION
FOR PARTICIPATION IN ACCESS
(Form 120)**

Clinical Center: _____ Clinical Center No.: ____ ____ ____

This form is to be completed signed, and submitted to the Clinical Coordinating Center by the Principal Investigator when the Clinical Center is ready to begin recruitment. In order to begin recruitment for ACCESS, each Clinical Center must have IRB approval and at least one staff member certified in the categories listed in Part I. The completed form will be reviewed by the Executive Committee. Permission to initiate patient recruitment is contingent upon approval of the Executive Committee and the NHLBI Contract Office.

I. Staffing

	ACCESS Staff No.	Certification/Registration Month Day Year
A. Research Coordinator(s)		
_____	___ ___ ___-___ ___	___ ___ ___ - ___ ___ - ___ ___ ___ ___
_____	___ ___ ___-___ ___	___ ___ ___ - ___ ___ - ___ ___ ___ ___
B. Physician(s) certified to perform physical examinations on ACCESS cases		
_____	___ ___ ___-___ ___	___ ___ ___ - ___ ___ - ___ ___ ___ ___
_____	___ ___ ___-___ ___	___ ___ ___ - ___ ___ - ___ ___ ___ ___

C. Certified Spirometry Laboratory

Clinical Center Spirometry Laboratory adheres to performance and quality control guidelines of the American Thoracic Society ( )

Quality control procedures in Spirometry Laboratory documented in log as specified in Chapter 10 of Procedures Manual Volume I ( )

Principal Investigators or Co-Investigator will review all spirograms for ACCESS to assure tracings are adequate ( )

D. Certified interviewer(s)

_____ ___ ___ ___-___ ___ ___ ___ ___ - ___ ___ - ___ ___ ___ ___

_____ ___ ___ ___-___ ___ ___ ___ ___ - ___ ___ - ___ ___ ___ ___

E. Certified Data Management Preparations

Secure location for ACCESS Microcomputer ( )

Direct line for Data Transmission Telephone Number (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Area Code

II. Submission of Documents

Informed Consent Form ( )

IRB Approval ( )

Conflict of Interest Forms for Principal Investigator, Co-Investigators, Research Coordinators ( )

ATRS Application ( )

Principal Investigator Assurances

All phases of certification have been completed except certification of data management staff ( )

_____ ACCESS Staff No.: ___ - ___ ___
Principal Investigator Signature

Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

EXHIBIT 10-2
REQUEST FOR CERTIFICATION
ACCESS SPIROMETRY LABORATORY
(Form 103)

Clinical Center:_____ Clinical Center No.:___ ___ ___

To be certified, the ACCESS Spirometry Laboratory must meet the following requirements:

1. The laboratory adheres to performance and quality control guidelines of the American Thoracic Society *(Crapo, et a., 1995. Am J Respir. Crit. Care Med. 152:1107-1136.)*

2. The following quality control procedures are documented in a log:

    a) 3L calibration syringe check daily;
    b) Leak check daily;
    c) Linearity check weekly;
    d) Repeat spirometry performed on healthy lab staff member(s) or other volunteer(s) to check for consistency monthly;
    e) Spirometry thermistor compared to a reference thermometer monthly.

Principal Investigator:

Signature: _____

Date: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

EXHIBIT 10-3
REQUEST FOR CERTIFICATION
ACCESS RESEARCH COORDINATOR/INTERVIEWER
(Form 101)

Clinical Center: _____ Clinical Center No.:___ ___ ___

Certification as ACCESS Research Coordinator/Interviewer is requested for:

Name: _____

To be certified, the Research Coordinator/Interviewer must undergo training and demonstrate proficiency in the use of the ACCESS forms.

1. Training: The individual named above has attended a training session for Research Coordinators/Interviewers on _____ (Dates) or received equivalent training at an ACCESS Clinical Center by _____ who is a fully-certified ACCESS Research Coordinator/Interviewer.

2. ACCESS Forms Use:

   The individual named above has successfully coordinated the completion and review of data collection forms and other materials and submitted them to the Clinical Coordinating Center.

Patient ID No.	Form* 10	12	22
____ ____ ____ - ____ ____ ____ ____	( )	( )	( )
____ ____ ____ - ____ ____ ____ ____	( )	( )	( )

3. The individual named above has read and understood the ACCESS Protocol.

Principal Investigator:

Signature: _____

Date: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

EXHIBIT 10-4

REQUEST FOR CERTIFICATION
ACCESS PHYSICIAN
(Form 102)

Clinical Center: _____ Clinical Center No.:___ ___ ___

Certification as ACCESS Physician is requested for:

Name: _____

1. The above named physician has read and understands the ACCESS Protocol.

2. The above named physician is proficient in the procedures required for examining ACCESS patients.

Principal Investigator:

Signature: _____

Date: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

EXHIBIT 10-5

REQUEST FOR CERTIFICATION
ACCESS ATRS STAFF
(Form 104)

Clinical Center: _____ Clinical Center No.:___ ___ ___

Certification in ATRS use for:

Name: _____

To be certified, the person must undergo training and demonstrate proficiency in the use of the Automated Telephone Response System (ATRS).

1. Training: The individual named above has attended a training session on use of the ATRS on _____.
(Dates)

2. ATRS use:
The individual named above has successfully conducted one practice session using the ATRS.

Principal Investigator:
Signature: _____

Date: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

APPENDIX A

CONFLICT OF INTEREST STATEMENT FOR ACCESS INVESTIGATORS
CONFIDENTIAL

Except as noted below:

- I am not a part-time, full-time, paid or unpaid employee of any organizations:

  (a)whose products or services will be used or tested in the study under review, or (b) whose products or services would be directly and predictably affected in a major way by the outcome of the study;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations; and

- I do not have any financial interests or assets in any organizations meeting the above criteria, nor does my spouse, dependent children, nor organizations with which I am connected.

PLEASE COMPLETE THE APPROPRIATE BOX BELOW.

9 NO RELEVANT INTERESTS OR ACTIVITIES.

9 EXCEPTIONS ARE NOTED IN THE ATTACHED LETTER.

I will notify the Clinical Coordinating Center Principal Investigator promptly if:

- a change occurs in any of the above during the tenure of my responsibilities; or

- I discover that an organization with which I have a relationship meets the criteria for a conflict of interest.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

_____ _____

Investigator (type name) Signature

_____

Date

CHAPTER 11

DATA ANALYSIS PLANS

11.1 INTRODUCTION

ACCESS has two components: a Case Control Study designed to determine the etiology of sarcoidosis; and a Clinical Course Study designed to define categories of outcome that may be related to the etiology of sarcoidosis and to describe the clinical course of patients with sarcoidosis.

The primary investigation is the study of the etiology which will be based on the data from 720 patients with sarcoidosis representing both men and women, white and minority race/ethnicity, and the spectrum of disease severity in comparison with the data from 720 age, gender and race/ ethnicity matched controls recruited through random digit dialing to represent the general population. The Case Control Study is designed to investigate genetic, environmental, infectious, and immune dysregulation hypotheses. A systematic approach to the analysis of all of the variables collected in ACCESS has been developed by the investigators. Each exposure as well as combinations of exposures will be analyzed. Six Data Analysis Working Groups (see Exhibit 11-1) were established in 1998. These working groups have discussed how infectious agents, environmental exposures, and genetic factors might interact to cause sarcoidosis. Since the cause of sarcoidosis may not prove to be a single known exposure, combinations of exposures, interactions of factors, and results for subgroups will be investigated; the Data Analysis Working Groups are in the process of defining the combinations and subgroups to consider in the analysis. Specific hypotheses are being formulated by Data Analysis Working Groups for review at the April 1999 meeting of the Steering Committee.

The Clinical Course Study is a prospective cohort study of the first 252 cases enrolled in the Case Control Study. The study is designed to: 1) define sarcoidosis cases that do or do not clinically resolve over a two-year period of follow-up, and 2) develop a clinical/radiologic/ physiologic assessment system for reporting the extent of sarcoidosis organ involvement.

Statistical considerations and data analysis approaches for the two studies are presented in this chapter and in Chapter 12 of the ACCESS Protocol.

11.2 STATISTICAL CONSIDERATIONS - CASE CONTROL STUDY

11.2.1 Power

The goal of 720 cases and 720 controls was determined by the ACCESS investigators so that the proposed study would have sufficient power (80 to 90%) to identify associations between exposure and case status with odds ratios $\geq$ 2.0 even when the prevalence of the exposure is small. There will be at least 90% power to identify associations between exposures and case status with odds ratios of $\geq$ 2.0 when the proportion of exposed controls is 0.05 and 78% power to detect odds ratios $\geq$ 1.8 with the same frequency of exposed controls. It was decided that any exposure linked to the occurrence of sarcoidosis with an odds ratio of $\geq$ 2.0 would be an important association to detect even though odds ratios $\geq$ 3.0 establish with greater certainty that a causal association exists (Taubes G, 1995). The methods for calculating power and the power for tests of hypotheses under different assumptions are presented in more detail in Chapter 12 of the Protocol.

This large number of cases and controls provides adequate power to investigate associations for subgroups and to identify interactions between genetic markers and environmental exposures. For instance, blacks may have a different set of risk factors than whites. There will be at least 88% power to detect odds ratios $\geq$ 2.0 and 82% power to detect odds ratios $\geq$ 1.8 in a selected subset representing half of the study population (360 cases and 360 controls) if the prevalence of the exposure in the control population is 0.1. The efficiency of an interaction test between a genetic factor and an exposure with one half of the patients in each of two genetic groups is approximately one half the efficiency of the test for the exposure in all cases and controls (Peterson and George, 1993). The test for interaction will have 80 to 90% power to detect changes in the ratio of the exposure-sarcoidosis odds ratios $\geq$ 2.0 when comparing the two genetic groups.

11.2.2 Significance Levels

The primary hypotheses are being specified without investigator review of the preliminary data. These hypotheses will be tested at an 0.05 alpha level. It is possible that certain associations may become apparent after the data are reviewed by the investigators. These results will be distinguished from those that were developed before the data were reviewed. In recognition of the large number of hypotheses being considered in this study, the investigators have specified that associations identified after the data are reviewed will not be considered statistically significant unless the p-value for the odds ratio is less than 0.01. Even with this restriction, some spurious associations may be identified. The strength of the association and its clinical plausibility in the light of the other associations found in ACCESS will be used to determine whether the association is spurious or not. It is expected that a limited number of exposures will be significantly associated with sarcoidosis and these findings will lead to further investigation into the etiology of sarcoidosis.

11.2.3 Analysis Plans for Unmatched Cases at the End of the Study

If the number of unmatched cases remains less than 5% (36 pairs), the analyses will be performed without the unmatched cases. As part of the final analysis of ACCESS data, the Clinical Coordinating Center staff will perform sensitivity analyses to determine if the addition of the unmatched cases has a substantial impact on the findings in ACCESS. The sensitivity analyses will be conducted under a “worst case scenario” (the case control pair would provide information opposite in direction to that which has been observed in other pairs), and under a “neutral scenario” (the odds ratio of association for this pair is 1.0). A Monte Carlo simulation of the “neutral scenario” will be performed to estimate the conditional power of rejecting the null hypothesis given the observed data and no association for the unmatched pairs.

If the percentage of unmatched pairs is greater than 5%, the Clinical Coordinating Center will implement a procedure to match unmatched cases to other enrolled controls on the basis of age, race, and gender. An attempt will be made to match the unmatched case to another control

enrolled at the same Clinical Center. If no match can be made on the basis of age, race, and gender, the age criterion will be relaxed until a match is found. If there are no matches at the same Clinical Center, the unmatched case will be matched to a control at another Clinical Center. The cases that are not exactly matched within a Clinical Center will be flagged and sensitivity analyses performed to determine the impact of the inclusion of these data on study results.

11.3 STATISTICAL CONSIDERATIONS - CLINICAL COURSE STUDY

11.3.1 Power

The Clinical Course Study is conducted on the first 252 (goal was 240) cases enrolled into ACCESS; the majority of Clinical Centers enrolled at least 20 cases. The total number of cases is sufficient to detect small differences in means (three-quarters of a standard deviation) among defined subgroups, and moderate differences (odds ratios of 3) in categorical outcomes. See Chapter 12 of the ACCESS Protocol for additional information on power for this study.

11.3.2 Significance Levels

The specific hypotheses formulated by the Data Analysis Working Groups in advance of reviewing the data will be tested at the 0.05 alpha level. All other hypotheses will be tested at the 0.01 alpha level.

11.4 DATA ANALYSIS FOR THE CASE CONTROL STUDY

11.4.1 Introduction

Although the etiology study includes as possible etiologic agents a wide range of environmental, infectious, and sociodemographic exposure variables, the analytic plans for all of these agents are similar. Except for certain genetic studies, a matched case control design is used to identify those exposures or variables that have different prevalence or quantitative levels between cases and controls. Once these factors are identified, multivariate models are used to determine if the list of possible etiologic agents can be further reduced to those that provide unique contributions to the risk equation.

11.4.2. Matched Pair Analysis

Data Monitoring Reports have been prepared at six-month intervals beginning September 1997. Since the review of the interim data was to have no effect on recruitment plans, no adjustment in the overall alpha level for the study is made for interim evaluation. These reports have included detailed univariate analysis performed on each of the exposure variables collected in the Case Control Study. All categorical exposure variables have been dichotomized (made into yes-no response) and the results presented using a common format (see Exhibit 11-2). Nine columns are used to present the results for the analysis of a dichotomized exposure variable. The first column shows the number of pairs that are available for analysis. The second column shows the proportion of cases who have the exposure of interest. The third column shows the proportion of controls who have the exposure of interest. These two columns provide estimates of the prevalence of the exposure in the case and control groups. In a matched design, a case control pair must be discordant (case exposure status does not equal the matched control exposure status) in order for it to be informative (that is, provide statistical information about the hypothesis being tested). The fourth column shows the number of informative pairs for the statistical test being performed. If the null hypothesis is true, it is expected that the case will have been exposed in half of the informative pairs, and the control will have been exposed in the other half. The fifth column shows the proportion (p) of informative pairs with the case having been exposed. The more different this proportion is from 0.5, the greater the association between the exposure variable and the presence of sarcoidosis. Mc Nemar's test (Mc Nemar, 1947) has been used to calculate the statistical significance of the reported association. This is a test that the proportion of informative pairs with the case having been exposed is one half the number of informative pairs. The p-value from the test is obtained from the PROBBNML (p,n,m) function in SAS; the null hypothesis specifies that p is 0.5, n is the number of informative pairs, and m is the number of pairs with the case exposed. A two-sided p-value is used for all inferences. Column seven is the odds ratio for the exposure variable.

The odds ratio (p/1-p from column five) is the standard measure of association in case control studies. The confidence interval (columns eight and nine) is calculated using the formula in Breslow and Day (Breslow and Day, 1980).

Continuous variables are compared using paired t-tests. The format for presentation of continuous variables is given in Exhibit 11-3.

Logistic regression using forward selection (significance level of 0.05) identifies those variables that are independently related to case status. The beginning set of independent variables for the logistic regression contains any variable that had a univariate association with case status at the 0.1 alpha level or below. The model proceeds by sequentially adding any variable that has statistical significance in the model at the 0.05 level or below. Variables that have a univariate significance of 0.1 can have a significance level in the model that is 0.05 or below. The variable with the lowest univariate p-value is added first. The procedure continues until no variable remaining out of the model is statistically significant at the 0.05 significance level or below when added to the model. The variables in the model are said to be independently associated with case status since the inclusion of other significant variables does not remove the significance of the variable being reviewed.

11.4.3 Subgroups

It will not be feasible to estimate odds ratios for age, gender, race or geographic area (controls are chosen from the same area code or from the same ZIP Code as cases), since these are matching variables, however, interaction terms between age, gender, race and geographic area and other exposure variables will be estimated and statistical tests will be performed to determine if these odds ratio estimates are homogenous across the different matching strata. An analysis to determine whether one type of exposure is associated with a genetic predisposition to sarcoidosis will be performed using interaction terms in conditional logistic regression models.

11.5 DATA ANALYSIS FOR THE CLINICAL COURSE STUDY

Analytic techniques for the Clinical Course Study will include analysis of variance, regression, life table analysis, and standard analyses for categorical variables. It is planned to analyze follow-up data for the patients enrolled in the Clinical Course Study using the Generalized Estimating Equations (GEE) program (Liang and Zeger, 1986; Zeger and Liang, 1986) that runs under the SAS system using a combination of GENMOD and IML. The GEE model is robust in that it allows for the inclusion of correlations and dependence structures in the serial data being collected for each of the cases. The model has the added advantage that the results are presented much like the results from more standard linear models. The GEE model can be used to analyze outcome measures with continuous distributions, and outcomes that are binary or categorical. The GEE model also allows for the inclusion of fixed covariates or time-dependent covariates (variables that change over the course of time, and influence the risk of progression or regression of disease in accordance with these variations).

Survival analysis techniques are the most appropriate type of analysis for the dependent variables that can be structured in the form of a time-to-event. Event rates are calculated using Kaplan-Meier methods (Kaplan and Meier, 1958), and confidence intervals are obtained using Greenwood's formula (Greenwood, 1926). If multivariate analyses are contemplated, the Cox proportional hazards model (Cox, 1972) is used to perform multivariate analyses. This model permits the inclusion of fixed and time-dependent covariates, and allows for differences in the length of time that cases are followed. Tests for interactions can be included in all of the above models. Dependent variables of interest include measures of progression and regression of sarcoidosis symptoms.

EXHIBIT 11-1

ACCESS DATA ANALYSIS WORKING GROUPS

Family and Genetics

Michael Iannuzzi, M.D. (Chair)
David Moller, M.D.
Robert Musson, Ph.D.
Milton Rossman, M.D.
Ben Rybicki, Ph.D.
Bruce W. Thompson, Ph.D.

Infectious Agents

Steven Weinberger, M.D. (Chair)
Louis DePalo, M.D.
Gary Hunninghake, M.D.
Geoffrey McLennan, M.D.
David Moller, M.D.
Robert Musson, Ph.D.
Lee Newman, M.D.
Michael Terrin, M.D.

Environmental Agents

Lee Newman, M.D. (Chair)
Eddy Bresnitz, M.D.
Robert Musson, Ph.D.
Cecile Rose, M.D.
Milton Rossman, M.D.
Michael L. Terrin, M.D.

Socioeconomic Status

Marc Judson, M.D. (Chair)
Genell L. Knatterud, Ph.D.
Daniel Lackland, Ph.D.
David Rabin, M.D.
Margaret Wu, Ph.D.

Clinical Outcome

Robert Baughman, M.D. (Chair)
Carol Johns, M.D.
Marc Judson, M.D.
Genell L. Knatterud, Ph.D.
Milton Rossman, M.D.
Alvin Teirstein, M.D.
Margaret Wu, Ph.D.
Henry Yeager, M.D.

Nucleic Acids

Milton Rossman, M.D. (Chair)
Robert Baughman, M.D.
Michael Iannuzzi, M.D.
Dimitri Monos, Ph.D.
Robert Musson, Ph.D.
Lee Newman, M.D.
Janardan Pandey, Ph.D.
Bruce W. Thompson, Ph.D.

Sample of Univariate Analysis - Discrete Variables
Activities on the Job (Form 12) - At any Time in the Past

Variable	Number of Pairs	Prop of Cases Exposed	Prop of Controls Exposed	Informative Pairs	Prop of IP Case Exposed	P-value (1 df)	Odds Ratio	95% CI Lower Bound	95% CI Upper Bound
Job in jewelry making									
Job in laundry/dry cleaning									
Job as machine operator									
Job in meat packing									
job in meat wrapping									
Job in any type of mining									
Job in nursing home/LTC									
Job as nurses aide									
Job as RN or LPN									
Job as hospital worker									
Job as medical technologist									
Job as social / MH worker									
Job as physician									
Job in dental work									
Job in respiratory therapies									
Job as motor vehicle operator									
Job as florist or in nursery									
Job in plastics manufacturing									
Job working with resins									
Job in poly foam manufacturing									
Job as postal worker									
Job in pottery making/ceramics									
Job working in a quarry									
Job in sales									
Job in sandblasting									
Job smelting in a foundry									
Job stone cutting/polishing									
Job as teacher, pre-K & K									
Job as teacher, Grade 1-6									
Job as teacher, middle & high									

IP = Informative Pairs.

EXHIBIT 11-3

Sample of Univariate Analysis - Continuous Variables
Psychosocial Data (Forms 15, 16, 17, 18)

Variable	Number of Pairs	Difference (Mean)	Cases (Mean)	Controls (Mean)	Paired t-stat	P-value (1 df)
Depression Score						
No. of Close Friends / Relatives						
Support from Others Score						
Somebody Available When Needed						
Mood and Attitude Score						
General Health						
Health Compared to One Year Ago						

t-stat = t-test statistic.

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

REFERENCES

Breslow, N.E. and Day, N.E. (1980). Statistical methods in cancer research. Volume 1 - The analysis of case control studies. International Agency for Research on Cancer, Lyon. *IARC Scientific Publication.* **32.** 84-119.

Cox, D.R. (1972). Regression models and life tables. *J. R. Stat. Soc. B.* **34.** 187-200.

Crapo, R.O., Hankinson, J.L., Irvin, C., MacIntyre, N.R., Voter, K.Z., and Wise R.A. (1995). Standardization of spirometry: 1994 update. Official statement of the American Thoracic Society. *AM. J. Resp. Crit. Care Med.* **152.** 1107-1136.

Greenwood, M. (1926). The natural duration of cancer. *Reports on Public Health and Medical Subjects.* **33.** 1-26.

Kaplan, E. and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53.** 457-481.

Liang, K.Y. and Zeger, S.L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika.* **73.** 13-22.

McNemar, Q. (1947). Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*, 12, 153-157.

Peterson, B. and George, S.L. (1993). Sampe size requirements and length of study for testing interaction in a 2 X K factorial design when time-to-failure is the outcome. *Controlled Clinical Trials*. **14.** 511-522.

Scadding, J.G. (1961). Prognosis of intrathoracic sarcoidosis in England. *Br. Med. J.* **2.** 1165-1172.

Sheffield EA and Jones Williams W. Pathology in sarcoidosis and other granulomatous disorders, ed. D. Gerent James. Marcel Dekker, Inc. New York. 1994; 45-68.

Sokolowski RW, Burgher LW, Jones FL, et al. (1987) Guidelines for fiberoptic bronchoscopy in adults. *AM. J. Resp. Dis.* **136.** 1066.

Taubes, G. (1995). Epidemiology faces its limits. Special News Report. *Science*. **2191**. 164-169.

Zeger, S.L. and Liang, K.Y. (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* **42.** 121-130.

A Case Control Etiologic Study of Sarcoidosis (ACCESS)

PROCEDURES MANUAL
Volume I

GLOSSARY

ACUTE SARCOIDOSIS

A patient with signs and symptoms of sarcoidosis beginning within one year of tissue diagnosis.

ALVEOLAR INFILTRATION

Alveolar infiltration presents in the lung parenchyma. It may be diffuse, patchy, nodular, or localized to a particular lung zone (e.g. upper lung fields) or lobe.

ANEMIA WITH LOW MCV

Hemoglobin less than the lower limits of normal with a low mean corpuscular volume (MCV).

ANNULAR LESIONS

Purple-red, annular, indurated shiny skin lesions which spread peripherally with central clearing. Central area may be pigmented or pale, and may be atrophic.

ASEPTIC NECROSIS

A condition characterized by painful destructive degeneration of the hips occasionally seen after prolonged usage of adrenal corticosteroids for sarcoidosis or for other inflammatory conditions.

BAL - BRONCHOALVEOLAR LAVAGE

(SEE DEFINITION BELOW).

BASELINE EVALUATION

Includes collection of demographic information, medical history, environmental and occupational history exposures, questions about the individual's family (first degree relatives), standardized psychological data on health related quality of life and medical care usage.

BERYLLIUM

A metal used in many high-tech alloys and, in the past, in flourescent lights. It causes a disease known as berylliosis.

BLINDNESS

Visual acuity less than 20/200.

BONE BIOPSY - POSITIVE FOR SARCOIDOSIS

Biopsy of bone revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

BONE MARROW - SARCOIDOSIS INVOLVEMENT

Bone marrow granulomas can be attributed to sarcoidosis in patients with known sarcoidosis and who have no evidence of infection.

BONE MARROW BIOPSY - POSITIVE FOR SARCOIDOSIS

Biopsy of the bone marrow revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

BRAIN BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the brain showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

BREATHING TESTS

(SEE PULMONARY FUNCTION TESTS).

BRONCHOALVEOLAR LAVAGE (BAL)

This is a procedure of washing out (with sterile physiological solution) an area of the lung involved with sarcoidosis; it is a routine part of the most frequent work-up given when pulmonary sarcoidosis is suspected; lavage samples are sent for examination for possible infectious causes of the syndrome, and cells are often sent for lymphocyte count and CD4, CD8 sub-typing.

BRONCHODILATOR

A medicine given by an inhaler or a nebulizer to dilate bronchial tubes in asthma, chronic obstructive pulmonary disease, and occasionally sarcoidosis. Bronchodilators are often given at the time of pulmonary function tests to assess the reversibility of any airway obstruction that is found.

BRONCHOSCOPY

Examination of the tracheobronchial airways with a flexible instrument with a fiber optic lens system and a channel for instillation of sterile physiological solution(s) for taking lavage samples, doing biopsies, etc.

BTPS

Body Temperature and Pressure, Standardized. The standard way to report expired volumes and lung volumes in pulmonary function studies. The values in tables of normal values are expressed in these terms and, to get fair estimations of % of predicted, the measurements obtained at spirometry have to be expressed this way.

CASE

A person with a relatively recent tissue diagnosis of sarcoidosis (within the past six months) who will have an extensive series of questionnaires and examinations to see if associations can be found that are of importance in the causation of sarcoidosis.

CASE CONTROL STUDY

A type of study looking for the cause of a disease; cases and controls are selected on the basis of whether they do or do not have the disease, and then compared as to whether they do or do not have a history of exposure to or contact with a particular agent.

CATARACT

Opacification of the intraocular lens.

CD_4 Cells

T-lymphocytes carrying the CD_4 antigen site (sometimes called, “helper cells”).

CD_8 Cells

T-lymphocytes carrying the CD_8 antigen (sometimes called “suppressor cells”).

CERTIFICATION

There is a defined training and evaluation of all the component entities and persons involved with ACCESS, as spelled out in Chapter 10 of this Volume of the Procedures Manual.

CHAMPUS

(SEE PUBLIC HEALTH INSURANCE).

CHAMPVA

(SEE PUBLIC HEALTH INSURANCE).

CHROMIUM

A metal used as a coating over other metals in electroplating, as well as in many chemical and high-tech metal production processes.

CHRONIC SARCOIDOSIS

A patient with signs of sarcoidosis for more than one year.

CIGARILLOS

Cigar-like tobacco products in the size and shape of cigarettes.

CLINICAL CENTER (CC)

One of ten medical centers across the United States with a sizable number of sarcoidosis patients that is a center enrolling new sarcoidosis cases and controls matched for age, gender, and self-designated race for detailed studies during ACCESS.

CLINICAL CENTER CERTIFICATION

For a Clinical Center to be certified, it must have at least one certified Research Coordinator, one physician certified to perform physical examinations, one individual certified to use the Automated Telephone Response System (ATRS) and a certified Spirometry Laboratory. In addition, it will have to show initial and annual evidence of approval of the Institutional Review Board of its institution. Conflict of Interest statements also have to be submitted annually for each ACCESS staff member. See Chapter 10 of this Volume of the Procedures Manual.

CLINICAL COORDINATING CENTER (CCC)

Clinical Trials & Surveys Corp. (C-TASC), located in Baltimore, Maryland, is the Clinical Coordinating Center for the ACCESS research effort funded by The National Heart, Lung, and Blood Institutes (NHLBI).

COBALT

A metal used in many high-tech alloys.

COHORT STUDY

Prospective study of the cases enrolled in the case control study and who agreed to follow-up; the data for these cases will be used to define categories of outcome which may be related to the etiology of sarcoidosis, and to describe the clinical course of sarcoidosis.

CONJUNCTIVA BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the conjunctiva revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

CONTROL

A person who does not suffer from sarcoidosis matched to a case on age (±5 years), gender and self-designated race.

CYSTIC CHANGES OF HANDS AND PHALANGES - SARCOIDOSIS INVOLVEMENT

A positive radiologic change for sarcoidosis in the hand is present when the focal trabecular pattern is coarsened because of adjacent bone resorption, cysts (oval, circular or irregular), more than 1 mm in diameter surrounded by trabeculae are present, or when focal destructive bone lesions are present. Some, but not all, of the cystic change may involve the articular surface.

$DLCO_{SB}$

Diffusing capacity of the lungs for carbon monoxide, single breath (SB). In the single breath technique, the patient maximally inspires a gas mixture containing 0.2% carbon monoxide, holds his breath for approximately 10 seconds and then slowly exhales the gas, which is collected for analysis.

DOCTOR'S PRIVATE OFFICE

An individual office in a freestanding or office building or a suite of offices occupied by several doctors.

DURA BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of dura showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

DYSPNEA AND DYSPNEA SCALE

Dyspnea refers to shortness of breath or trouble breathing and, along with dry cough, is usually the most distressing part of having sarcoidosis of the lungs. There are reasonably reproducible ways of semi-quantitating dyspnea by scales of the type of activity that brings on shortness of breath. One of these will be used in assessing the case's shortness of breath in ACCESS.

EAR/NOSE/THROAT BIOPSY - POSITIVE FOR SARCOIDOSIS

Biopsy of ears, nose, or throat revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

EDIT STATEMENTS

A list of edit messages for a specific form. A separate message is printed for each query identified by computer edits which are done both at the local Clinical Center and at the Clinical Coordinating Center. Edit messages for unanswered items and for out-of-range items are printed first, followed by the edit messages for inconsistencies and date checks. See Chapter 7 of this Volume of the Procedures Manual.

ELEVATED ALKALINE PHOSPHATASE

Serum alkaline phosphatase greater than upper limits of laboratory normal.

ERYTHEMA NODOSUM

This is a skin inflammation in which painful, rather flat red bumps 1-2 cm across appear on the lower legs. The syndrome occurs in sarcoidosis, in response to various infections, TB, leprosy, streptococcal infections, drug allergies, and other agents.

ETHNIC ORIGIN

(SEE RACE).

EXTRAPULMONARY SARCOIDOSIS

A patient whose sarcoidosis has its major expression in organs outside the lungs.

FAMILY INCOME

The money income before deducting for taxes, retirement, insurance, union dues, etc. This includes the income of the participant plus that of all his/her relatives who are currently household members, including Armed Forces members living at home and children, or other persons temporarily absent but usually resident in the home. Income includes: (a) Wages and salaries including tips, commissions, Armed Forces pay and cash bonuses as well as subsistence allowances; (b) Net income from unincorporated businesses, professional practices, farms or from rental property. ("Net" means after deducting business expenses, but before deducting personal taxes); (c) Social Security or Supplement Security Income; (d) Retirement, disability, and survivor pension; (e) Interest and dividends; (f) Cash public assistance payments (welfare), excluding food stamps; (g) Veterans' payments; (h) Unemployment or workers compensation; (i) Alimony and child support; (j) Money regularly received from friends and relatives not living in the household; and (k) Other periodic money income.

FEV_1

(SEE PULMONARY FUNCTION TESTS).

FIBROTIC LUNG DISEASE

A patient whose chest X-rays show linear streaks, small and large bullae, and retraction of the hilar areas cephalad. There may be obstructive as well as restrictive dysfunction. All have some degree of permanent lung damage resistant to current therapies.

FOLLOW-UP EVALUATION

Includes a medical history, physical examination, chest X-ray, spirometry, routine biochemistry, complete blood count and differential, and additional tests as clinically required.

FORM EDITING

Forms will be edited for valid codes, valid ranges and logical consistency by electronic checks during data entry at the Clinical Center. After the form has passed this local edit process, the data are transmitted to the CCC.

FORM REQUISITION SHEET

A form to be used by each Clinical Center Research Coordinator for ordering forms and manuals from the Clinical Coordinating Center.

GALLIUM SCAN

This procedure requires the injection of a radioactive element, Gallium 67. The gallium collects in areas of the body affected by inflammation. Two days after the injection, the body is scanned for radioactivity. Since any type of inflammation will cause the gallium to collect, a positive scan does not necessarily signal sarcoidosis.

GENERAL PRACTITIONER

A generalist medical doctor, family physician, pediatrician, or internist (treats adults) who provides comprehensive medical care on a continuing basis to patients of any age or gender regardless of the specific nature of the patient' s health problems.

GENES

The biologic unit of heredity, self-reproducing and located at a definite position on a particular chromosome.

GLAUCOMA

Diagnosed by the combination of elevated intraocular pressure and changes in the patient's central and peripheral vision. Intraocular pressure should be determined by tonometry.

GRANULOMA

A collection of inflammatory cells, mostly epithelioid cells (transformed monocytes) and lymphocytes, without obvious microbial, mineral or other cause, in round or ovoid configuration.

HEART BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the heart revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

HILAR ADENOPATHY

Enlarged hilar structures, usually oblong, often not compressing the airways significantly, that are thought to represent hilar lymph node enlargement.

HOMELESS

Someone without a usual place of residence.

HOSPITAL EMERGENCY ROOM

The unit of a hospital where persons may receive medical care, often of an urgent nature, without or before being admitted. Emergency rooms are usually open 24 hours a day.

HOSPITAL OUTPATIENT CLINIC

The unit of a hospital where persons go for medical care without being admitted. Outpatient clinics usually provide routine, non-emergency medical care and are usually open only during specific hours.

HYPERCALCEMIA

Serum calcium concentration greater than the upper limits of normal OR a serum ionized calcium greater than the upper limits of normal.

HYPERSPLENISM

A condition of over activity of the spleen occasionally seen in sarcoidosis. The spleen is enlarged, and there is a decreased circulating number of one or more of the circulating blood cell elements, and the bone marrow is hyperplastic. The condition may be greatly improved by splenectomy.

INSTITUTIONAL ASSURANCE OF COMPLIANCE

A document which explains how the hospital protects people who join studies.

INTERSTITIAL INFILTRATES

Interstitial infiltration present in the lung parenchyma. It may be diffuse, patchy, nodular, or localized to a particular lung zone (e.g., upper lung fields).

KIDNEY BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the kidney revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

KVEIM TEST

A skin test used occasionally in the diagnosis of sarcoidosis. A specially processed extract (0.15 ml) of sarcoidosis spleen, carefully handled so as to exclude as much as possible any content of transmissible infectious agents, is injected into the skin. After four to eight weeks, in a significant number of sarcoidosis patients (75%) in some series with a "high quality" antigen, sarcoid granuloma form at the site of injection. There are very few false positive tests, according to investigators with the most experience with the test. This test is sometimes known as the Kveim-Siltzbach, after Dr. L. Siltzbach who contributed a great deal to development of the test. The test can be used to help diagnose sarcoidosis in the ACCESS study in patients with Löfgren's Syndrome (defined by presence of erythema nodosum).

LACRIMAL GLAND SWELLING

The palpebral lobes of the lacrimal gland are normally not palpable in the superior lateral quadrant of the eye socket. Patients with sarcoidosis frequently have firm, non-tender mass in the superior lateral quadrant of the eye socket. This can be palpated by pressing the thumb gently along the inside of the eye socket at the lateral aspect of the eyebrow. If a mass is felt, this is consistent with sarcoidosis.

LAVAGE

(SEE BRONCHOALVEOLAR LAVAGE).

LIVER BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the liver showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

LIVING IN THE HOME

The individuals living in the home include the entire group of persons who live in one housing unit. It may be several persons living together or one person living alone. It includes the respondent, any relatives living in the unit, and may also include roomers, servants, or other persons not related to the respondent.

LÖFGREN'S SYNDROME

A syndrome of erythema nodosum, often with fever, arthralgias and arthritis of large joints, especially the ankles, along with hilar adenopathy. This is a common presentation in Irish, Scandinavian and Puerto Rican patients; it is relatively less common in African-American patients in the US. A patient with a constellation of signs including erythema nodosum, fever, swollen tender joints (usually ankles) and an abnormal chest X-ray. Patients need not exhibit every feature, but all should have erythema nodosum. (Approximately 10% of patients with erythema nodosum will have a normal chest X-ray.)

LUPUS PERNIO

Bluish red to violaceous, indurated papules usually distributed symmetrically on the nose, cheeks, ears and lips. Surface of lesions may be shiny with large, dilated pores on surface. Lesions rarely ulcerate.

LYMPH NODE BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of lymph node showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

LYMPH NODE >2 cm BY CT SCAN

The lymph node must have an axial diameter greater than 2 cm in a CT scan slice taken in the axial dimension.

MACULOPAPULAR LESIONS

Waxy, translucent, flat-topped, red-brown to orange to purple papules 2-6 mm in diameter; there may be few to hundreds of papules which often develop in crops. Most common on the face, neck, upper back, extensor aspects of limbs. Flatter, macular lesions and scaling may occur.

MEDICARE

Medicare refers to the Federal health insurance coverage most common for persons aged 65 years and over. In certain situations, people under 65 may be covered.

MEDICATIONS

Pharmaceutical treatments prescribed by a doctor.

MILITARY HEALTH CARE

Military health care refers to health care available to active duty personnel and their dependents. In addition, the Veterans Administration (VA) provides medical assistance to veterans of the Armed Forces, particularly those with service-connected ailments.

MISSED APPOINTMENT

An appointment that was scheduled or requested by the doctor but not made or not kept. A scheduled appointment that is canceled but rescheduled and kept would not be missed.

MUSCLE BIOPSY- POSITIVE FOR SARCOIDOSIS

A biopsy of muscle showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

MYCETOMA

Round or ovoid water density structure present in an air density structure on chest X-ray. An air-crescent sign may be present.

NEW PALPABLE LYMPH NODE

This is a lymph node 1 cm or greater newly discovered either by the patient or the physician.

NEW PALPABLE NODE ABOVE THE WAIST

This includes any lymph node 1 cm or greater above the waist either noted by the patient for the first time or discovered by the physician without previous record of a positive lymph node.

NEWLY DIAGNOSED CASES

Patients who have tissue confirmation of granuloma less than six months prior to entry into the study.

NICKEL

A metal used in the manufacture of various forms of steel and in jewelry making.

NODULES

Red to reddish-brown to violaceous nodules; soft or firm; larger than 5 mm in diameter; usually single to a few lesions. Present on face, extremities, trunk. May see telangiectasias on surface. Center of nodule may become depressed as lesions involute.

NON-HOSPITAL CLINICAL CENTER

A private clinical facility that provides ambulatory care and is freestanding in the community. Examples include: urgent care centers, private walk-in care centers, hospital- related centers not located within the hospital, and commercially (health care system)-run centers of salaried doctors.

OPTIC NEURITIS

Inflammation of the optic nerve characterized by decreased vision and decreased peripheral vision with appropriate ophthalmologic findings.

PANDA SIGN

A gallium scan showing uptake in both the lacrimal and salivary glands.

PAROTID BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the parotid gland revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

PATIENT PRIVACY, CONFIDENTIALITY OF DATA, AND DATA SECURITY

To maintain patient privacy, the records submitted to the CCC will not contain participant's name, address, or other identifying information. Each participant's record is identified by a unique identification (ID) number at the Clinical Center on a special form (ACCESS Form 01 - Participant Information). A variety of back-up systems are used to safeguard information at the CCC. CCC staff will provide a computer program on the distributed data management system for routine use by Clinical Center staff to locally archive the database and programs and copy them to magnetic tape.

PERICARDIUM BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the pericardium revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

PERIPHERAL NERVE BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of peripheral nerve showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

PHLEBOTOMY

Blood drawing from a vein.

PLEURAL BIOPSY - POSITIVE FOR SARCOIDOSIS

Any biopsy of pleural tissue (closed or open pleural biopsy) which reveals noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

PLATINUM

A metal used in jewelry manufacture, high-tech industries and as an additive in chemical manufacture.

PRIVATE HEALTH INSURANCE

Any type of health insurance (other than public programs), including coverage by a health maintenance organization (HMO) and single service plans.

PROSPECTIVE COHORT STUDY

A type of study in which subjects are followed after exposure to an agent or a disease to see outcome measures.

PROTOCOL ADHERENCE AIDS

The ACCESS Distributed Data Management System (described in Volume III of the Procedures Manual) includes programs to generate a list of cases whose visit window begins in a designated time period and other reminders.

PUBLIC HEALTH CLINIC

A publicly (i.e., locally, state or federally) supported facility where one or more physicians provide walk-in ambulatory medical care. This also includes community health clinics which accept insurance but are federally sponsored clinics in under-served areas.

PUBLIC HEALTH INSURANCE

Public plans refer to state or federal health insurance programs: (1) CHAMPUS (Comprehensive Health and Medical Plans for the Uniformed Services) provides health care in private facilities for dependents of military personnel on active duty or retired for reasons other than disability; and (2) CHAMPVA (pronounced CHAMP V-A) (comprehensive health and Medical Plan of the Veterans Administration) provides health care for the spouse, dependents, or survivors of a veteran who has a permanent service connected disability.

PULMONARY FUNCTION TESTS

Lung function tests to see how much, if any, lung function may have been altered by the patient's having sarcoidosis or other disease. In the ACCESS study, we measure the tests called FEV_1, (Forced Expired Volume in One Second), FVC (Forced Vital Capacity), and the ratio between the two. The lung tests are done with a machine called a spirometer and the procedure is called spirometry. The first two are expressed as percent of predicted, BTPS, and the third is a ratio.

PULMONARY HYPERTENSION

Enlarged main pulmonary arteries OR right ventricular enlargement present.

RACE (ETHNIC ORIGIN)

The racial designations applied to patients and controls will be self-declared. The subjects are asked to choose one of the following: black, white, Asian/Pacific Islander, native American/Alaskan native, other. In the first two categories, they are asked to identify whether they consider themselves Hispanic or not.

RANDOM DIGIT DIALING (RDD)

The method by which controls for ACCESS are obtained. Households are contacted by dialing randomly selected telephone numbers, in the same telephone exchange as the patient, until a willing subject is found of the same age (within ± 5 years), gender, and self-designated race of the case.

REGULAR DOCTOR

The doctor the respondent usually visits when in need of medical care or advice for either preventive, curative, or continuing health care. The doctor to go to for a new complaint or coordination of care.

ROENTGENOGRAM

X-ray picture.

SALIVARY GLAND BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of a salivary gland revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

SARCOIDOSIS

A disease of unknown cause, in which areas of inflammation develop in various parts of the body, most commonly in the lungs and lymph nodes which drain the lungs, but also in the skin, liver, spleen, heart, central nervous system, and at times almost any part of the body. These small areas of inflammation were thought to resemble small fleshy tumors of the type called "sarcomas" by early investigators. The lesions were described as "sarcoma-like", or "sarcoid", and the disease called "sarcoidosis". Later, under the microscope, the sarcoid lesions were found to resemble the round or oval collections of white blood cells called "granulomas" as seen in tuberculosis and various other diseases. Sarcoidosis is a disease in which multiple granulomas of unknown cause develop in various parts of the body. Cases of sarcoidosis are accepted into ACCESS only if they have a clinical picture consistent with sarcoidosis, have had a biopsy showing noncaseating granulomas within six months of enrollment in the study, and there is no apparent reason for the granulomas (no history of beryllium exposure, or no evidence of TB or fungus in the granulomas on special stains).

SCLERAL BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the sclera revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

SCREENING LOG FOR CASES

This is a log in which all newly diagnosed sarcoidosis cases are listed who are considered for enrollment in ACCESS.

SCREENING LOG FOR CONTROLS

This should be used to chart progress in contacting and recruiting potential controls for ACCESS.

SICCA

The patient is unable to produce adequate tear film to moisturize the eye. Requires a positive Schirmer's test.

SIC/SOC CODING

The occupational history of every case and control is reviewed. Every company or industry listed is assigned a SIC (Standard Industrial Code) from the 1987 Standard Industrial Code Classification Manual. Every job or occupation listed is assigned a SOC (Standard Occupational Code) from the 1980 Standard Occupational Classification Manual.

SILICA

Sand used in mining, sandblasting, foundries, and many other types of work.

SKIN BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the skin revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

SPECIALIST

A medical doctor whose practice is limited to a particular branch of medicine or surgery or who is a pediatric or internal medicine physician who treats one organ system or category of disease. A specialist has advanced training and is certified by a specialty board as being qualified to limit his/her practice to that field. Examples of specialists are surgeons, internists specializing in pulmonary (lung) diseases, pediatricians specializing in heart problems, psychiatrists, etc.

SPIROMETRY

(SEE PULMONARY FUNCTION TESTS).

SPLEEN BIOPSY - POSITIVE FOR SARCOIDOSIS

A biopsy of the spleen (including splenectomy) revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

SPLENIC ENLARGEMENT BY CT SCAN

The spleen is enlarged if it is visible on 12 cm of contiguous computerized tomography (CT) slices (15 8mm spiral slices) or if the splenic index (length times width times depth) is greater than 480 mm).

SPLENIC ENLARGEMENT BY EXAMINATION

If the spleen is palpable on physical examination, it is considered enlarged.

SPLENIC ENLARGEMENT BY RADIONUCLIDE SCAN

Spleen length on the posterior image is greater than 13 cm.

STAGE 4 DISEASE

Fibronodular disease present with significant lung distortion. May be diffuse or localized to a particular lung zone (usually upper lobes).

STEROID RESPONSIVE RENAL FAILURE

A decrease in serum creatinine of ≥ 1.0 mg/dL if the peak creatinine is ≥ 1.5 mg/dL OR a decrease in serum creatinine of > 0.5 mg/dL if the peak serum creatinine is < 1.5 mg/dL, and only if the patient is not hypercalcemic.

SYNOVIUM BIOPSY - POSITIVE FOR SARCOIDOSIS

Biopsy of synovium revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

TALC

A fibrous mineral used commercially for coating and as an ingredient in health care products.

TITANIUM

A metal frequently used as a pigment to color paints as well as an additive to high-tech metal alloys.

TREATMENT RESPONSIVE CARDIOMYOPATHY

A documented improvement of congestive heart failure symptoms, echocardiographic systolic function, or restrictive hemodynamics after treatment.

TU

Tuberculin units.

UNEXPLAINED ANEMIA - ATTRIBUTED TO SARCOIDOSIS

Hemoglobin less than the lower limits of normal without any likely alternative explanation than sarcoidosis based on clinical data,(e.g., normal iron studies, reticulocyte count).

UNEXPLAINED LEUKOPENIA - ATTRIBUTED TO SARCOIDOSIS

White blood cell count less than 3500/cu. mm without any likely alternative explanation than sarcoidosis based on clinical data.

UNEXPLAINED THROMBOCYTOPENIA - ATTRIBUTED TO SARCOIDOSIS

Platelet count less than 100,000/cu. mm without any likely alternative explanation than sarcoidosis based on clinical data.

UVEITIS

A broad category of ocular inflammation. Patients with uveitis may have red, inflamed appearing eyes. They may complain of photophobia and acute onset visual loss. Slit lamp examination establishes the diagnosis.

VITAL CAPACITY

(SEE PULMONARY FUNCTION TESTS).

ZIRCONIUM

A metal used in the manufacture of metal alloys.

A CASE CONTROL ETIOLOGIC STUDY OF SARCOIDOSIS

ACCESS

PROCEDURES MANUAL

VOLUME IIA

November 1998*

NOTICE: **The contents of this Procedures Manual are confidential and are not to be cited or discussed except with individuals to whom it has been distributed on behalf of the ACCESS Steering Committee.**

Prepared by:

Clinical Trials & Surveys Corp.
The Village of Cross Keys
350 West Quadrangle
Baltimore, Maryland 21210

*** Selected pages revised.**

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL

Volume IIA
STUDY FORMS

FORM NUMBER	FORM
	Screening Log for RDD Controls
Form 01	Participant Information
Form 02	Confirmation of Eligibility (Cases)
Form 03	Case Registration Worksheet (ATRS)
Form 04	Case Enrollment/Non-Enrollment Worksheet (ATRS)
Form 05	Confirmation of Eligibility (Controls)
Form 06	Control Status Worksheet (ATRS)
Form 09	Enrollment Confirmation Form (from ATRS)
Form 10	Demographics and Medical History Questionnaire
Form 11	Occupational History Worksheet*
Form 12	Occupational and Recreational Questionnaire
Form 13	Environmental Questionnaire
Form 14	Medications Questionnaire
Form 15	Questionnaire 15
Form 16	Questionnaire 16
Form 17	Questionnaire 17
Form 18	Questionnaire 18
Form 19	Questionnaire 19
Form 20	Relationship Questionnaire A
Form 21	Relationship Questionnaire B
Form 22	Family History Questionnaire

*Revised 11/98.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL

Volume IIA
STUDY FORMS
(Continued)

FORM NUMBER	FORM
Form 23	Family History Supplement
Form 24	Physical Examination Form*
Form 25	Laboratory Data Form
Form 26	Baseline Questionnaire for Cases Only
Form 28	Telephone Contact Summary*
Form 29	Affected Relative Report Form*
Form 30	Chest Roentgenography Interpretation Form
Form 31	Diagnostic Specimen Report
Form 32	Bronchoalveolar Lavage Form
Form 33	Missed Contact/Visit Form**
Form 35	Follow-up Questionnaire for Cases Only (Part I)***
Form 36	Follow-up Questionnaire for Cases Only (Part II)***
Form 37	Change in Organ Involvement Since Initial Examination***
Form 40	Tissue Sample Shipping Form
Form 70	Request to Extend Time Window

* Revised 3/97
** Added 7/98
*** Added 11/98

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL

Volume II

PREFACE

Volume II of the ACCESS Procedures Manual is divided into two parts. Part A contains a sample copy of each form and the supporting scales for the forms and Part B contains the scripts and instructions for ACCESS study forms. The volume has been divided so that the user can look at the scripts and form questions without having to flip pages back and forth. The suggested procedure for using this volume of the Procedures Manual is to place the two notebooks side by side and open each to the form number you plan to review. As you read the scripts and instructions, they will provide you with the general concepts and intent of each question. The volume of forms (Part A) should not be used for data collection but should serve as a reference for the completion of study forms that are being used in ACCESS. Study forms that are used to record data for cases and controls at your Clinical Center will be provided by the Clinical Coordinating Center. If you need additional forms, a request form should be filled out and sent to the Clinical Coordinating Center.

INSTRUCTIONS: Record information for any person who has been referred as a potential RDD control in ACCESS.

CLINICAL CENTER ___________________________

CLINICAL CENTER NUMBER __________________

ID NUMBER	INITIALS	DATE OF INITIAL CONTACT Month Day Year	AGE	GENDER M or F	SELF-DESIGNATED RACE 1 = White 2 = Black 3 = Asian/Pacific Islander 4 = American Indian or Alaska Native 5 = Other 6 = No contact with patient	HISPANIC? 1 = Yes 2 = No 3 = No contact with patient	ENROLLED Y or N	ANY EXCLUSIONS Y or N	REASON(S) FOR INELIGIBILITY OR REFUSAL See attached list of codes Code all that apply.	HEALTH CARE COVERAGE 1 = Private Insurance 2 = Medicare 3 = Medicaid 4 = Other Public Plan 5 = None 6 = Don't Know / No Answer
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_
___ - ____	___	__/__/____	__	_	_	_	_	_		_

ACCESS LOG FOR RDD CONTROLS

Reason for ineligibility or refusal

A = Less than 18 years old

B = Active tuberculosis or taking anti-tuberculosis therapy

C = History of sarcoidosis

D = History of primary biliary cirrhosis

E = History of Crohn's disease

F = Had systemic chemotherapy for histoplasmosis or other fungal infections

G = Chronic beryllium disease

H = Does not want to make time commitment

I = Physician advised against participation

J = Considered study an invasion of privacy

K = Dropped by Clinical Center staff because he/she failed to keep three successive appointments for a clinic visit

L = Had tuberculosis

M = Demographic mismatch

N = Other*

O = Did not want to give blood

P = Transportation/child care difficulties

Q = Did not speak or understand English

R = Family objections

* In order to avoid data analysis problems, "other" retains the same code as in the original code list. "Other" refers to other than the complete list of reasons, not just reasons A-M.

A Case Control Etiologic Study of Sarcoidosis

Participant Information

TO BE FILLED OUT BY THE RESEARCH COORDINATOR AND KEPT AT THE CLINICAL CENTER. DO NOT MAIL TO THE CLINICAL COORDINATING CENTER.

ID No. ☐☐☐ - ☐☐☐☐

1. What is your name?

☐ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ☐ ___ ___ ___ ___ ___ ___ ___ ___
(First Name) (Middle Name)

☐ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___
(Last Name)

Maiden name? (if applicable): _____

2. Are you male or female? Male ( ) Female ( )

3. What is your date of birth? ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

4. Where were you born? _____
City State

_____
Country

5. What is your current address? _____

_____
(City) (State) (Zip Code)

6. What is your home telephone? (_____) ____ ____ ____-____ ____ ____ ____

What is the best time of the day to call you? _____

QUESTIONS 7-12 ARE SUGGESTED AS THE MEANS OF OBTAINING INFORMATION THAT WOULD BE HELPFUL IN LOCATING CASES FOR FOLLOW-UP CONTACTS AND VISITS. WHICH OF THESE QUESTIONS ARE ASKED, AT WHAT POINT IN THE INTERVIEW PROCESS THEY ARE ASKED AND HOW THEY ARE ASKED IS LEFT TO THE DISCRETION OF THE INTERVIEWER.

7. What is the full name of your spouse/partner? _____

8. What is your current place of employment? (This information is needed from controls if the control wishes to be interviewed in the workplace.)

   _____

   Address? _____

   Telephone? (_____) ____ ____ ____ - ____ ____ ____ ____

9. Please give me the names and addresses of two people (relatives or friends) not residing in the same household with you who would know your place of residence. **(RECORD IN ITEMS 10 AND 11.)**

10. Name: _____

    Relationship: _____

    Address: _____

    City/State: _____

    Telephone: (____ ____ ____) ____ ____ ____ - ____ ____ ____ ____

11. Name: _____

    Relationship: _____

    Address: _____

    City/State: _____

    Telephone: (____ ____ ____) ____ ____ ____ - ____ ____ ____ ____

12. **[CASES ONLY]** What is the name of the physician who referred you to this Clinical Center?

    Name: _____

    Address: _____

    City/State: _____

    Telephone: (____ ____ ____) ____ ____ ____ - ____ ____ ____ ____

13. **Research Coordinator**:

    A. **Signature**: _____

    B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

14. **Date form completed**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

Date of Contact	Notes

A Case Control Etiologic Study of Sarcoidosis

Confirmation of Eligibility (Cases)

ID No.				-				
Form Type	**C**	**A**	**0**	**1**				

INSTRUCTION: ABSTRACT QUESTIONS 1 AND 4 FROM PARTICIPANT INFORMATION FORM (FORM 01). IF AT ANY TIME, THE RESPONSE TO A QUESTION IS A <u>STOP</u> CONDITION, DO NOT COMPLETE THIS FORM.

1. **CASE'S INITIALS:** ____ ____ ____

2. **DATE OF CONFIRMATION OF ELIGIBILITY:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. **HAS THE CASE AGREED TO BE IN THIS STUDY?** Yes (1) No (STOP)

4. **CASE'S GENDER:** (1) Male (2) Female

5. What is your age? ____ ____

   A. **CASE IS LESS THAN 18 YEARS OLD** Yes (STOP) No (2)

6. Do you consider yourself:
   INTERVIEWER READ LIST

   White (1)
   Black or African American (2)
   Asian/Pacific Islander (3)
   American Indian or Alaska Native (4)
   Other (5)

   Specify:_____

		Yes	No
7.	Are you Hispanic?	(1)	(2)

8. **DID THE CASE MEET ANY OF THE FOLLOWING EXCLUSION CRITERIA. INTERVIEWER ASK EACH QUESTION.**

		Yes	No
A.	Has a doctor told you that you now have active tuberculosis or are you now taking any medication for tuberculosis?	(STOP)	(2)
B.	Has a doctor ever told you that you had tissue diagnosis of sarcoidosis more than six months prior to today?	(STOP)	(2)
C.	Has a doctor ever told you that you have primary biliary cirrhosis?	(STOP)	(2)
D.	Has a doctor ever told you that you have Crohn's disease?	(STOP)	(2)
E.	Have you ever had medication for histoplasmosis or other fungal infections of your lungs?	(STOP)	(2)
F.	Has a doctor ever told you that you have chronic beryllium disease?	(STOP)	(2)

INSTRUCTION: THE REMAINDER OF THESE QUESTIONS ARE NOT ASKED OF THE CASE.

		Yes	No
9.	**HAS TISSUE SPECIMEN BEEN OBTAINED FOR DIAGNOSIS?**	(1)	(STOP)

A. **IF YES, DATE OF BIOPSY:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

(Date of biopsy must be six months or less prior to enrollment.)

10. **WHERE WERE THE DIAGNOSTIC BIOPSIES PERFORMED?**

		ACCESS Clinical Center	Other Medical Center	Not Done
A.	**BRONCHOSCOPY**	(1)	(2)	(3)
B.	**LYMPH NODE**	(1)	(2)	(3)
C.	**SKIN**	(1)	(2)	(3)
D.	**KVEIM/OTHER**	(1)	(2)	(3)

Specify: _____

REMINDER: REQUEST PATHOLOGICAL REVIEW OF THE SPECIMEN FOR MYCOBACTERIA AND FUNGI.

11. **HAS PATHOLOGY REPORT (ACCESS FORM 31) BEEN COMPLETED?** Yes (1) No (2)

IF NO, GO TO QUESTION 14.

A. **DATE OF REPORT:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

B. **TISSUE PATHOLOGY REPORT CONCERNING THE PRESENCE OF NONCASEATING GRANULOMA(S) CONSISTENT WITH THE DIAGNOSIS OF SARCOIDOSIS.**

Definitely positive	(1)
Probable	(2)
Possible	(3)
Definitely negative	(STOP)

C. **ANY PATHOLOGY EXCLUSION (HISTOPLASMOSIS, TUBERCULOSIS, FUNGAL).** Yes (STOP) No (2)

IF PATHOLOGY REPORT INDICATES PROBABLE OR POSSIBLE DIAGNOSIS OF SARCOIDOSIS, SUBMIT TISSUE SPECIMEN TO TISSUE SAMPLE READING PROGRAM. COMPLETE FORM 40, TISSUE SAMPLE SHIPPING FORM.

12. **WERE SPECIMENS SENT FOR CULTURE?**

	(1) Acid Fast Bacilli		(2) Fungus		(3) Other	
	Yes	No	Yes	No	Yes	No
A. **LUNG BIOPSY**	(1)	(2)	(1)	(2)	(1)	(2)
B. **LYMPH NODE**	(1)	(2)	(1)	(2)	(1)	(2)
C. **BRONCHIAL LAVAGE OR WASHINGS**	(1)	(2)	(1)	(2)	(1)	(2)
D. **OTHER**	(1)	(2)	(1)	(2)	(1)	(2)

Specify: _____

13. **WAS THE CULTURE POSITIVE FOR ACID FAST BACILLI, FUNGUS OR OTHER EXCLUDED INFECTIOUS AGENT IN ANY OF THE SPECIMENS?**

Yes	No
(STOP)	(2)

14. **HAVE ANY STOP RESPONSES BEEN CHECKED?**

Yes	No
(STOP)	(2)

IF YES, CASE CANNOT BE REGISTERED.
IF NO, CASE CAN BE REGISTERED. COMPLETE ACCESS FORM 03 AND CALL ATRS.

15. **Research Coordinator**:

A. **Signature**: _____

B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

16. **Date form completed**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

A Case Control Etiologic Study of Sarcoidosis
Automated Telephone Response System
Case Registration Worksheet

Complete this Worksheet **before** you place the phone call.

1. Dial the ATRS at (410) 435-0408.
2. Enter your 5-digit **Personal Identification Number** (**PIN**).
3. Enter the 4-digit **Clinical Center Password** (**CP**).

4. Enter the 7-digit Study Identificatin Number of Case: ___ ___ ___ - ___ ___ ___ ___

5. Using the chart below, translate each character of the case's initials into 2-digit character code. You will be entering these character codes over the telephone.

A = 21	D = 31	G = 41	J = 51	M = 61	P = 71	S = 73	V = 83	Y = 93
B = 22	E = 32	H = 42	K = 52	N = 62	Q = 74	T = 81	W = 91	Z = 94
C = 23	F = 33	I = 43	L = 53	0 = 63	R = 72	U = 82	X = 92	

(For any missing initial, enter an "X" and character code 92)

Case's Initials: ___ ___ ___

Character Codes: ___ ___ ___ ___ ___ ___

6. Case's Age: ___ ___

7. Gender: (1) Male (2) Female

8. Race:
   - White (1)
   - Black or African American (2)
   - Asian/Pacific Islander (3)
   - American Indian or Alaska Native (4)
   - Other (5)

9. Is case Hispanic? (1) Yes (2) No

10. Date biopsy performed: ___ ___ - ___ ___ - ___ ___ ___ ___
    (Note: Use numeric month) Month Day Year

11. Tissue pathology report concerning the presence of noncaseating granuloma(s) consistent with the diagnosis of sarcoidosis:
    - Definitely Positive (1)
    - Possible/Probable (2)
    - Definitely Negative (3)
    - Pending (4)

12. Case's Home Telephone Number: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
    area code

13. Case's Home Zip Code: ___ ___ ___ ___ ___

If you experience problems registering this subject over the telephone, please call 410-435-0663 (between 9:00 A.M. and 5:00 P.M. (EST) for assistance.

A Case Control Etiologic Study of Sarcoidosis
Automated Telephone Response System
Case Enrollment/Non-Enrollment Worksheet

Complete this Worksheet **before** you place the phone call.

1. Dial the ATRS at (410) 435-0408.
2. Enter your 5-digit **Personal Identification Number** (**PIN**).
3. Enter the 4-digit **Clinical Center Password** (**CP**).

4. Enter the 7-digit Study Identification Number of Case: ___ ___ ___ - ___ ___ ___ ___

5. Using the chart below, translate each character of the case's initials into 2-digit character code. You will be entering these character codes over the telephone.

A = 21	D = 31	G = 41	J = 51	M = 61	P = 71	S = 73	V = 83	Y = 93
B = 22	E = 32	H = 42	K = 52	N = 62	Q = 74	T = 81	W = 91	Z = 94
C = 23	F = 33	I = 43	L = 53	0 = 63	R = 72	U = 82	X = 92	

(For any missing initial, enter an "X" and character code 92)

Case's Initials: ___ ___ ___

Character Codes: ___ ___ ___ ___ ___ ___

6. Tissue pathology report concerning the presence of noncaseating granuloma(s) was consistent with a positive diagnosis of sarcoidosis? (1) Yes (2) No

   If **NO**, go to Question 8.

7. Has the case signed the informed consent for this study? (1) Yes (2) No

8. Was the case enrolled? (1) Yes (2) No

If you experience problems registering this subject over the telephone, please call 410-435-0663 (between 9:00 A.M. and 5:00 P.M. EST) for assistance.

A Case Control Etiologic Study of Sarcoidosis

Confirmation of Eligibility (Controls)

ID No.				-				
Form Type	**C**	**O**	**0**	**1**				

INSTRUCTION: ABSTRACT QUESTIONS 1 AND 5 FROM PARTICIPANT INFORMATION FORM (FORM 01). IF AT ANY TIME THE RESPONSE TO A QUESTION IS A <u>STOP</u> CONDITION, DO NOT COMPLETE THIS FORM. HOWEVER, THE ATRS FORM 06 SHOULD BE COMPLETED AND THE ATRS CALLED.

1. **CONTROL'S INITIALS:** ____ ____ ____

2. **DATE OF TELEPHONE CONTACT:** ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

		Yes	No
3.	**HAS THE CONTROL AGREED TO BE INTERVIEWED**	(1)	(STOP)
4.	**HAS THE CONTROL AGREED TO BE IN THIS STUDY?**	(1)	(STOP)
5.	**CONTROL'S GENDER:**	(1) Male	(2) Female
6.	What is your age?		____ ____
	A. **CONTROL IS LESS THAN 18 YEARS OLD**	(STOP)	(2)

7. Do you consider yourself:
   INTERVIEWER READ LIST

White	(1)
Black or African American	(2)
Asian/Pacific Islander	(3)
American Indian or Alaska Native	(4)
Other	(5)

Specify:_____

		Yes	No
8.	Are you Hispanic?	(1)	(2)

9. **DID THE CONTROL MEET ANY OF THE FOLLOWING EXCLUSION CRITERIA. INTERVIEWER ASK EACH QUESTION:**

		Yes	No
A.	Has a doctor told you that you now have active tuberculosis or are you now taking any medication for tuberculosis?	(STOP)	(2)
B.	Has a doctor ever told you that you have sarcoidosis?	(STOP)	(2)
C.	Has a doctor ever told you that you have granulomatous hepatitis?	(STOP)	(2)
D.	Has a doctor ever told you that you have primary biliary cirrhosis?	(STOP)	(2)
E.	Has a doctor ever told you that you have Bell's palsy?	(STOP)	(2)
F.	Has a doctor ever told you that you have uveitis?	(STOP)	(2)
G.	Has a doctor ever told you that you have Crohn's disease?	(STOP)	(2)
H.	Has a doctor ever told you that you have erythema nodosum but that he/she does not know the cause?	(STOP)	(2)
I.	Have you ever had medication for histoplasmosis or other fungal infections of your lungs?	(STOP)	(2)
J.	Has a doctor ever told you that you have chronic beryllium disease?	(STOP)	(2)

		Yes	No
10.	**HAVE ANY STOP RESPONSES BEEN CHECKED?**	(STOP)	(2)

IF YES, CONTROL CANNOT BE ENROLLED. COMPLETE ACCESS FORM 06 AND CALL ATRS.

IF NO, CONTROL CAN BE ENROLLED. COMPLETE ACCESS FORM 06 AND CALL ATRS.

11. **Research Coordinator**:

    A. **Signature**: _____

    B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

12. **Date form completed**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

A Case Control Etiologic Study of Sarcoidosis
Automated Telephone Response System
Control Status Worksheet

Complete this Worksheet **before** you place the phone call.

1. Dial the ATRS at (410) 435-0408.
2. Enter your 5-digit **Personal Identification Number** (**PIN**).
3. Enter the 4-digit **Clinical Center Password** (**CP**).

4. Enter the 7-digit Study Identification Number of Control: ___ ___ - ___ ___ ___ ___

5. Using the chart below, translate each character of the control's initials into 2-digit character code. You will be entering these character codes over the telephone.

A = 21	D = 31	G = 41	J = 51	M = 61	P = 71	S = 73	V = 83	Y = 93
B = 22	E = 32	H = 42	K = 52	N = 62	Q = 74	T = 81	W = 91	Z = 94
C = 23	F = 33	I = 43	L = 53	0 = 63	R = 72	U = 82	X = 92	

(For any missing initial, enter an "X" and character code 92)

Control's Initials: ___ ___ ___

Character Codes: ____ ____ ____ ____ ____ ____

6. Final study status:
   - Control gave consent and interviewed (1)
   - Control refused (2)
   - Control ineligible (3)
   - Control did not keep three appointments (4)
   - Control could not be contacted (5)

7. Date of first telephone contact: ___ ___ - ___ ___ - ___ ___ ___ ___
   (Note: Use numeric month) Month Day Year

8. Linked to Case:

   A. Case's Study Identification Number: ___ ___ ___ - ___ ___ ___ ___

   B. Case's Initials: ___ ___ ___

   Character Codes: ___ ___ ___ ___ ___ ___

If you experience problems registering this subject over the telephone, please call 410-435-0663 (between 9:00 A.M. and 5:00 P.M. EST) for assistance.

ACCESS Form 09
Enrollment Confirmation Form
8/22/96

This is a confirmation of enrollment of a Case.

ID NO.:	**999-1125**
Form Type:	**RV01**
Initials:	**GRB**
Date of Enrollment:	**SEP-17-1996**
Confirmation Number:	**41961**
Age:	**53**
Gender:	**Male**
Race:	**Black or African American**
Hispanic:	**No**

Please **key** this form in the ACCESS Distributed Data Management System prior to entry of Case evaluations.

This is a confirmation of enrollment of a Control.

ID NO.:	**999-1128**
Form Type:	**RV01**
Initials:	**NMB**
Date of Enrollment:	**SEP-17-1996**
Confirmation Number:	**46488**

Please **key** this form in the ACCESS Distributed Data Management System prior to entry of Control evaluations.

DEMOGRAPHICS AND MEDICAL HISTORY QUESTIONNAIRE

ID No.				-				
Form Type	**D**	**H**	**0**	**1**				

I. PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   A. **REFERENCE DATE: (COMPLETE PRIOR TO INTERVIEW)** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   B. **REFERENCE PERIOD: (COMPLETE PRIOR TO INTERVIEW)**
   (1) ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year
   to
   (2) ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

I would like to thank you for agreeing to participate in this study. I will be asking some questions about your health insurance and your medical history. But first, I'd like to begin by asking a few questions about your background.

II. DEMOGRAPHICS

3. What is your birth date? ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

(A) (B) (C)

4. Where were you born? _____ ____ ____ ____ ____ ____
   city state country
   If not US

5. Are you now married, widowed, divorced, separated, or have you never been married?
INTERVIEWER READ LIST

Presently Married	(1)
Living in a marriage-like relationship	(2)
Widowed	(3)
Divorced or Separated	(4)
Never married	(5)

6. Including yourself, how many people are now living in your home? ____ ____

A. **Check here if Homeless** (1)

7. What grade of schooling have you completed?
INTERVIEWER READ LIST

1-8	(1)
9-12	(2)
High school graduate	(3)
College graduate	(4)
Post graduate	(5)

III. ACCESS TO HEALTH CARE SERVICES

Now I would like to ask you about your usual source of health care, that is the place you go when you are sick or need medical advice.

8. Currently, what is your main health insurance plan?
INTERVIEWER READ LIST

Private insurance company	(1)
Medicare	(2)
Medicaid	(3)
Other public plan	(4)
None	(5)
Don't know/No answer	(6)

IF NONE OR DON’T KNOW, GO TO QUESTION 9.

8. (Continued)

		Yes	No	Don't Know
A.	Does your insurance plan allow you to pay less money if you visit certain doctors?	(1)	(2)	(3)
B.	Does your insurance plan allow you to pay less money if you visit a specific clinic or health center?	(1)	(2)	(3)
C.	Does your insurance plan limit your ability to receive care from a medical specialist of your choice?	(1)	(2)	(3)

9. Is there one particular clinic, health center, doctor's office, or other place that you <u>usually</u> go to if you are sick or need advice about your health? Yes (1) No (2)

A. **IF YES**, What type of place is it?
INTERVIEWER READ LIST

- Doctor's private office (1)
- Hospital emergency room (2)
- Hospital out-patient clinic (3)
- Non-hospital clinical center (4)
- Public health clinic (5)
- Don't know (6)
- Other (7)

Specify: _____

IF 9A IS ANSWERED, GO TO QUESTION 10.

B. **IF NO**, Is there one particular place where you <u>would</u> go if you were sick or needed advice about your health? Yes (1) No (2)

IF NO, GO TO QUESTION 10.
IF YES, ANSWER 9C.

C. What type of place is it?
INTERVIEWER READ LIST

- Doctor's private office (1)
- Hospital emergency room (2)
- Hospital out-patient clinic (3)
- Non-hospital clinical center (4)
- Public health clinic (5)
- Don't know (6)
- Other (7)

Specify: _____

10. Is your <u>regular</u> doctor a general practitioner, internist, family doctor or doctor who treats a variety of illnesses and gives preventive care or is he or she a specialist (a doctor who mainly treats just one type of health problem)?

General practitioner/internist/family doctor/other doctor	(1)
Specialist	(2)
Don't have a regular doctor	(3)
Don't know	(4)

	Yes	No
11. During the last 12 months, was there any time when you wanted to see a doctor but could not?	(1)	(2)

A. **IF YES**, Why?
INTERVIEWER READ LIST

(1)	There was a lack of money or insurance to pay for the care	(1)	(2)
(2)	It was too far or too expensive to get to care	(1)	(2)
(3)	You were not able to get an appointment for care	(1)	(2)
(4)	Some other reason	(1)	(2)

Specify: _____

	Yes	No
12. During the past 12 months, have you delayed seeking medical care because of worry about the cost?	(1)	(2)

A. **IF YES**, Approximately how many times? ____ ____

	Yes	No
13. In the past 12 months have you delayed or had difficulty getting medicine prescribed when you needed it?	(1)	(2)

A. **IF YES**, Was it because of:

(1)	Cost	(1)	(2)
(2)	Did not feel it was needed/helpful	(1)	(2)
(3)	Could not get to a drug store or other place to fill the prescription	(1)	(2)
(4)	Other	(1)	(2)

Specify: _____

IV. MEDICAL HISTORY

I am going to read you a list of health problems. For each health problem, please tell me if you have ever had the problem. If you have had the problem, I will ask you to tell me your age when you first got it and whether you still have it.

		A			**B**	**C**		
		Yes	No	Don't Know	Age?	Still Have It?		
						Yes	No	Don't Know
14.	Asthma	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
15.	Chronic bronchitis	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
16.	Emphysema	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
17.	Sinus trouble	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
18.	Allergies	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
19.	Heart disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
20.	High blood pressure	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
21.	Kidney disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
22.	Liver disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
23.	Arthritis	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
24.	Skin disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
25.	Cancer	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
26.	Lupus	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
27.	Diabetes	(1)	(2)	(3)	____ ____	(1)	(2)	(3)

28. Have you had any other health problems I have not asked you about? Yes (1) No (2)

IF YES, Please specify all the problems.

A. _____

B. _____

C. _____

D. _____

E. _____

29. Were you pregnant between **[REFERENCE PERIOD START DATE]** and **[REFERENCE PERIOD END DATE]**? (1) Yes (2) No (3) Not Applicable

30. DATE BLOOD DRAWN: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year
Not done (1)

31. TOTAL VOLUME OF BLOOD DRAWN: ____ ____ ____ ____ **cc**

32. LABEL SHEET NUMBER: ____ ____ ____ ____

Affix Blood Specimen Sheet Label Here

33. WHERE WAS BLOOD SHIPPED?	**Yes**	**No**
A. DNA Core Laboratory	**(1)**	**(2)**
B. RNA Study (Dr. Finn)	**(1)**	**(2)**
C. L-forms (Dr. Almenoff)	**(1)**	**(2)**

34. PARTICIPANT HAS CONSENTED TO THE FOLLOWING USE OF HIS/HER BLOOD SPECIMENS:

USE IN ACCESS OR OTHER RESEARCH ACTIVITIES **(1)**

USE ONLY IN ACCESS STUDIES **(2)**

PARTICIPANT MUST BE CONTACTED BEFORE SPECIMEN IS USED IN ANY STUDY NOT CURRENTLY PART OF THE ACCESS STUDIES **(3)**

V. ADMINISTRATIVE MATTERS

35. WHERE WAS INTERVIEW CONDUCTED?

Clinical Center **(1)**
Home **(2)**
Workplace **(3)**
Other **(4)**

Specify: _____

36. INTERVIEWER:

A. SIGNATURE: _____

B. ACCESS STAFF NO.: ____ ____ ____ - ____ ____

37. RESEARCH COORDINATOR:

A. SIGNATURE: _____

B. ACCESS STAFF NO.: ____ ____ ____ - ____ ____

38. DATE FORM COMPLETED: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

39. When were the blood specimens obtained?

Before the interview (1)
After the interview (2)

OCCUPATIONAL HISTORY WORKSHEET

ID No.				-					
Form Type	**O**	**W**							

#IF THIS IS A BASELINE INTERVIEW, USE FORM TYPE 0W01.

#IF THIS IS A FOLLOW-UP INTERVIEW, USE FORM TYPE 0W02.

1. **PARTICIPANT'S INITIALS:** ___ ___ ___

2. **DATE OF INTERVIEW:** ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

A. REFERENCE DATE: ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

[COMPLETE BEFORE BEGINNING INTERVIEW]

3. INDICATE THE TIME OF INTERVIEW:

Baseline (01)
Follow-up (02)

If this is a baseline interview, ask Question 4, and then go to Question 6.
If this is a follow-up interview, ask Question 3A.

3A. Has case been selected to give complete job history?

Yes	(01)
No	(02)

If Yes, ask Questions 4 and 5.
If No, skip Question 4 and ask Question 5.

4. What was your job status as of the reference date?
INTERVIEWER READ LIST

Employed full-time	(01)
Employed part-time	(02)
Homemaker, never held a full-time or part-time job for as long as six months	(03)
Homemaker, previously held a job for at least six months	(04)
Homemaker who works part-time	(05)
Retired	(06)
Unemployed, with previous work experience	(07)
Unemployed with no work experience (never worked)	(08)
Student	(09)
Disabled, with previous work experience	(10)
Disabled, without previous work experience	(11)

IF THIS IS THE BASELINE INTERVIEW AND THE RESPONSE TO THIS QUESTION IS 03, 08 OR 11, COMPLETE ONLY ITEMS 12 TO 14.

5. What is your current job status?
INTERVIEWER READ LIST

Employed full-time	(01)
Employed part-time	(02)
Homemaker, never held a full-time or part-time job for as long as six months	(03)
Homemaker, previously held a job for at least six months	(04)
Homemaker who works part-time	(05)
Retired	(06)
Unemployed, with previous work experience	(07)
Unemployed with no work experience (never worked)	(08)
Student	(09)
Disabled, with previous work experience	(10)
Disabled, without previous work experience	(11)

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

I would like some information about each of the jobs, either part-time or full-time, that you have held for 6 months or more beginning with the job you held just prior to **[REFERENCE DATE]**.* If you changed jobs (e.g., promotion) in the same company, consider this as a new job.

6A What was your job or occupation as of the **[REFERENCE DATE]***

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6B What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
A.					19 ___ ___	__ __ / __ __ years / months
B.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

6C What job or occupation did you have before the one we just discussed?

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6D What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB.

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
C.					19 ___ ___	__ __ / __ __ years / months
D.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

6E What job or occupation did you have before the one we just discussed?

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6F What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB.

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
E.					19 ___ ___	__ __ / __ __ years / months
F.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

6G What job or occupation did you have before the one we just discussed?

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6H What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB.

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
G.					19 ___ ___	__ __ / __ __ years / months
H.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

6I What job or occupation did you have before the one we just discussed?

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6J What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB.

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
I.					19 ___ ___	__ __ / __ __ years / months
J.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

6K What job or occupation did you have before the one we just discussed?

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6L What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB.

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
K.					19 ___ ___	__ __ / __ __ years / months
L.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

Occupational History Worksheet

THE OCCUPATIONAL HISTORY WORKSHEET IS COMPLETED IN REVERSE CHRONOLOGICAL ORDER STARTING WITH THE MOST RECENT JOB AS OF THE REFERENCE DATE.*

6M What job or occupation did you have before the one we just discussed?

IF A PERSON WORKED FOR A COMPANY/GOVERNMENT AGENCY THAT REQUIRED CHANGES IN LOCATION WITHOUT A CHANGE IN JOB DUTIES, THEN THE JOB SHOULD BE LISTED ONCE AND THE DURATION OF THE JOB SHOULD BE THE APPROXIMATE SUM OF THE AMOUNT OF TIME SPENT AT ALL THE WORK SITES.

7. What were your job duties when you worked in this job?

8. What was the name of the employer you worked for in this job?

9. What kind of place was (NAME OF COMPANY); that is, what did they make or do?

10. In what year did you start as a (JOB TITLE)?

11. How long (in years) did you work at this job?

6N What job or occupation did you have before the one we just discussed?

REPEAT ITEMS 6-11 FOR THIS JOB.

	Q6 JOB OR OCCUPATION	Q7 JOB DUTIES	Q8 NAME OF COMPANY	Q9 TYPE OF BUSINESS	Q10 YEAR STARTED	Q11 DURATION OF JOB
M.					19 ___ ___	__ __ / __ __ years / months
N.					19 ___ ___	__ __ / __ __ years / months

*For follow-up cases, use current date rather than reference date. If case has been selected to give complete job history, ask for jobs back to beginning of employment. If case has not been selected to give complete job history, ask for jobs back to date of baseline interview.

12. **Interviewer**:

    A. **Signature**: _____

    B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

13. **Research Coordinator**:

    A. **Signature**: _____

    B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

14. **Date form completed**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

OCCUPATIONAL AND RECREATIONAL QUESTIONNAIRE

ID No.				-				
Form Type	**O**	**R**	**0**	**1**				

1. **SUBJECT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   A. **REFERENCE DATE: (COMPLETE PRIOR TO INTERVIEW)** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   B. **REFERENCE PERIOD: (COMPLETE PRIOR TO INTERVIEW)** (1) ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year
   to
   (2) ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. **WAS PARTICIPANT UNEMPLOYED WITH NO WORK EXPERIENCE OR DISABLED WITHOUT PREVIOUS WORK EXPERIENCE? (SEE FORM 11, QUESTION 3.)** Yes (1) No (2)

   IF YES, GO TO QUESTION 80.
   IF NO, CONTINUE WITH SCRIPT.

ACTIVITIES ON THE JOB

Now I would like to ask you some questions about specific job related activities. I will read slowly from a long list and ask you whether you have **ever** had a job — even if the job lasted less than six months and was before [reference period] — that involved any of the following activities. Please tell me if you have worked in any of them and if you worked on the job for more or less than one year. I will also be asking if the activity occurred during the reference period. As you think about this, please feel free to use the anchor dates we discussed to help you determine if the activity was near one of the special dates.

USE THE ANCHOR DATES TO ESTABLISH IF THE EVENT HAPPENED IN THE REFERENCE PERIOD. IF PARTICIPANT ANSWERS "NEVER", GO TO THE NEXT ACTIVITY.

ASK EACH ACTIVITY IN TURN AND PAUSE BRIEFLY. FOR EACH ACTIVITY, IF PATIENT DOESN'T ANSWER, CHECK NEVER AND GO TO THE NEXT ACTIVITY.

		A Employment			B More Than One Year	
		Never	Ended Job Before Reference Period	Current Employment or Ended in the Reference Period	Yes	No
4.	Aircraft manufacturing	(1)	(2)	(3)	(1)	(2)
5.	U.S. Army	(1)	(2)	(3)	(1)	(2)
6.	U.S. Navy	(1)	(2)	(3)	(1)	(2)
7.	U.S. Air Force	(1)	(2)	(3)	(1)	(2)
8.	U.S. Marines	(1)	(2)	(3)	(1)	(2)
9.	Other branch of armed forces	(1)	(2)	(3)	(1)	(2)
10.	Nuclear worker	(1)	(2)	(3)	(1)	(2)
11.	Animal laboratory worker	(1)	(2)	(3)	(1)	(2)
12.	Assembling or fabricating	(1)	(2)	(3)	(1)	(2)
13.	Auto or truck repair	(1)	(2)	(3)	(1)	(2)
14.	Automotive manufacturing	(1)	(2)	(3)	(1)	(2)
15.	Bank teller (1)	(2)	(3)	(1)	(2)	
16.	Raising birds	(1)	(2)	(3)	(1)	(2)
17.	Carpentry or woodworking	(1)	(2)	(3)	(1)	(2)
18.	Cashier	(1)	(2)	(3)	(1)	(2)
19.	Child care worker (i.e., children under the age of 18)	(1)	(2)	(3)	(1)	(2)
20.	Cleaning private household, domestic worker (Do not include cleaning your own house.)	(1)	(2)	(3)	(1)	(2)
21.	Clerical or office work	(1)	(2)	(3)	(1)	(2)
22.	Construction	(1)	(2)	(3)	(1)	(2)

		A Employment			B More Than One Year	
		Never	Ended Job Before Reference Period	Current Employment or Ended in the Reference Period	Yes	No
23.	In a cork factory	(1)	(2)	(3)	(1)	(2)
24.	Demolition of buildings	(1)	(2)	(3)	(1)	(2)
25.	Cotton ginning	(1)	(2)	(3)	(1)	(2)
26.	Textile making or garment industry	(1)	(2)	(3)	(1)	(2)
27.	Data processor, typist; computer programmer	(1)	(2)	(3)	(1)	(2)
28.	Electrical or electronic worker	(1)	(2)	(3)	(1)	(2)
29.	Farming, ranching, farm laborer (wage laborer)	(1)	(2)	(3)	(1)	(2)
30.	Fire fighter	(1)	(2)	(3)	(1)	(2)
31.	Flight attendant	(1)	(2)	(3)	(1)	(2)
32.	Forestry work	(1)	(2)	(3)	(1)	(2)
33.	In a sawmill	(1)	(2)	(3)	(1)	(2)
34.	In a pulpmill	(1)	(2)	(3)	(1)	(2)
35.	Glass making	(1)	(2)	(3)	(1)	(2)
36.	Hairdressing or cosmetology	(1)	(2)	(3)	(1)	(2)
37.	House painting	(1)	(2)	(3)	(1)	(2)
38.	Commercial printing	(1)	(2)	(3)	(1)	(2)
39.	Jewelry making	(1)	(2)	(3)	(1)	(2)
40.	Laundry and dry cleaning	(1)	(2)	(3)	(1)	(2)
41.	Machine operator, assembler or inspector	(1)	(2)	(3)	(1)	(2)
42.	Meat packing	(1)	(2)	(3)	(1)	(2)

		A Employment			B More Than One Year	
		Never	Ended Job Before Reference Period	Current Employment or Ended in the Reference Period	Yes	No
43.	Meat wrapping	(1)	(2)	(3)	(1)	(2)
44.	Any type of mining	(1)	(2)	(3)	(1)	(2)
45.	In a nursing home or long-term care facility	(1)	(2)	(3)	(1)	(2)
46.	Nurses' aide	(1)	(2)	(3)	(1)	(2)
47.	Registered nurse or licensed practical nurse	(1)	(2)	(3)	(1)	(2)
48.	Hospital worker	(1)	(2)	(3)	(1)	(2)
49.	Medical technologist or medical technician	(1)	(2)	(3)	(1)	(2)
50.	Social worker/mental health worker	(1)	(2)	(3)	(1)	(2)
51.	Physician	(1)	(2)	(3)	(1)	(2)
52.	Dentist, dental product maker, or dental technician	(1)	(2)	(3)	(1)	(2)
53.	Respiratory therapies	(1)	(2)	(3)	(1)	(2)
54.	A motor vehicle operator (truck, bus, car driver)	(1)	(2)	(3)	(1)	(2)
55.	In plant nursery or as a florist	(1)	(2)	(3)	(1)	(2)
56.	Plastics manufacturing	(1)	(2)	(3)	(1)	(2)
57.	Working with resins	(1)	(2)	(3)	(1)	(2)
58.	Polyurethane foam manufacturing	(1)	(2)	(3)	(1)	(2)
59.	Postal worker	(1)	(2)	(3)	(1)	(2)
60.	Pottery making or ceramics	(1)	(2)	(3)	(1)	(2)

			A Employment		B More Than One Year	
		Never	Ended Job Before Reference Period	Current Employment or Ended in the Reference Period	Yes	No
61.	Working in a quarry	(1)	(2)	(3)	(1)	(2)
62.	In a sales occupation	(1)	(2)	(3)	(1)	(2)
63.	Sandblasting	(1)	(2)	(3)	(1)	(2)
64.	Smelting in a foundry	(1)	(2)	(3)	(1)	(2)
65.	Stone cutting or polishing	(1)	(2)	(3)	(1)	(2)
66	Teacher (preschool and kindergarten)	(1)	(2)	(3)	(1)	(2)
67.	Teacher (elementary 1 through 6)	(1)	(2)	(3)	(1)	(2)
68.	Teacher (middle and secondary)	(1)	(2)	(3)	(1)	(2)
69.	Teacher (post-high school educator)	(1)	(2)	(3)	(1)	(2)
70.	Tunnel construction	(1)	(2)	(3)	(1)	(2)
71.	Veterinarian/veterinary work	(1)	(2)	(3)	(1)	(2)
72.	Waitress or waiter	(1)	(2)	(3)	(1)	(2)
73.	Food preparation	(1)	(2)	(3)	(1)	(2)
74.	Welding	(1)	(2)	(3)	(1)	(2)
75.	Rubber factory worker	(1)	(2)	(3)	(1)	(2)
76.	In a pet store	(1)	(2)	(3)	(1)	(2)
77.	In an occupation with radiation exposure	(1)	(2)	(3)	(1)	(2)

TELL RESPONDENT "THIS IS THE END OF THE LIST."

78. In your office or indoor working environment, other than in the workplace bathrooms have you ever noticed any of the following conditions? **IF YES, DETERMINE IF IN REFERENCE PERIOD AND IF DURATION IS MORE THAN ONE YEAR.**

		A Exposure			B More Than One Year	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
(1)	High humidity	(1)	(2)	(3)	(1)	(2)
(2)	Water damage to furnishings, ceiling, tiles, or carpets	(1)	(2)	(3)	(1)	(2)
(3)	Obvious mold or mildew not in a bathroom	(1)	(2)	(3)	(1)	(2)
(4)	Musty or moldy odors	(1)	(2)	(3)	(1)	(2)

79. Were you ever around any animals in your work? (1) (2) (3) (1) (2)

IF YES, DETERMINE IF IN REFERENCE PERIOD AND IF DURATION IS MORE THAN ONE YEAR, AND ANSWER ITEM C.
IF NO, GO TO QUESTION 80.

C. What types of animals?

(1) _____

(2) _____

(3) _____

(4) _____

ACTIVITIES NOT RELATED TO WORK

Now I want to ask about some activities that you may have been involved in which were not related to your work, either at home or elsewhere. Once again, I am going to read slowly from a long list of activities. For each activity, please tell me whether you ever did the activity, whether you did it between [reference period start date] and [reference period end date] and whether you continued the activity for more or less than one year.

These are not questions about cumulative time spent in the activity; rather they are questions about the time intervals over which the case/control participated in the activity. If an activity is seasonal, count one season as a year (e.g., swimming for the summer is one year).

			A Exposure		**B** More Than One Year	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
80.	Auto or truck repair	(1)	(2)	(3)	(1)	(2)
81.	Raising or tending birds	(1)	(2)	(3)	(1)	(2)
82.	Carpentry or woodworking	(1)	(2)	(3)	(1)	(2)
83.	Child care or baby sitting your own children	(1)	(2)	(3)	(1)	(2)
84.	Regular home cleaning	(1)	(2)	(3)	(1)	(2)
85.	Exercising in a health club	(1)	(2)	(3)	(1)	(2)
86.	Farming	(1)	(2)	(3)	(1)	(2)
87.	Ranching	(1)	(2)	(3)	(1)	(2)
88.	Firefighting	(1)	(2)	(3)	(1)	(2)
89.	Gardening	(1)	(2)	(3)	(1)	(2)
90.	Hairdressing or cosmetology	(1)	(2)	(3)	(1)	(2)
91.	Hospital or health care volunteer	(1)	(2)	(3)	(1)	(2)
92.	Jewelry making	(1)	(2)	(3)	(1)	(2)
93.	Leather working	(1)	(2)	(3)	(1)	(2)
94.	U.S. Army Reserves / National Guard	(1)	(2)	(3)	(1)	(2)
95.	U.S. Navy Reserves	(1)	(2)	(3)	(1)	(2)

		A Exposure			B More Than One Year	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
96.	U.S. Air Force Reserves / National Guard	(1)	(2)	(3)	(1)	(2)
97.	U.S. Marines Reserves	(1)	(2)	(3)	(1)	(2)
98.	Other branch of armed forces reserves	(1)	(2)	(3)	(1)	(2)
99.	Pottery making (ceramics)	(1)	(2)	(3)	(1)	(2)
100.	Painting pictures	(1)	(2)	(3)	(1)	(2)
101.	Printing	(1)	(2)	(3)	(1)	(2)
102.	Spray painting automobiles or other vehicles	(1)	(2)	(3)	(1)	(2)
103.	Spinning or weaving	(1)	(2)	(3)	(1)	(2)
104.	Stone cutting or polishing	(1)	(2)	(3)	(1)	(2)
105.	Swimming in an indoor pool	(1)	(2)	(3)	(1)	(2)
106.	Using a hot tub or whirlpool	(1)	(2)	(3)	(1)	(2)
107.	Using a sauna	(1)	(2)	(3)	(1)	(2)
108.	Welding	(1)	(2)	(3)	(1)	(2)
109.	Other exposure	(1)	(2)	(3)	(1)	(2)
	Specify: _____					
110.	Other exposure	(1)	(2)	(3)	(1)	(2)
	Specify: _____					

111. **INTERVIEWER:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

112. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

113. **DATE FORM COMPLETED:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

Use this card for Form 13 (Environmental Questionnaire),

Items 60B, 61B, 62B and 63 B.

Not at All	(1)
Slightly	(2)
Moderately	(3)
Deeply	(4)

ENVIRONMENTAL QUESTIONNAIRE

ID No.				-				
Form Type	**E**	**Q**	**0**	**1**				

1. **SUBJECT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   A. **REFERENCE DATE: (COMPLETE PRIOR TO INTERVIEW)** ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   B. **REFERENCE PERIOD: (COMPLETE PRIOR TO INTERVIEW)** (1) ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year
   to
   (2) ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

HOUSEHOLD CHARACTERISTICS

Now I want to ask some questions about the house(s) you have lived in. As we talk about these conditions or exposures, please tell me if you have been exposed to these conditions and if you were exposed for more or less than one year. I will also be asking if any exposure occurred during the reference period. As you think about this, please feel free to use the anchor dates we discussed to help you determine if the exposure was near one of the special dates. We are looking for total exposure, so if you had an exposure for six months in one period and an exposure of eight months in another period, your total exposure would be for more than one year. Respond to seasonal exposures as if they were for a full year even if the exposure was for a few months (e.g., swimming).

USE THE ANCHOR DATES TO ESTABLISH IF THE EXPOSURE HAPPENED IN THE REFERENCE PERIOD. IF PARTICIPANT ANSWERS "NEVER" to EXPOSURE, GO TO THE NEXT ACTIVITY.

	A Exposure			**B** More Than One Year	
	Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
3. Have you ever used a wood or coal stove to heat your home?	(1)	(2)	(3)	(1)	(2)

IF YES, DETERMINE IF IN REFERENCE PERIOD AND IF MORE THAN ONE YEAR DURATION AND ANSWER ITEM C.
IF NO, GO TO QUESTION 4.

C. During the heating season, did you use the wood or coal stove:

INTERVIEWER READ LIST

Daily	(1)
Several times/week	(2)
Weekly	(3)
Less than weekly	(4)
Unknown	(5)

4. Have you ever used a wood or coal burning fireplace with an open flame in your home?	(1)	(2)	(3)	(1)	(2)

IF YES, DETERMINE IF IN REFERENCE PERIOD AND IF MORE THAN ONE YEAR DURATION AND ANSWER ITEM C
IF NO, GO TO QUESTION 5.

4. (Continued)

C. During the heating season, did you use the fireplace:

INTERVIEWER READ LIST

Daily	(1)
Several times/week	(2)
Weekly	(3)
Less than weekly	(4)
Unknown	(5)

I'm going to read you a list of devices. For each device, tell me if you ever used it in your home, whether you used it during the reference period and whether the period of use was more than one year.

	A Exposure			**B** More Than One Year	
	Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
5. Humidifier	(1)	(2)	(3)	(1)	(2)
6. Air cleaner or purifier	(1)	(2)	(3)	(1)	(2)
7. Cool mist vaporizer	(1)	(2)	(3)	(1)	(2)
8. Sauna	(1)	(2)	(3)	(1)	(2)
9. Hot tub	(1)	(2)	(3)	(1)	(2)

Next, I'm going to read you a list of types of cooling equipment. We'll be using the same type of responses we just used for other devices.

10.	Central air conditioning	(1)	(2)	(3)	(1)	(2)
11.	Window air conditioners	(1)	(2)	(3)	(1)	(2)
12.	Fans	(1)	(2)	(3)	(1)	(2)
13.	Evaporative (swamp cooler)	(1)	(2)	(3)	(1)	(2)
14.	Other types of cooling equipment	(1)	(2)	(3)	(1)	(2)

Now I am going to ask you about other conditions in your home.

		A Exposure			B More Than One Year	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
15.	Did your bathroom(s) ever have visible mold or mildew on indoor surfaces?	(1)	(2)	(3)	(1)	(2)
16.	Did any other room, including the basement, ever have visible mold or mildew?	(1)	(2)	(3)	(1)	(2)
17.	Did your home or basement ever have a problem with leaks or water damage?	(1)	(2)	(3)	(1)	(2)
	IF NEVER, GO TO QUESTION 19 OTHERWISE ANSWER QUESTION 18.					
18.	Were the carpets wet in the area where there were leaks or water damage?	(1)	(2)	(3)	(1)	(2)
19.	Did you ever vent your clothes dryer exhaust into the house or basement?	(1)	(2)	(3)	(1)	(2)
20.	Did you ever see rats or mice or rat or mouse droppings where you lived?	(1)	(2)	(3)	(1)	(2)
21.	Have you ever had a problem with large numbers of insects in your home?	(1)	(2)	(3)	(1)	(2)

I'm going to read a list of animals. Please tell me if you, or anyone living in your house, ever had any of these animals that stayed inside your home. I will also ask if you had these animals during the reference period and if you had them for more than one year.

		A Exposure			**B** More Than One Year	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
22.	Dogs	(1)	(2)	(3)	(1)	(2)
23.	Cats	(1)	(2)	(3)	(1)	(2)
24.	Rabbits	(1)	(2)	(3)	(1)	(2)
25.	Gerbils, hamsters, or guinea pigs	(1)	(2)	(3)	(1)	(2)
26.	Other mammals	(1)	(2)	(3)	(1)	(2)
	Specify: _____					
27.	Pigeons	(1)	(2)	(3)	(1)	(2)
28.	Parakeets	(1)	(2)	(3)	(1)	(2)
29.	Other birds	(1)	(2)	(3)	(1)	(2)
	Specify: _____					
30.	Fish in a large fish tank (more than 10 gallons)	(1)	(2)	(3)	(1)	(2)
31.	Fish in a small fish tank (less than 10 gallons)	(1)	(2)	(3)	(1)	(2)
32.	Turtles	(1)	(2)	(3)	(1)	(2)
33.	Lizards or snakes	(1)	(2)	(3)	(1)	(2)
34.	Frogs or salamanders	(1)	(2)	(3)	(1)	(2)

I'm going to read a list of birds. Please tell me if you, or anyone living in your house, ever raised or bred the following birds, whether you or they raised these birds during the reference period and if you or they raised them for more than one year.

		A Exposure			**B** More Than One Year	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Yes	No
35.	Chickens	(1)	(2)	(3)	(1)	(2)
36.	Turkeys	(1)	(2)	(3)	(1)	(2)
37.	Pigeons	(1)	(2)	(3)	(1)	(2)

		Yes	No
38.	Have you ever raised any <u>other</u> animals?	(1)	(2)

IF YES, ASK THE PARTICIPANT WHAT TYPE OF ANIMAL, WHETHER THEY RAISED THE ANIMAL DURING THE REFERENCE PERIOD AND IF THEY RAISED THEM FOR MORE THAN ONE YEAR. IF NO, GO TO QUESTION 39.

(A) Animal	(B) More Than One Year		(C) During Reference Period	
	Yes	No	Yes	No
(1) _____	(1)	(2)	(1)	(2)
(2) _____	(1)	(2)	(1)	(2)
(3) _____	(1)	(2)	(1)	(2)
(4) _____	(1)	(2)	(1)	(2)

I am going to read you a list of pillow stuffings. For each one, please tell me if you ever used pillows with that stuffing and if you did, whether you used it during the reference period, whether you used it for more than one year, and if this stuffing seemed to cause wheezing, coughing or breathing problems.

IF NEVER OR DON'T KNOW, GO TO NEXT QUESTION.

	A Exposure				**B** More Than One Year		**C** Breathing Problems	
	Never	Ended Before Reference Period	Current or Ended in the Reference Period	Don't Know	Yes	No	Yes	No
39. Feathers or down	(1)	(2)	(3)	(4)	(1)	(2)	(1)	(2)
40. Straw	(1)	(2)	(3)	(4)	(1)	(2)	(1)	(2)
41. Corn husks	(1)	(2)	(3)	(4)	(1)	(2)	(1)	(2)
42. Foam	(1)	(2)	(3)	(4)	(1)	(2)	(1)	(2)

43. As part of your normal routine, do you usually take a bath or a shower?
ANSWER BOTH IF PARTICIPANT SAYS SOMETIMES HE/SHE DOES ONE AND SOMETIMES THE OTHER OR IF HE/SHE SAYS "SHOWER IN MORNING AND BATH AT NIGHT" ETC.

Bath	(1)
Shower	(2)
Both	(3)
Neither	(4)

A. How often do you take a bath or shower?

Daily	(1)
Several times per week	(2)
Weekly	(3)
Less than weekly	(4)

SPECIFIC EXPOSURES CHART

Now I would like to ask some questions that deal with specific materials or substances that have been in the air (as dust, fumes or vapor) in your JOBS or in your HOBBIES, at work or at home. Wearing these metals in jewelry does not count as an exposure.

ASK ITEM A FOR EACH MATERIAL LISTED IN THE SPECIFIC EXPOSURES CHART.

A. Have you ever been exposed to [material/substance] as dust or fumes? **IF NEVER OR DON'T KNOW, ASK EXPOSURE (ITEM A) ABOUT NEXT MATERIAL.**

B. Were you exposed to [material/ substance] for more than one year?

C. Was your exposure on the job or away from the job? **OBTAIN SUFFICIENT INFORMATION TO ESTABLISH IF EXPOSURE OCCURRED ON THE JOB (OCCUPATIONAL) OR IN SOME OTHER NON-OCCUPATIONAL SETTING (NON-OCC). EXPOSURE OCCURRING BECAUSE OF LIVING NEAR A FACTORY OR OTHER SOURCE IS NON-OCCUPATIONAL. IF AFTER TALKING TO THE RESPONDENT, YOU CANNOT MAKE A DECISION ABOUT THE TYPE OF EXPOSURE, CHECK "UNSURE."**

MATERIAL	A EXPOSURE?	B MORE THAN ONE YEAR?	C MANNER OF EXPOSURE? (describe) (code)
44. Aluminum	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
45. Beryllium	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
46. Chromium	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
47. Cobalt	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
48. Gold	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
49. Nickel	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)

SPECIFIC EXPOSURES CHART

ASK ITEM A FOR EACH MATERIAL LISTED IN THE SPECIFIC EXPOSURES CHART.

A. Have you ever been exposed to [material/substance] as dust or fumes? **IF NEVER OR DON'T KNOW, ASK EXPOSURE (ITEM A) ABOUT NEXT MATERIAL.**

B. Were you exposed to [material/ substance] for more than one year?

C. Was your exposure on the job or away from the job? **OBTAIN SUFFICIENT INFORMATION TO ESTABLISH IF EXPOSURE OCCURRED ON THE JOB (OCCUPATIONAL) OR IN SOME OTHER NON-OCCUPATIONAL SETTING (NON-OCC). EXPOSURE OCCURRING BECAUSE OF LIVING NEAR A FACTORY OR OTHER SOURCE IS NON-OCCUPATIONAL. IF AFTER TALKING TO THE RESPONDENT, YOU CANNOT MAKE A DECISION ABOUT THE TYPE OF EXPOSURE, CHECK "UNSURE."**

MATERIAL	A EXPOSURE?	B MORE THAN ONE YEAR?	C MANNER OF EXPOSURE? (describe) (code)
50. Platinum	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
51. Titanium	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
52. Zirconium	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
53. Other metals, specify: (1) _____ (2) _____	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
54. Talc	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
55. Silica	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)

SPECIFIC EXPOSURES CHART

ASK ITEM A FOR EACH MATERIAL LISTED IN THE SPECIFIC EXPOSURES CHART.

A. Have you ever been exposed to [material/substance] as dust or fumes? **IF NEVER OR DON'T KNOW, ASK EXPOSURE (ITEM A) ABOUT NEXT MATERIAL.**

B. Were you exposed to [material/ substance] for more than one year?

C. Was your exposure on the job or away from the job? **OBTAIN SUFFICIENT INFORMATION TO ESTABLISH IF EXPOSURE OCCURRED ON THE JOB (OCCUPATIONAL) OR IN SOME OTHER NON-OCCUPATIONAL SETTING (NON-OCC). EXPOSURE OCCURRING BECAUSE OF LIVING NEAR A FACTORY OR OTHER SOURCE IS NON-OCCUPATIONAL. IF AFTER TALKING TO THE RESPONDENT, YOU CANNOT MAKE A DECISION ABOUT THE TYPE OF EXPOSURE, CHECK "UNSURE."**

MATERIAL	A EXPOSURE?	B MORE THAN ONE YEAR?	C MANNER OF EXPOSURE? (describe) (code)
56. Insecticides or Pesticides	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
57. Vegetable dust, e.g., cotton, jute, other specify: (1) _____ _____ (2) _____ _____	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
58. Animal dust, e.g., dander, bird droppings, wool, other specify: (1) _____ _____ (2) _____ _____	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)
59. Hairspray	Never (1) Ended before reference period (2) Current or ended in the reference period (3) Don't know (4)	Yes (1) No (2)	Occup (1) Non-occup (2) Both (3) Unsure (4)

SMOKING AND NICOTINE USE

60. Have you ever smoked cigarettes? (1) Yes (2) No
IF RESPONDENT SAYS HE/SHE EXPERIMENTED WITH THEM BRIEFLY OR SMOKED LESS THAN ONE PER WEEK, ANSWER "NO."

IF YES, ANSWER ITEMS A THROUGH D.
IF NO, SKIP TO QUESTION 61.

A. How many cigarettes did(do) you smoke per day during the time you smoked? ____ ____ • ____

B. Did you inhale:
INTERVIEWER READ LIST
Not at all (1)
Slightly (2)
Moderately (3)
Deeply (4)

C. How old were you when you started smoking cigarettes? ____ ____ age in years

D. Do you now smoke cigarettes? (1) Yes (2) No

IF YES, GO TO QUESTION 61.
IF NO, ANSWER ITEM (1).

(1) How old were you when you stopped? ____ ____ age in years

61. Have you ever smoked cigarillos? (1) Yes (2) No
IF RESPONDENT SAYS HE/SHE EXPERIMENTED WITH THEM BRIEFLY OR SMOKED LESS THAN ONE PER WEEK, ANSWER "NO."

IF YES, ANSWER ITEMS A THROUGH D.
IF NO, GO TO QUESTION 62.

A. How many cigarillos did(do) you smoke per day during the time you smoked? ____ ____ • ____

B. Did you inhale:
INTERVIEWER READ LIST
Not at all (1)
Slightly (2)
Moderately (3)
Deeply (4)

C. How old were you when you started smoking cigarillos? ____ ____ age in years

61. (Continued)

D. Do you now smoke cigarillos? (1) Yes (2) No

IF YES, GO TO QUESTION 62.
IF NO, ANSWER ITEM (1).

(1) How old were you when you stopped? ____ ____ age in years

62. Have you ever smoked cigars? (1) Yes (2) No
IF RESPONDENT SAYS HE/SHE EXPERIMENTED WITH THEM BRIEFLY OR SMOKED LESS THAN ONE PER WEEK, ANSWER "NO."

IF YES, ANSWER ITEMS A THROUGH D.
IF NO, SKIP TO QUESTION 63.

A. How many cigars did(do) you smoke per day during the time you smoked? ____ ____ • ____

B. Did you inhale:
INTERVIEWER READ LIST

Not at all	(1)
Slightly	(2)
Moderately	(3)
Deeply	(4)

C. How old were you when you started smoking cigars? ____ ____ age in years

D. Do you now smoke cigars? (1) Yes (2) No

IF YES, GO TO QUESTION 63.
IF NO, ANSWER ITEM (1).

(1) How old were you when you stopped? ____ ____

63. Have you ever smoked a pipe? (1) Yes (2) No
IF RESPONDENT SAYS HE/SHE EXPERIMENTED WITH THEM BRIEFLY OR SMOKED LESS THAN ONE PER WEEK, ANSWER "NO."

IF YES, ANSWER ITEMS A THROUGH D.
IF NO, SKIP TO QUESTION 64.

A. How many times per day did(do) you smoke a pipe during the time you smoked? ____ ____ • ____

63. (Continued)

B. Did you inhale:
INTERVIEWER READ LIST

Not at all	(1)
Slightly	(2)
Moderately	(3)
Deeply	(4)

C. How old were you when you started smoking a pipe?
____ ____
age in years

D. Do you now smoke a pipe? (1) Yes (2) No

IF YES, GO TO QUESTION 64.
IF NO, ANSWER ITEM (1).

(1) How old were you when you stopped?
____ ____
age in years

64. Are there now smokers [not including yourself] in your household? (1) Yes (2) No

IF YES, ANSWER ITEMS A AND B.
IF NO, GO TO QUESTION 65.

A. Do they include:

	Yes	No
(1) Your spouse?	(1)	(2)
(2) One or more of your children?	(1)	(2)
(3) Others?	(1)	(2)

B. Total number of smokers who live with you now, NOT INCLUDING YOURSELF: ____ ____ smokers

65. Are there now smokers near you where you work?

Yes	No	Not Applicable
(1)	(2)	(3)

IF YES, ANSWER ITEM A.
IF NO, GO TO QUESTION 66.

A. Do they smoke in an area where you might inhale their smoke? (1) Yes (2) No

66. Do you spend more than 3 hours a week in rooms with smoke from other smokers? (1) Yes (2) No

67. **INTERVIEWER:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

68. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

69. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

MEDICATION QUESTIONNAIRE

ID No.				-				
Form Type	**M**	**Q**	**0**	**1**				

1. **SUBJECT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   A. **REFERENCE DATE: (COMPLETE PRIOR TO INTERVIEW)** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

   B. **REFERENCE PERIOD: (COMPLETE PRIOR TO INTERVIEW)**
   (1) ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year
   to
   (2) ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

Now I will read slowly from a long list of things which some people have taken to improve or maintain their health. For each item, please tell me whether you have ever taken it regularly — that is, once a week for three months or more. If you have ever taken it regularly, I will ask you if you took it regularly for more than one year and whether you took it during the reference period.

IF A NAME IS GIVEN IN PARENTHESES ASK THE FIRST NAME, WHICH IS ALSO KNOWN AS (SECOND NAME).

		A Use				**B** One or More Years	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Unknown	Yes	No
3.	Nonprescription stool softeners (such as Ex-Lax, Metamucil, prunes)	(1)	(2)	(3)	(4)	(1)	(2)
4.	Non-prescription medicines for indigestion	(1)	(2)	(3)	(4)	(1)	(2)

		A				B	
		Use				One or More Years	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Unknown	Yes	No
5.	Non-prescription medicines for allergies	(1)	(2)	(3)	(4)	(1)	(2)
6.	Non-prescription medicines for coughs or colds	(1)	(2)	(3)	(4)	(1)	(2)
7.	Non-prescription medicines for diarrhea	(1)	(2)	(3)	(4)	(1)	(2)
8.	Non-prescription medicines to help you sleep	(1)	(2)	(3)	(4)	(1)	(2)
9.	Non-prescription vitamins and minerals	(1)	(2)	(3)	(4)	(1)	(2)
10.	Aspirin	(1)	(2)	(3)	(4)	(1)	(2)
11.	Acetaminophen (Tylenol)	(1)	(2)	(3)	(4)	(1)	(2)
12.	Non-prescription, non-steroidal anti-inflammatory drugs (Motrin, Advil, Alleve)	(1)	(2)	(3)	(4)	(1)	(2)
13.	Goldenseal (yellowroot)	(1)	(2)	(3)	(4)	(1)	(2)
14.	Sassafras	(1)	(2)	(3)	(4)	(1)	(2)
15.	Comfrey	(1)	(2)	(3)	(4)	(1)	(2)
16.	Bloodroot	(1)	(2)	(3)	(4)	(1)	(2)
17.	Tansy	(1)	(2)	(3)	(4)	(1)	(2)
18.	Senna	(1)	(2)	(3)	(4)	(1)	(2)
19.	Beth Root (birthroot)	(1)	(2)	(3)	(4)	(1)	(2)
20.	Ginseng (gensang)	(1)	(2)	(3)	(4)	(1)	(2)
21.	Ginkgo	(1)	(2)	(3)	(4)	(1)	(2)
22.	Echinacea	(1)	(2)	(3)	(4)	(1)	(2)
23.	Astragalus	(1)	(2)	(3)	(4)	(1)	(2)

		A Use				**B** One or More Years	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Unknown	Yes	No
24.	Other herbs	(1)	(2)	(3)	(4)	(1)	(2)
	(1) **IF YES**, Specify which ones						
25.	Dr. John's (or Father John's) Medicine	(1)	(2)	(3)	(4)	(1)	(2)
26.	Black Draught	(1)	(2)	(3)	(4)	(1)	(2)
27.	Other traditional remedies	(1)	(2)	(3)	(4)	(1)	(2)
28.	Lecithin	(1)	(2)	(3)	(4)	(1)	(2)
29.	Clay (eating)	(1)	(2)	(3)	(4)	(1)	(2)
30.	Starch (eating raw starch from box)	(1)	(2)	(3)	(4)	(1)	(2)
31.	Other dietary supplements	(1)	(2)	(3)	(4)	(1)	(2)
	(1) **IF YES**, Specify which ones						
32.	Melatonin	(1)	(2)	(3)	(4)	(1)	(2)
33.	Coffee/tea (by this I mean at least two cups once a day for three months or more)	(1)	(2)	(3)	(4)	(1)	(2)

Now I want to ask some questions about your use of prescription medications.

		Yes	No
34.	Have you ever taken any heart or blood pressure medicine?	(1)	(2)

IF YES, ANSWER QUESTIONS 35 - 43.
IF NO, GO TO QUESTION 44.
IF RESPONSE IN COLUMN A IS NEVER OR UNKNOWN, GO TO THE NEXT QUESTION.

		A				B	
		Use				One or More Years	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Unknown	Yes	No
35.	Amiodarone (Cordarone)	(1)	(2)	(3)	(4)	(1)	(2)
36.	Atenolol (Tenoretic, Tenormin)	(1)	(2)	(3)	(4)	(1)	(2)
37.	Diltiazem (Cardiazem, Dilacor)	(1)	(2)	(3)	(4)	(1)	(2)
38.	Hydralazine (Apresazide, Apresoline, Serapes, Hydrazide)	(1)	(2)	(3)	(4)	(1)	(2)
39.	Methyldopa (Aldomet, Aldoclor, Aldocil)	(1)	(2)	(3)	(4)	(1)	(2)
40.	Procainamide (Procan SR)	(1)	(2)	(3)	(4)	(1)	(2)
41.	Propanolol (Inderal, Inderide)	(1)	(2)	(3)	(4)	(1)	(2)
42.	Quinidine (Cardioquin, Quinidex)	(1)	(2)	(3)	(4)	(1)	(2)
43.	Thiazide diuretics (such as Moduretic, Diazide, Hydrodiuril)	(1)	(2)	(3)	(4)	(1)	(2)
44.	Did you ever take medicines to fight infections? **IF YES, ANSWER QUESTIONS 45-46.** **IF NO, GO TO QUESTION 47.**					Yes (1)	No (2)
45.	Nitrofurantoin (Macrobid, Macrodantin)	(1)	(2)	(3)	(4)	(1)	(2)
46.	Penicillin	(1)	(2)	(3)	(4)	(1)	(2)
47.	Did you ever take medicines for birth control?	(1)	(2)	(3)	(4)	(1)	(2)

		Yes	No
48.	Did you ever take any anti-inflammatory medicine?	(1)	(2)
49.	Did you ever take cancer treatment?	(1)	(2)

IF YES TO QUESTION 48 OR 49, ANSWER QUESTIONS 50-58.
IF NO TO BOTH QUESTIONS 48 AND 49, GO TO QUESTION 59.

		A Use				**B** One or More Years	
		Never	Ended Before Reference Period	Current or Ended in the Reference Period	Unknown	Yes	No
50.	Allopurinol (Zyloprim)	(1)	(2)	(3)	(4)	(1)	(2)
51.	Alpha-Interferon (Alferon-N, Intron-A, Roferon-A)	(1)	(2)	(3)	(4)	(1)	(2)
52.	Azathioprine (Imuran)	(1)	(2)	(3)	(4)	(1)	(2)
53.	Bleomycin (Blenoxane)	(1)	(2)	(3)	(4)	(1)	(2)
54.	D-Penicillamine (Cuprimine, Depen)	(1)	(2)	(3)	(4)	(1)	(2)
55.	Gold Salts (Myochrysine, Gold Sodium Thiomalate)	(1)	(2)	(3)	(4)	(1)	(2)
56.	Methotrexate (Rheumatrex)	(1)	(2)	(3)	(4)	(1)	(2)
57.	Minocycline (Dynacin, Minocin)	(1)	(2)	(3)	(4)	(1)	(2)
58.	Vincristine (Oncovin)	(1)	(2)	(3)	(4)	(1)	(2)

		Yes	No
59.	Have you ever taken any seizure or tranquilizer medicine?	(1)	(2)

IF YES, ANSWER QUESTIONS 60-62.
IF NO, GO TO QUESTION 63.

60.	Carbamazepine (Tegretol)	(1)	(2)	(3)	(4)	(1)	(2)
61.	Diazepam (Librium, Valium)	(1)	(2)	(3)	(4)	(1)	(2)
62.	Phenytoin (Dilantin)	(1)	(2)	(3)	(4)	(1)	(2)

63. Have you had a joint (knee or hip) replacement? Yes (1) No (2)

IF YES, ANSWER ITEM A.
IF NO, GO TO QUESTION 64.

A. What year did you receive the replacement? ____ ____ ____ ____ year

64. Do you have or have you ever had silicone implants or injections? Yes (1) No (2)

IF YES, ANSWER ITEMS A AND B.
IF NO, GO TO QUESTION 65.

A. What year did you receive the implant(s) or injections? ____ ____ ____ ____ year

B. Do you still have the implant(s) or injections? (1) Yes (2) No

(1) **IF NO**, What year was (were) the implant(s) or injections removed? ____ ____ ____ ____ year

65. **INTERVIEWER:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

66. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

67. **DATE FORM COMPLETED:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

Use this card for Form 15

(Scale A)

Rarely (less than 1 day)	(0)
Some of the time (1-2 days)	(1)
Moderate amount of the time (3-4 days)	(2)
Most of the time (almost every day)	(3)

ACCESS QUESTIONNARIE 15

ID No.				-					
Form Type	**S**	**A**	**0**	**1**					

GENERAL INSTRUCTIONS: COMPLETE AN ACCESS QUESTIONNAIRE 15 FOR EACH PARTICIPANT AT BASELINE. IF PARTICIPANT HAS ELECTED TO HAVE YOU READ THE QUESTIONS, GIVE THE PARTICIPANT THE SCALE A RESPONSE CARD NOW.

PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

The following questions ask about your feelings during the past week. For each of the statements, please indicate if you felt that way rarely or never, some of the time, a moderate amount of time, or most of the time.

		Rarely (less than 1 day)	**Some of the time (1 - 2 days)**	**Moderate amount of the time (3 - 4 days)**	**Most of the time (almost everyday)**
3.	I was bothered by things that don't usually bother me.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
4.	I did not feel like eating, my appetite was poor.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
5.	I had trouble keeping my mind on what I was doing.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
6.	I felt everything I did was an effort.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
7.	I felt sad.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
8.	I felt hopeful about the future.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
9.	I felt fearful.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
10.	My sleep was restless.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
11.	I was happy.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
12.	I felt lonely.	$(_0)$	$(_1)$	$(_2)$	$(_3)$
13.	I could not get going.	$(_0)$	$(_1)$	$(_2)$	$(_3)$

ADMINISTRATION

14. **INTERVIEWER**:

    A. **SIGNATURE**: _____

    B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

15. **RESEARCH COORDINATOR:**

    A. **SIGNATURE:** _____

    B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

16. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

Use this card for Form 16

(Scale B)

None of the time	(1)
Little of the time	(2)
Some of the time	(3)
Most of the time	(4)
All of the time	(5)

ACCESS QUESTIONNAIRE 16

ID No.				-				
Form Type	**S**	**B**	**0**	**1**				

GENERAL INSTRUCTIONS: COMPLETE AN ACCESS QUESTIONNAIRE 16 FOR EACH PARTICIPANT AT BASELINE. IF THE PARTICIPANT HAS ELECTED TO HAVE YOU READ THE QUESTIONS, GIVE THE PARTICIPANT THE SCALE B CARD NOW.

PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

The following questions ask about the support from other people that is available to you.

3. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on you mind)? Write in the number of close friends and relatives:

____ ____ ____

4. People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to you if you need it? (*Check the answer*.)

A. Someone to help you if you were confined to bed.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

B. Someone you can count on to listen to you when you need to talk.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

C. Someone to give you good advice about a crisis.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

D. Someone to take you to the doctor if you needed it.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

E. Someone who shows you love and affection.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

4. (Continued)

F. Someone to have a good time with.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

G. Someone to give you information to help you understand a situation.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

H. Someone to confide in or talk to about yourself or your problems.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

I. Someone who hugs you.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

J. Someone to get together with for relaxation.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

K. Someone to prepare your meals if you were unable to do it yourself.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

L. Someone whose advice you really want.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

4. (Continued)

M. Someone to do things with to help you get your mind off things.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

N. Someone to help with daily chores if you were sick.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

O. Someone to share your most private worries and fears with.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

P. Someone to turn to for suggestions about how to deal with a personal problem.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

Q. Someone to do something enjoyable with.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

R. Someone who understands your problems.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

S. Someone to love and make you feel wanted.

(1)	(2)	(3)	(4)	(5)
None of the time	Little of the time	Some of the time	Most of the time	All of the time

5. During the past four weeks was someone available to help you if you needed and wanted help (e.g., if you needed someone to talk to or if you needed help with daily chores)? (*Check the answer*.)

(1)	(2)	(3)	(4)	(5)
Yes, as much as I wanted	Yes, quite a bit	Yes, a fair amount	Yes, a little bit	No, not at all

ADMINISTRATION

6. **INTERVIEWER**:

   A. **SIGNATURE**: _____

   B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

7. **RESEARCH COORDINATOR:**

   A. **SIGNATURE:** _____

   B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

8. **DATE FORM COMPLETED:** ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

Use this card for Form 17

(Scale C)

Strongly Agree	(1)
Agree	(2)
Neutral	(3)
Disagree	(4)
Strongly Disagree	(5)

ACCESS QUESTIONNAIRE 17

ID No.				-				
Form Type	**S**	**C**	**0**	**1**				

GENERAL INSTRUCTIONS: COMPLETE AN ACCESS QUESTIONNAIRE 17 FOR EACH PARTICIPANT AT BASELINE. IF PARTICIPANT HAS ELECTED TO HAVE YOU READ THE QUESTIONS, GIVE THE PARTICIPANT THE SCALE C CARD NOW.

PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

The following questions ask about your mood and attitudes.

		Strongly Agree	**Agree**	**Neutral**	**Disagree**	**Strongly Disagree**
3.	In uncertain times, I usually expect the best.	(1)	(2)	(3)	(4)	(5)
4.	It's easy for me to relax.	(1)	(2)	(3)	(4)	(5)
5.	If something can go wrong for me, it will.	(1)	(2)	(3)	(4)	(5)
6.	I always look on the bright side of things.	(1)	(2)	(3)	(4)	(5)
7.	I'm always optimistic about my future.	(1)	(2)	(3)	(4)	(5)
8.	I enjoy my friends a lot.	(1)	(2)	(3)	(4)	(5)
9.	It's important for me to keep busy.	(1)	(2)	(3)	(4)	(5)
10.	I hardly ever expect things to go my way.	(1)	(2)	(3)	(4)	(5)
11.	Things never work out the way I want them to.	(1)	(2)	(3)	(4)	(5)
12.	I don't get upset too easily.	(1)	(2)	(3)	(4)	(5)
13.	I'm a believer in the idea that "every cloud has a silver lining."	(1)	(2)	(3)	(4)	(5)
14.	I rarely count on good things happening to me.	(1)	(2)	(3)	(4)	(5)

ADMINISTRATION

15. **INTERVIEWER**:

A. **SIGNATURE**: _____

B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

16. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

17. **DATE FORM COMPLETED:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

Use this card for Form 18

(Scale D)

Items 5A - 5J

Yes, limited a lot	(1)
Yes, limited a little	(2)
No, not limited at all	(3)
Not applicable	(4)

Use this card for Form 18

(Scale E)

Items 11A - 11I

All of the time	(1)
Most of the time	(2)
A good bit of the time	(3)
Some of the time	(4)
A little of the time	(5)
None of the time	(6)

Use this card for Form 18

(Scale F)

Items 13A - 13D

Definitely True	(1)
Mostly true	(2)
Don’t Know	(3)
Most False	(4)
Definitely False	(5)

ACCESS QUESTIONNAIRE 18

ID No.				-				
Form Type	**S**	**D**	**0**	**1**				

GENERAL INSTRUCTIONS: COMPLETE AN ACCESS QUESTIONNAIRE 18 FOR EACH PARTICIPANT AT BASELINE. IF PARTICIPANT HAS ELECTED TO HAVE YOU READ THE QUESTIONS, GIVE THE PARTICIPANT THE SCALE D, E AND F CARDS NOW.

PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

The following questions ask about your health.

3. In general, would you say your health is:

(1)	(2)	(3)	(4)	(5)
Excellent	Very Good	Good	Fair	Poor

4. Compared to a year ago, how would you rate your health in general now?

(1)	(2)	(3)	(4)	(5)
Much better now than 1 year ago	Somewhat better now than 1 year ago	About the same	Somewhat worse now than 1 year ago	Much worse now than 1 year ago

5. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Check **one** answer on each line.)

		Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**	**Not Applicable**
A.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	(1)	(2)	(3)	(4)
B.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	(1)	(2)	(3)	(4)
C.	Lifting or carrying groceries?	(1)	(2)	(3)	(4)
D.	Climbing several flights of stairs?	(1)	(2)	(3)	(4)
E.	Climbing one flight of stairs?	(1)	(2)	(3)	(4)
F.	Bending, kneeling, or stooping?	(1)	(2)	(3)	(4)
G.	Walking more than a mile?	(1)	(2)	(3)	(4)
H.	Walking several blocks?	(1)	(2)	(3)	(4)
I.	Walking one block?	(1)	(2)	(3)	(4)
J.	Bathing or dressing yourself?	(1)	(2)	(3)	(4)

6. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Check **one** answer on each line.)

		Yes	No
A.	Cut down on the amount of time you spent on work or other activities	(1)	(2)
B.	Accomplished less than you would like	(1)	(2)
C.	Were limited in the kind of work or other activities	(1)	(2)
D.	Had difficulty performing the work or other activities (for example, it took extra effort)	(1)	(2)

7. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Check **one** answer on each line.)

		Yes	No
A.	Cut down on the amount of time you spent on work or other activities	(1)	(2)
B.	Accomplished less than you would like	(1)	(2)
C.	Didn't do work or other activities as carefully as usual	(1)	(2)

8. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Check **one** answer.)

(1)	(2)	(3)	(4)	(5)
Not at all	Slightly	Moderately	Quite a bit	Extremely

9. How much bodily pain have you had during the past 4 weeks? (Check **one** answer.)

(1)	(2)	(3)	(4)	(5)	(6)
None	Very Mild	Mild	Moderate	Severe	Very Severe

10. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Check **one** answer.)

(1)	(2)	(3)	(4)	(5)
Not at all	A little bit	Moderately	Quite a bit	Extremely

11. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks ... (Check **one** answer on each line.)

	All of the Time	**Most of the Time**	**A Good bit of Time**	**Some of the Time**	**A little of the Time**	**None of the Time**
A. Did you feel full of pep?	(1)	(2)	(3)	(4)	(5)	(6)
B. Have you been a very nervous person?	(1)	(2)	(3)	(4)	(5)	(6)
C. Have you felt so down in the dumps that nothing could cheer you up?	(1)	(2)	(3)	(4)	(5)	(6)
D. Have you felt calm and peaceful?	(1)	(2)	(3)	(4)	(5)	(6)
E. Did you have a lot of energy?	(1)	(2)	(3)	(4)	(5)	(6)
F. Have you felt down-hearted and blue?	(1)	(2)	(3)	(4)	(5)	(6)
G. Did you feel worn out?	(1)	(2)	(3)	(4)	(5)	(6)
H. Have you been a happy person?	(1)	(2)	(3)	(4)	(5)	(6)
I. Did you feel tired?	(1)	(2)	(3)	(4)	(5)	(6)

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Check **one** answer.)

(1)	(2)	(3)	(4)	(5)
All of the time	Most of the time	Some of the time	A little of the time	None of the time

13. How true or false is each of the following statements for you? (Check **one** answer on each line.)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
A. I seem to get sick a little easier than other people	(1)	(2)	(3)	(4)	(5)
B. I am as healthy as anybody I know	(1)	(2)	(3)	(4)	(5)
C. I expect my health to get worse	(1)	(2)	(3)	(4)	(5)
D. My health is excellent	(1)	(2)	(3)	(4)	(5)

ADMINISTRATION

14. **INTERVIEWER**:

    A. **SIGNATURE**: _____

    B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

15. **RESEARCH COORDINATOR:**

    A. **SIGNATURE:** _____

    B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

16. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

Use this card for Form 19

CARD I

Items 11 and 12.

21 . . . . . 20,000 - 24,999

22 . . . . . 25,000 - 29,999

23 . . . . . 30,000 - 34,999

24 . . . . . 35,000 - 39,999

25 . . . . . 40,000 - 44,999

26 . . . . . 45,000 - 49,999

27 . . . . . 50,000 and over

Use this card for Form 19

CARD J

Items 11 and 12.

1	. . . . .	Less than 1,000 (including loss)
2	. . . . .	1,000 - 1,999
3	. . . . .	2,000 - 2,999
4	. . . . .	3,000 - 3,999
5	. . . . .	4,000 - 4,999
6	. . . . .	5,000 - 5,999
7	. . . . .	6,000 - 6,999
8	. . . . .	7,000 - 7,999
9	. . . . .	8,000 - 8,999
10	. . . . .	9,000 - 9,999
11	. . . . .	10,000 - 10,999
12	. . . . .	11,000 - 11,999
13	. . . . .	12,000 - 12,999
14	. . . . .	13,000 - 13,999
15	. . . . .	14,000 - 14,999
16	. . . . .	15,000 - 15,999
17	. . . . .	16,000 - 16,999
18	. . . . .	17,000 - 17,999
19	. . . . .	18,000 - 18,999
20	. . . . .	19,000 - 19,999

ACCESS QUESTIONNAIRE 19

ID No.				-					
Form Type	**S**	**E**	**0**	**1**					

GENERAL INSTRUCTIONS: COMPLETE AN ACCESS QUESTIONNAIRE 19 FOR EACH PARTICIPANT AT BASELINE. GIVE THE PARTICIPANT THE I AND J CARDS NOW.

PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

The following questions ask about what kinds of communities you have lived in, your well-being and your income. If you do not know how many people lived in the towns or cities where you have lived, give the best answer you can.

3. Which of the following best describes the places you lived in as a child (age newborn to ten)?

		Yes	No
A.	Town (population 1 - 50,000)	(1)	(2)
B.	Small city (population 50,000 - 300,000)	(1)	(2)
C.	Large city (population over 300,000)	(1)	(2)
D.	Don't know	(1)	(2)

4. Which of the following best describes the kind of communities you lived in as a child (age newborn to ten)?

A.	Lived within the city (town) limits	(1)	(2)
B.	Lived in a suburban setting (within 15 miles of a small or large city)	(1)	(2)
C.	Lived in a rural setting	(1)	(2)
D.	Don't know	(1)	(2)

5. Which of the following best describes the places where you have lived during the past three years?

A.	Town (population 1 - 50,000)	(1)	(2)
B.	Small city (population 50,000 - 300,000)	(1)	(2)
C.	Large city (population over 300,000)	(1)	(2)
D.	Don't know	(1)	(2)

6. Which of the following best describes the kind of communities you have lived during the past three years?

		Yes	No
A.	Lived within the city (town) limits	(1)	(2)
B.	Lived in a suburban setting (within 15 miles of a small or large city)	(1)	(2)
C.	Lived in a rural setting	(1)	(2)
D.	Don't know	(1)	(2)

7. Do you think you have a physical disability? (1) (2)

8. Do you think you have a mental or emotional disability? (1) (2)

9. Have you ever applied for disability payments or services? (1) (2)

10. Have you been awarded disability payments or services? (1) (2)

Income is important in analyzing the health information we collect. For example, this information helps us to learn whether persons in one income group use certain types of medical care services or have certain conditions more or less often than those in another group.

11. Was your total combined FAMILY income during the past 12 months more or less than $20,000 -- that is, yours as well as that of all the members of your household. **CHECK ONLY ONE.**

(1)	(2)
$20,000 or more (Use Card I)	Less than $20,000 (Use Card J)

12. Look at cards I and J to find the group in which your <u>total</u> FAMILY income falls. Write the number of this group in the blanks. ____ ____

ADMINISTRATION

13. **INTERVIEWER**:

    A. **SIGNATURE**: _____

    B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

14. **RESEARCH COORDINATOR:**

    A. **SIGNATURE:** _____

    B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

15. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

RELATIONSHIP QUESTIONNAIRE A

ID No.				-				
Form Type	**S**	**T**	**0**	**1**				

Beginning script:
I would like to ask you some questions about any spouses or mates with whom you had children and some questions about your children.

1. **PARTICIPANT INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. With how many spouse(s)/mate(s) have you had children? By this I mean birth children. Do not count adopted, foster or stepchildren. ____ ____

   IF RESPONSE IS 0, SKIP TO QUESTION 5.

4. What is the total number of birth children you have had with these spouses/mates? ____ ____

5. **INTERVIEWER:**

   A. **SIGNATURE:** _____

   B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

6. **RESEARCH COORDINATOR:**

   A. **SIGNATURE:** _____

   B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

7. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

RELATIONSHIP QUESTIONNAIRE B

ID No.				-				
Form Type	**R**	**Q**						

GENERAL INSTRUCTIONS: COMPLETE A RELATIONSHIP QUESTIONNAIRE B FOR EACH SPOUSE/MATE WITH WHOM THE PARTICIPANT HAS HAD BIRTH CHILDREN. GIVE EACH FORM A SEQUENTIAL FORM TYPE NUMBER. START WITH THE CURRENT OR MOST RECENT SPOUSE/MATE AND WORK BACKWARDS. THE FIRST TIME YOU USE THIS FORM, READ THE "BEGINNING SCRIPT". FOR ALL SUBSEQUENT TIMES YOU USE THIS FORM, READ THE "CONTINUING SCRIPT".

Beginning script:
I would like to ask you some questions about your most recent spouse or mate with whom you had children and some questions about your children. If you are unsure of any of the answers, please respond with "I don't know."

Continuing script:
I would now like to ask you some questions about the spouse or mate with whom you had children just prior to the spouse/mate we just talked about.

I. PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. Spouse/mate initials: ____ ____ ____

II. SPOUSE / MATE

4. Of the following, which one best describes this person's race?
   INTERVIEWER, READ LIST.

   White (1)
   Black or African American (2)
   Asian/Pacific Islander (3)
   American Indian or Alaska Native (4)
   Other (5)

   If Other, specify: _____

   Don't know (6)

5. Is/was this person Hispanic? (1) Yes (2) No (3) Don't know

6. Is this person now alive? (1) Yes (2) No (3) Don't know

7. How old is this person? (If dead, how old was this person when he/she died?) Age: ____ ____

8. About how many years have you lived (did you live) with this person? Years lived together: ____ ____

9. Has this person ever had sarcoidosis? (1) Yes (2) Probable (3) No (4) Don't know

IF YES, ANSWER QUESTION 10.
OTHERWISE, PROCEED TO SECTION III.

10. How old was this person when he/she got sarcoidosis?

    A. Age when he/she got sarcoidosis: ____ ____

    B. How many years did you live with this person after he/she got sarcoidosis? ____ ____

III. CHILDREN OF PARTICIPANT AND SPOUSE/MATE

I am going to ask you some questions about all the birth children living and no longer living you had with your spouse/mate. **(IN ORDER TO MAKE SURE PARTICIPANT IS TALKING ABOUT CHILDREN WITH SPOUSE/MATE FOR WHOM THIS FORM IS BEING COMPLETED, REPEAT INITIALS OF SPOUSE/MATE.)** Please start with the oldest child and proceed to the youngest.

11. Child's initials	12. Gender of child **[USE CODE: MALE = 1 FEMALE = 2]**	13. Is this child still alive? **[INDICATE WITH FOLLOWING CODES: YES = 1 NO = 2 DK = 3]**	14. What is [was] this child's current age? **[AGE AT DEATH]: [DON'T KNOW = 98]**	15. About how many years did you live in the same household with this child? **[DON'T KNOW = 98]**	16. Did this child ever have sarcoidosis? **[YES = 1 PROBABLE = 2 NO = 3 DK = 4 [DON'T KNOW = 98] IF YES, ASK QUESTIONS IN COLUMNS 17 AND 18.]**	17. How old was this child when he/she got sarcoidosis? **[DON'T KNOW = 98]**	18. How many years did you live with this child after he/she got sarcoidosis? **[DON'T KNOW = 98]**
A.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
B.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
C.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
D.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
E.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
F.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
G.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
H.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
I. ___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
J.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
K.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __
L.___ ___ ___	_____	_____	__ __	___ ___	_____	___ ___	__ __

IV. MULTIPLE BIRTHS:

	Yes	No
19. Were any of these children twins, triplets, quadruplets, etc.	(1)	(2)

IF NO, GO TO SECTION V.

IF YES, IN ITEMS A TO F BELOW, IDENTIFY CHILDREN IN EACH SET OF MULTIPLE BIRTHS BY ENTERING ROW LETTERS FROM SECTION III, QUESTION 11 FOR EACH CHILD ON THE FIRST LINE OF THAT SET. LIST OLDEST SET IN ITEM A BELOW, NEXT OLDEST IN ITEM C BELOW, AND YOUNGEST IN ITEM E BELOW.

ON THE SECOND LINE (DESIGNATION LINE) OF THE SET, IDENTIFY THE RELATIONSHIP (IDENTICAL (I), FRATERNAL (F)) AND THE APPROPRIATE GROUPINGS FOR ALL SETS OF CHILDREN. USE SEQUENTIAL NUMBERS I_1, I_2, I_3 ETC. TO IDENTIFY EACH GROUP OF IDENTICAL BIRTHS. FRATERNAL BIRTHS ARE ALL DESIGNATED F_1. FOR INSTANCE, A MULTIPLE BIRTH OF QUINTUPLETS WITH TWO SETS OF IDENTICAL TWINS AND ONE FRATERNAL QUINT (WITH THE SETS IN ORDER) WOULD HAVE THE FOLLOWING DESIGNATIONS:

I_1 I_1 I_2 I_2 F_1

IF PARTICIPANT ASKS THE MEANING OF IDENTICAL, SAY "ALIKE AS TWO PEAS IN A POD".

		(1)	(2)	(3)	(4)	(5)
A.	Multiple birth 1	____	____	____	____	____
B.	Designation	___ ___	___ ___	___ ___	___ ___	___ ___
C.	Multiple birth 2	____	____	____	____	____
D.	Designation	___ ___	___ ___	___ ___	___ ___	___ ___
E.	Multiple birth 3	____	____	____	____	____
F.	Designation	___ ___	___ ___	___ ___	___ ___	___ ___

V. ADMINISTRATIVE MATTERS

20. **INTERVIEWER:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

21. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ - ____ ____

22. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

IF THE RESPONDENT HAS HAD MORE THAN ONE SPOUSE/MATE WITH WHOM HE/SHE HAD CHILDREN, PLEASE COMPLETE ANOTHER RELATIONSHIP QUESTIONNAIRE B FOR EACH ADDITIONAL SPOUSE/MATE.

FAMILY HISTORY QUESTIONNAIRE

ID No.				-				
Form Type	**F**	**H**	**0**	**1**				

GENERAL INSTRUCTIONS: ASK PARTICIPANT ALL QUESTIONS, SKIPPING OVER SECTIONS WHEN APPROPRIATE.

Beginning script:
The following questions have to do with your blood relatives (for example your birth mother, your birth father, etc.). Please answer these questions to the best of your knowledge. If you are unsure of any of the answers, please respond with "I don't know". Remember, these questions are about blood relatives.

I. PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

3. Do you know who at least one of your birth parents are? (1) Yes (2) No (3) Unknown

Please answer **NO** if you only know about your adoptive, foster or step-parents.

IF YES, ANSWER ALL REMAINING QUESTIONS.
IF NO OR UNKNOWN, GO TO ITEM 33 OF THIS QUESTIONNAIRE.

First Degree Blood Relatives

II. MOTHER

4. What best describes your mother's race?

White	(1)
Black or African American	(2)
Asian/Pacific Islander	(3)
American Indian or Alaska Native	(4)
Other	(5)
IF OTHER, specify: _____	
Don't know	(6)

5. Is/was your mother Hispanic? (1) Yes (2) No (3) Don't know

6. Is your mother now alive? (1) Yes (2) No (3) Don't know

7. How old is your mother? (If dead, how old was she when she died?) Age: ____ ____

8. About how many years did you live with your mother? Years lived together: ____ ____

9. Has(did) your mother ever had(have) sarcoidosis? (1) Yes (2) Probable (3) No (4) Don't know

(REVIEW LAY DEFINITION OF DISEASE)

IF YES, ANSWER QUESTION 10.
OTHERWISE, GO TO SECTION III, QUESTION 11.

10. How old was she when she got sarcoidosis?

A. Age when she got sarcoidosis: ____ ____

B. How many years did you live with your mother after she got sarcoidosis? ____ ____

III. FATHER

11. What best describes your father's race?

White	(1)
Black or African American	(2)
Asian/Pacific Islander	(3)
American Indian or Alaska Native	(4)
Other	(5)
IF OTHER, specify: _____	
Don't know	(6)

12. Is/was your father Hispanic? (1) Yes (2) No (3) Don't know

13. Is your father now alive? (1) Yes (2) No (3) Don't know

14. How old is your father? (If dead, how old was he when he died?) Age: ____ ____

15. About how many years did you live with your father? Years lived together: ____ ____

16. Has(did) your father ever had(have) sarcoidosis? (1) Yes (2) Probable (3) No (4) Don't know

IF YES, ANSWER QUESTION 17.
OTHERWISE, GO TO SECTION IV, QUESTION 18.

17. How old was he when he got sarcoidosis?

A. Age when he got sarcoidosis: ____ ____

B. How many years did you live with your father after he got sarcoidosis? ____ ____

IV. SIBLINGS

(ASK QUESTIONS 20-28 FOR EACH SIBLING. START FROM THE OLDEST AND GO TO THE YOUNGEST SIBLING. BEGIN QUESTIONS ABOUT EACH SIBLING BY ASKING THE INITIALS OF THE SIBLING AND INDICATE SUCH IN THE FIRST COLUMN OF THE TABLE.)

The next set of questions are about your brothers and sisters:

18. How many full and half brothers and sisters do you have living and deceased? This does not include adopted, foster or step brothers and adopted, foster or step sisters. Number ____ ____
(IF 0, GO TO SECTION VI)

19. What number were you in the birth order of your brothers and sisters? Birth order # ____ ____

Starting with your oldest sibling and proceeding to the youngest, please answer the following set of questions for each. Start by telling me what the sibling's initials are (were):

20. Brother's / sister's initials	21. Brother or Sister? **(USE CODE: BROTHER = 1 SISTER =2)**	22. Did this brother/ sister have: a. The same birth mother as you? b. The same birth father as you?	23. Is this brother/ sister still alive? **(INDICATE WITH FOLLOWING CODES: YES = 1 NO = 2 DK = 3)**	24. What is (was) the current age (age at death) of this brother/ sister? **(DON'T KNOW = 98)**	25. About how many years did you live in the same household with this brother/ sister? **(DON'T KNOW = 98)**	26. Did this brother/ sister ever have sarcoidosis? **(YES = 1 PROBABLE - 2 NO = 3 DK = 4 IF YES, ANSWER QUESTIONS IN COLUMNS 27 AND 28.)**	27. How old was this brother/ sister when he/ she got sarcoid-osis? **(DON'T KNOW = 98)**	28. About how many years did you live in the same house with this brother/ sister after he/she got sarcoidosis? **(DON'T KNOW = 98)**
A. ___ ___ ___	____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	___	__ __	___ ___	___	___ ___	___ ___
B. ___ ___ ___	____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	___	__ __	___ ___	___	___ ___	___ ___
C. ___ ___ ___	____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	___	__ __	___ ___	___	___ ___	___ ___
D. ___ ___ ___	____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	___	__ __	___ ___	___	___ ___	___ ___

IV. SIBLINGS (Continued)

20. Brother's / sister's initials	21. Brother or Sister? **(USE CODE: BROTHER = 1 SISTER =2)**	22. Did this brother/ sister have: a. The same birth mother as you? b. The same birth father as you?	23. Is this brother/ sister still alive? **(INDICATE WITH FOLLOWING CODES: YES = 1 NO = 2 DK = 3)**	24. What is (was) the current age (age at death) of this brother/ sister? **(DON'T KNOW = 98)**	25. About how many years did you live in the same household with this brother/ sister? **(DON'T KNOW = 98)**	26. Did this brother/ sister ever have sarcoidosis? **(YES = 1 PROBABLE - 2 NO = 3 DK = 4 IF YES, ANSWER QUESTIONS IN COLUMNS 27 AND 28.)**	27. How old was this brother/ sister when he/ she got sarcoid-osis? **(DON'T KNOW = 98)**	28. About how many years did you live in the same house with this brother/ sister after he/she got sarcoidosis? **(DON'T KNOW = 98)**
E. ___ ___ ___	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	___ ___	____	___ ___	___ ___
F. ___ ___ ___	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	___ ___	____	___ ___	___ ___
G. ___ ___ ___	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	___ ___	____	___ ___	___ ___
H. ___ ___ ___	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	___ ___	____	___ ___	___ ___
I. ___ ___ ___	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	___ ___	____	___ ___	___ ___

IF PARTICIPANT HAS MORE THAN 9 SIBLINGS, COMPLETE A FAMILY HISTORY SUPPLEMENT (FORM 23).

V. MULTIPLE BIRTHS AMONG BROTHERS AND SISTERS

29. Were any of your brothers and sisters twins, triplets, quadruplets, etc.?

Yes	No
(1)	(2)

IF NO, GO TO SECTION VI.
IF YES, IN ITEMS A TO F BELOW IDENTIFY BROTHERS AND SISTERS IN EACH SET OF MULTIPLE BIRTHS BY ENTERING ROW LETTERS FROM SECTION IV, QUESTION 20 FOR EACH BROTHER OR SISTER ON THE FIRST LINE OF THAT SET. IF THE PARTICIPANT IS ONE OF THE TWINS, TRIPLETS, ETC., THE ROW DESIGNATION IS P (FOR PARTICIPANT). LIST OLDEST SET IN ITEM A BELOW, NEXT OLDEST IN ITEM C BELOW, AND YOUNGEST IN ITEM E BELOW.

ON THE SECOND LINE (DESIGNATION LINE) IN EACH SET, IDENTIFY THE RELATIONSHIP (IDENTICAL (I), FRATERNAL (F)) AND THE APPROPRIATE GROUPINGS FOR ALL SETS OF BROTHERS OR SISTERS. USE SEQUENTIAL NUMBERS I_1, I_2, I_3 ETC. TO IDENTIFY EACH GROUP OF IDENTICAL BIRTHS. FRATERNAL BIRTHS ARE ALL DESIGNATED F_1. FOR INSTANCE, A MULTIPLE BIRTH OF QUINTUPLETS WITH TWO SETS OF IDENTICAL TWINS AND ONE FRATERNAL QUINT (WITH THE SET IN ORDER) WOULD HAVE THE FOLLOWING DESIGNATIONS:

I_1 I_1 I_2 I_2 F_1

IF PATIENT ASKS THE MEANING OF IDENTICAL, SAY "ALIKE AS TWO PEAS IN A POD".

		(1)	(2)	(3)	(4)	(5)
A.	Multiple birth 1	____	____	____	____	____
B.	Designation	___ ___	___ ___	___ ___	___ ___	___ ___
C.	Multiple birth 2	____	____	____	____	____
D.	Designation	___ ___	___ ___	___ ___	___ ___	___ ___
E.	Multiple birth 3	____	____	____	____	____
F.	Designation	___ ___	___ ___	___ ___	___ ___	___ ___

PLEASE NOTE THAT THE ROW DESIGNATION FROM FROM 22 AND ANY ADDITIONAL FORM 23s SHOULD BE ENTERED FOR THE ABOVE SET OF QUESTIONS.

VI. OTHER PEOPLE WITH SARCOIDOSIS

30. How many full brothers and sisters living and deceased do your parents have, that is, brothers and sisters with the same parents?

a. Paternal aunts _____ ____
b. Paternal uncles _____ ____
c. Maternal aunts _____ ____
d. Maternal uncles _____ ____

31. Did any of your grandparents or aunts and uncles, that is, your father's and mother's brothers and sisters, have sarcoidosis? This question asks only about blood relatives.

Yes	Probable	No	Don't Know
(1)	(2)	(3)	(4)

IF YES OR PROBABLE, ANSWER QUESTION 32.
IF NO OR DON'T KNOW, GO TO QUESTION 33.

32. Which of your relatives had sarcoidosis?

		(1) Paternal			(2) Maternal		
		Yes	No	Unknown	Yes	No	Unknown
A.	Grandfather	(1)	(2)	(3)	(1)	(2)	(3)
B.	Grandmother	(1)	(2)	(3)	(1)	(2)	(3)
		Number			Number		
C.	Aunt	___ ___			___ ___		
D.	Uncles	___ ___			___ ___		

33. Not counting spouses/mates with whom you had children, your children and other blood relatives, how many other persons (neighbors, co-workers, friends, etc.) have you known (before [reference date]) who have had sarcoidosis? This includes spouses / mates with whom you did not have children. _____ _____

IF 0, GO TO SECTION VII.

A. How many of these people did you actually have contact with?

(1) At home _____ _____

(2) At work _____ _____

(3) Other places _____ _____

IF 0, FOR (1), (2) AND (3), SKIP TO SECTION VII.

B. How old were you when you first met any of these people with sarcoidosis? _____ _____ years

33. (Continued)

C. How old were you when you last saw any of these people? _____ _____ years

D. How often did you generally see these people?

Less than once a month	(1)
Between once a month and once a week	(2)
More often than once a week	(3)

E.	Did you (or do you) live in the same house as any of these people?	Yes (1)	No (2)
F.	Did you (or do you) work in the same building as any of these people?	Yes (1)	No (2)
G.	Are you a close friend or co-worker with any of these people? Close friend or co-worker is someone you have face-to-face contact with at least once a week.	Yes (1)	No (2)

VII. ADMINISTRATIVE MATTERS

34. **INTERVIEWER:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

35. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

36. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

FAMILY HISTORY SUPPLEMENT

ID No.				-				
Form Type	**F**	**S**						

GENERAL INSTRUCTIONS: ASK QUESTIONS 3-11 FOR EACH SIBLING. START FROM THE OLDEST AFTER THE LAST ENTRY ON FORM 22 AND GO TO THE YOUNGEST SIBLING. BEGIN QUESTIONS ABOUT EACH SIBLING BY ASKING THE INITIALS OF THE SIBLING AND INDICATE SUCH IN THE FIRST COLUMN OF THE TABLE.

I. PARTICIPANT IDENTIFICATION

1. **PARTICIPANT'S INITIALS:** ____ ____ ____

2. **DATE OF INTERVIEW:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

II. SIBLINGS (Continued)

3. Brother's / sister's initials	4. Brother or Sister? **(USE CODE: BROTHER = 1 SISTER =2)**	5. Did this brother/sister have: a. The same birth mother as you? b. The same birth father as you?	6. Is this brother/ sister still alive? **(INDICATE WITH FOLLOWING CODES: YES = 1 NO = 2 DK = 3)**	7. What is (was) the current age (age at death) of this brother/ sister? **(DON'T KNOW = 98)**	8. About how many years did you live in the same household with this brother/sister? **(DON'T KNOW = 98)**	9. Did this brother/ sister ever have sarcoidosis? **(YES = 1 PROBABLE = 2 NO = 3 DK = 4 IF YES, ANSWER QUESTIONS IN COLUMNS 10 AND 11.)**	10. How old was this brother/sister when he/she got sarcoidosis? **(DON'T KNOW = 98)**	11. About how many years did you live in the same house with this brother/sister after he/she got sarcoidosis? **(DON'T KNOW = 98)**
A. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
B. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
C. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
D. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
E. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
F. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
G. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
H. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
I. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
J. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____

!I. SIBLINGS (Continued)

3. Brother's / sister's initials	4. Brother or Sister? **(USE CODE: BROTHER = 1 SISTER =2)**	5. Did this brother/sister have: a. The same birth mother as you? b. The same birth father as you?	6. Is this brother/ sister still alive? **(INDICATE WITH FOLLOWING CODES: YES = 1 NO = 2 DK = 3)**	7. What is (was) the current age (age at death) of this brother/ sister? **(DON'T KNOW = 98)**	8. About how many years did you live in the same household with this brother/sister? **(DON'T KNOW = 98)**	9. Did this brother/ sister ever have sarcoidosis? **(YES = 1 PROBABLE = 2 NO = 3 DK = 4 IF YES, ANSWER QUESTIONS IN COLUMNS 10 AND 11.)**	10. How old was this brother/sister when he/she got sarcoidosis? **(DON'T KNOW = 98)**	11. About how many years did you live in the same house with this brother/sister after he/she got sarcoidosis? **(DON'T KNOW = 98)**
K. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
L. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____
M. ____ ____ ____	_____	a. b. Yes (1) (1) No (2) (2) DK (3) (3)	____	___ ___	____ ____	____	____ ____	____ ____

COMPLETE AS MANY FAMILY HISTORY SUPPLEMENTS AS NEEDED TO COLLECT INFORMATION ON ALL SIBLINGS.

III. ADMINISTRATIVE MATTERS

12. **INTERVIEWER:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

13. **RESEARCH COORDINATOR:**

A. **SIGNATURE:** _____

B. **ACCESS STAFF NO.:** ____ ____ ____ **-** ____ ____

14. **DATE FORM COMPLETED:** ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

PHYSICAL EXAMINATION FORM

ID No.				-				
Form Type	**P**	**E**						

I. SUBJECT IDENTIFICATION

1. Case's initials: ____ ____ ____

2. Date of examination: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

II. PHYSICAL EXAMINATION

3. Height (cm) (999.8 if not measured): ____ ____ ____ ____

4. Weight (kg) (999.8 if not measured): ____ ____ ____ ____

5. Heart rate (beats/min) (998 if not measured): ____ ____ ____

6. Respiratory rate (breaths/min) (98 if not measured): ____ ____

7. Blood pressure:

   A. Systolic blood pressure: ____ ____ ____ mm Hg

   B. Diastolic blood pressure: ____ ____ ____ mm Hg

Lung Assessment

			Yes	No
8.	Is there lung involvement? **IF NO, GO TO QUESTION 13.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**		(1)	(2)
9.	Extent of involvement:	Definite Probable Possible	(1) (2) (3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 10A - 10G.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 11A - 11C.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 12A AND 12B.

10.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**		(1)	(2)
	A.	Positive lung biopsy	(1)	
	B.	Positive mediastinal/hilar lymph node biopsy	(1)	
	C.	Positive pleura biopsy	(1)	
	D.	Chest roentgenogram with bilateral hilar adenopathy	(1)	
	E.	Chest roentgenogram with diffuse infiltrates	(1)	
	F.	Chest roentgenogram with upper lobe fibrosis	(1)	
	G.	Restriction on PFTs	(1)	
11.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**		(1)	(2)
	A.	Lymphocytic alveolitis by BAL	(1)	
	B.	Any pulmonary infiltrates	(1)	
	C.	Isolated reduced DLCO	(1)	
12.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**		(1)	(2)
	A.	Any adenopathy	(1)	
	B.	Obstructive PFTs	(1)	

Non-Thoracic Involvement

13.	Is there definite, probable or possible non-thoracic involvement? **IF NO, GO TO QUESTION 80.** **IF YES, ANSWER QUESTIONS 14-79.**		(1)	(2)

Neurological Assessment

		Yes	No
14.	Is there neurological involvement? **IF NO, GO TO QUESTION 19.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

15.	Extent of involvement:	Definite	(1)
		Probable	(2)
		Possible	(3)

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 16A - 16H.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 17A - 17C.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 18A AND 18B.

16.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive MRI with uptake in meninges or brainstem	(1)	
	B. CSF with increased lymphocytes and/or protein	(1)	
	C. Diabetes insipidus	(1)	
	D. Bell's palsy	(1)	
	E. Cranial nerve dysfunction (other than Bell's palsy)	(1)	
	F. Positive brain biopsy	(1)	
	G. Positive dura biopsy	(1)	
	H. Positive peripheral nerve biopsy	(1)	

17.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Other abnormalities on MRI	(1)	
	B. Unexplained neuropathy	(1)	
	C. Positive EMG	(1)	
18.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Unexplained headaches	(1)	
	B. Peripheral nerve radiculopathy	(1)	

Non-Thoracic Lymph Node Assessment

			Yes	No
19.	Is there non-thoracic lymph node involvement? **IF NO, GO TO QUESTION 24.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**		(1)	(2)
20.	Extent of involvement:	Definite Probable Possible	(1) (2) (3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 21.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 22A and 22B.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 23.

21.	Is there definite involvement (positive lymph node biopsy)?	(1)	(2)
22.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. New palpable node above the waist	(1)	
	B. Lymph node > 2 cm. By CT scan	(1)	
23.	Is there possible involvement (new palpable femoral lymph node)?	(1)	(2)

Renal Assessment

24.	Is there renal involvement? **IF NO, GO TO QUESTION 29.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

25.	Extent of involvement:	Definite Probable Possible	(1) (2) (3)

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 26A and 26B.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 27.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 28.

		Yes	No
26.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive kidney biopsy	(1)	
	B. Treatment responsive renal failure	(1)	
27.	Is there probable involvement (steroid responsive renal failure in patient with diabetes and/or hypertension)?	(1)	(2)
28.	Is there possible involvement (renal failure in absence of other disease)?	(1)	(2)

Cardiac Assessment

29.	Is there cardiac involvement? **IF NO, GO TO QUESTION 34.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

30. Extent of involvement:

Definite	(1)
Probable	(2)
Possible	(3)

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 31A - 31E.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 32A - 32B.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 33A AND 33B.

31.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive heart biopsy	(1)	
	B. Positive pericardium biopsy	(1)	
	C. Treatment responsive cardiomyopathy	(1)	
	D. EKG showing IVCD or nodal block	(1)	
	E. Positive gallium scan of the heart	(1)	

		Yes	No
32.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. No other cardiac problem and either ventricular arrhythmias or cardiomyopathy	(1)	
	B. Positive nuclear medicine scan other than gallium scan	(1)	
33.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Cardiomyopathy in patient with diabetes and/or hypertension	(1)	
	B. Ventricular arrhythmias in patient with diabetes and/or hypertension	(1)	

Skin Assessment

34.	Is there skin involvement? **IF NO, GO TO QUESTION 39.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)
35.	Extent of involvement:	Definite (1) Probable (2) Possible (3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 36A - 36D.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 37A and 37B.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 38A - 38C.

36.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive skin biopsy	(1)	
	B. Lupus pernio	(1)	
	C. Erythema nodosum	(1)	
	D. Annular lesion	(1)	

		Yes	No
37.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Macular papular lesions	(1)	
	B. New nodules	(1)	
38.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Keloids	(1)	
	B. Hypopigmentation	(1)	
	C. Hyperpigmentation	(1)	

Eye Assessment

39.	Is there eye involvement? **IF NO, GO TO QUESTION 44.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)
40.	Extent of involvement: Definite	(1)	
	Probable	(2)	
	Possible	(3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 41A - 41E.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 42.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 43A - 43C.

41.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive conjunctiva biopsy	(1)	
	B. Positive sclera biopsy	(1)	
	C. Lacrimal gland swelling	(1)	
	D. Uveitis	(1)	
	E. Optic neuritis	(1)	
42.	Is there probable involvement (blindness)?	(1)	(2)

		Yes	No
43.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Glaucoma	(1)	
	B. Cataract	(1)	
	C. Sicca (dry eyes)	(1)	

Liver Assessment

44.	Is there liver involvement? **IF NO, GO TO QUESTION 48.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

45.	Extent of involvement:	Definite Probable	(1) (2)

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 46A AND 46B.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 47A AND 47B.

46.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive liver biopsy	(1)	
	B. Serum alkaline phosphatase greater than three times the upper limit of normal	(1)	
	C. Serum total bilirubin greater than three times the upper limit of normal	(1)	
	D. Serum aspartamine aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times the upper limit of normal	(1)	
	E. Serum albumin less than 3.0 mg/dl	(1)	

47.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Compatible CT scan	(1)	
	B. Elevated alkaline phosphatase	(1)	

Bone Marrow Assessment

			Yes	No
48.	Is there bone marrow involvement? **IF NO, GO TO QUESTION 52.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**		(1)	(2)
49.	Extent of involvement:	Definite Possible	(1) (3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 50A - 50D.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 51.

50.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**		(1)	(2)
	A.	Granulomas in bone marrow	(1)	
	B.	Unexplained anemia	(1)	
	C.	Leukopenia	(1)	
	D.	Thrombocytopenia	(1)	
51.	Is there possible involvement (anemia with low MCV)?		(1)	(2)

Spleen Assessment

52.	Is there spleen involvement? **IF NO, GO TO QUESTION 56.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**		(1)	(2)
53.	Extent of involvement:	Definite Probable	(1) (2)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 54.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 55A - 55C.

54.	Is there definite involvement (spleen biopsy)?		(1)	(2)
55.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**		(1)	(2)
	A.	Enlargement by examination	(1)	

		Yes	No
55.	(Continued)		
	B. Enlargement by CT scan	(1)	
	C. Enlargement by radioisotope scan	(1)	

Bone/Joint Assessment

56.	Is there bone/joint involvement? **IF NO, GO TO QUESTION 61.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

57.	Extent of involvement:	Definite	(1)
		Probable	(2)
		Possible	(3)

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 58A - 58C.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 59.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 60.

58.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Granulomas in bone biopsy	(1)	
	B. Granulomas in synovium biopsy	(1)	
	C. Cystic changes on hand or feet phalanges	(1)	
59.	Is there probable involvement (asymmetric, painful clubbing)?	(1)	(2)
60.	Is there possible involvement (arthritis with no other cause)?	(1)	(2)

Ear/Nose/Throat Assessment

61.	Is there ear/nose/throat involvement? **IF NO, GO TO QUESTION 66.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

			Yes	No
62.	Extent of involvement:	Definite	(1)	
		Probable	(2)	
		Possible	(3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 63.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 64.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 65A AND 65B.

63.	Is there definite involvement (granulomas in ear, nose or throat)?	(1)	(2)
64.	Is there probable involvement (unexplained hoarseness with examination consistent with granulomatous involvement)?	(1)	(2)
65.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. New onset sinusitis	(1)	
	B. New onset dizziness	(1)	

Parotid/Salivary Gland Assessment

66.	Is there parotid/salivary gland involvement? **IF NO, GO TO QUESTION 70.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**	(1)	(2)

67.	Extent of involvement:	Definite	(1)	
		Possible	(3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 68A - 68D.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 69A.

68.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Positive parotid biopsy	(1)	
	B. Positive salivary gland biopsy	(1)	
	C. Symmetrical parotitis with syndrome of mumps	(1)	
	D. Positive gallium scan (“Panda sign”)	(1)	
69.	Is there possible involvement (dry mouth)?	(1)	(2)

Muscle Assessment

			Yes	No
70.	Is there muscle involvement? **IF NO, GO TO QUESTION 75.** **IF YES, ANSWER THE FOLLOWING QUESTIONS.**		(1)	(2)
71.	Extent of involvement:	Definite Probable Possible	(1) (2) (3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 72A - 72B.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 73.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 74.

72.	Is there definite involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**		(1)	(2)
	A.	Granulomas in muscle	(1)	
	B.	Increased CPK/aldolase which decreases with treatment	(1)	
73.	Is there probable involvement (increased CPK/aldolase)?		(1)	(2)
74.	Is there possible involvement (myalgias responding to treatment)?		(1)	(2)

Calcium Metabolism Assessment

75.	Is there calcium metabolism (hypercalcemia/hypercalcuria/ nephrolithiasis) involvement?		(1)	(2)

IF NO, GO TO QUESTION 80.
IF YES, ANSWER THE FOLLOWING QUESTIONS.

76.	Extent of involvement:	Definite Probable Possible	(1) (2) (3)	

IF RESPONSE IS DEFINITE, ANSWER QUESTIONS 77.
IF RESPONSE IS PROBABLE, ANSWER QUESTIONS 78A AND 78B.
IF RESPONSE IS POSSIBLE, ANSWER QUESTIONS 79A AND 79B.

77.	Is there definite involvement (increased serum calcium) with no other cause?		(1)	(2)

		Yes	No
78.	Is there probable involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Increased urine calcium	(1)	
	B. Nephrolithiasis analysis showing calcium	(1)	
79.	Is there possible involvement? **IF YES, CHECK ALL THE CRITERIA WHICH APPLY.**	(1)	(2)
	A. Nephrolithiasis -- no stone analysis	(1)	
	B. Nephrolithiasis with negative family history for stones	(1)	

IV. SARCOIDOSIS ASSESSMENT SYSTEM
Pulmonary Severity

80. What is the patient's level of dyspnea? (*Check one.*)

Not troubled by breathlessness except with strenuous exercise	(1)
Troubled by shortness of breath when hurrying on the level or walking up a slight hill	(2)
Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level	(3)
Stops for breath after walking about 100 yards of after a few minutes on the level	(4)
Too breathless to leave the house or breathless when dressing or undressing	(5)

81. Radiographic findings (*Answer each question.*)

A.	Hilar adenopathy	(1)	(2)
B.	Alveolar infiltration	(1)	(2)
C.	Interstitial infiltrates	(1)	(2)
D.	Pulmonary hypertension	(1)	(2)
E.	Stage 4 disease	(1)	(2)
F.	Mycetoma	(1)	(2)
G.	Other	(1)	(2)

Specify: _____

Non-Thoracic Involvement

82. Evidence of involvement (ever):
(Problems must be documented in Section II.)

		Definite	Probable	Possible	No Involvement
A.	Neurologic	(1)	(2)	(3)	(4)
B.	Non-thoracic lymph node	(1)	(2)	(3)	(4)
C.	Kidney (not nephrolithiasis)	(1)	(2)	(3)	(4)
D.	Cardiac	(1)	(2)	(3)	(4)
E.	Skin	(1)	(2)	(3)	(4)
F.	Eyes	(1)	(2)	(3)	(4)
G.	Liver	(1)	(2)	(3)	(4)
H.	Bone marrow	(1)	(2)	(3)	(4)
I.	Spleen	(1)	(2)	(3)	(4)
J.	Bone/joints	(1)	(2)	(3)	(4)
K.	Ear/nose/throat	(1)	(2)	(3)	(4)
L.	Parotid/Salivary Glands	(1)	(2)	(3)	(4)
M.	Muscles	(1)	(2)	(3)	(4)
N.	Endocrine (hypercalcemia, hypercalcuria or nephrolithiasis)	(1)	(2)	(3)	(4)

83. Severity of current involvement (evaluation at the time of ACCESS physical examinaton only):

		Not Clinically Involved	Clinically Involved But Functioning	Organ Failure
A.	Neurologic	(1)	(2)	(3)
B.	Non-thoracic lymph node	(1)	(2)	(3)
C.	Kidney (not nephrolithiasis)	(1)	(2)	(3)
D.	Cardiac	(1)	(2)	(3)
E.	Skin	(1)	(2)	(3)
F.	Eyes	(1)	(2)	(3)
G.	Liver	(1)	(2)	(3)
H.	Bone marrow	(1)	(2)	(3)
I.	Spleen	(1)	(2)	(3)
J.	Bone/joints	(1)	(2)	(3)
K.	Ear/nose/throat	(1)	(2)	(3)

83. Continued

		Not Clinically Involved	Clinically Involved But Functioning	Organ Failure
L.	Parotid/Salivary Glands	(1)	(2)	(3)
M.	Muscles	(1)	(2)	(3)
N.	Endocrine (hypercalcemia, hypercalcuria or nephrolithiasis)	(1)	(2)	(3)

84. Is the patient currently on treatment for sarcoidosis? Yes (1) No (2)

V. ADMINISTRATIVE MATTERS

85. Pulmonary Physician:

A. Signature: _____

B. ACCESS Staff No.: ____ ____ ____ - ____ ____

86. Research Coordinator:

A. Signature: _____

B. ACCESS Staff No.: ____ ____ ____ - ____ ____

87. Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

88. When was the physical examination performed? Before interview (1) After interview (2)

LABORATORY DATA FORM

ID No.				-				
Form Type	**L**	**D**						

I. SUBJECT IDENTIFICATION

1. Case's initials: ____ ____ ____

2. Date of examination: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

II. SPIROMETRY

3. Date of most recent test: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

IF SPIROMETRY NOT DONE, GO TO QUESTION 9. Not done (1)

A. Pre-Bronchodilators

4. FEV-1: ____ C____ ____ L

5. FVC: ____ C____ ____ L

B. Post-Bronchodilators

Post-Bronchodilator spirometry is required if the FEV_1 is less than 80% of predicted or the ratio of FEV_1 to vital capacity is less than 75%

6. Post-Bronchodilator spirometry not done: (1)

If Post-Bronchodilator spirometry not done, go to Question 9.

7. FEV-1: ____ C____ ____ L

8. FVC: ____ C____ ____ L

III. BLOOD TESTS

A. CBC

9. Date of CBC: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

IF CBC NOT DONE, GO TO QUESTION 19. Not done (1)

10. WBC: ____ ____ . ____ x $10^3/mm^3$

11. Hgb: ____ ____ . ____ g/dL

12. Hematocrit: ____ ____ . ____ %

13. Platelets: ____ ____ ____ x $10^3/mm^3$

B. Differential

14. Neutrophils (include bands): ____ ____ %

15. Lymphocytes: ____ ____ %

16. Monocytes: ____ ____ %

17. Eosinophil: ____ ____ %

18. Other: ____ ____ %

IF OTHER, specify: _____

C. Lab Chemistries

19. Date of lab chemistries: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

IF NOT DONE, GO TO QUESTION 34 Not done (1)

20. Sodium: ____ ____ ____ m Eq/L

21. Potassium: ____ . ____ m Eq/L

22. Chloride: ____ ____ ____ m Eq/L

23. Bicarbonate: ____ ____ mEq/L

24. Creatinine: ____ C ____ mg/dL

25. Blood urea nitrogen (BUN): ____ ____ mg/dL

26. Glucose: ____ ____ ____ mg/dL

27. Albumin: ____ C ____ g/dL

28. Alkaline phosphatase: ____ ____ ____ IU/L

29 Total bilirubin: ____ C ____ mg/dL

30. Aspartamine aminotransferase (AST): ____ ____ ____ IU/L

31. Alanine aminotransferase (ALT): ____ ____ ____ IU/L

32. Calcium: ____ ____ C ____ mg/dL

33. Total protein: ____ ____ C ____ g/dL

IV. ADMINISTRATIVE MATTERS

34. Pulmonary Physician:

Signature: _____

ACCESS Staff No.: ____ ____ ____ - ____ ____

35. Research Coordinator:

Signature: _____

ACCESS Staff No.: ____ ____ ____ - ____ ____

36. Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

BASELINE QUESTIONNAIRE FOR CASES ONLY

ID No.				-				
Form Type	**C**	**B**	**0**	**1**				

General Instructions: Complete this questionnaire for all cases at baseline.

I. CASE IDENTIFICATION

1. **Case's initials**: ____ ____ ____

2. **Date of interview**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

II. ACCESS TO, USE OF, AND ADHERENCE WITH MEDICAL CARE FOR SARCOIDOSIS

Earlier in the interview I asked you about your ability to get health care when you are sick. Now I want to ask you about your ability to get health care for your sarcoidosis.

3. Has sarcoidosis affected your ability to obtain health insurance? (1) Yes (2) No (3) Not Applicable (4) Don't Know

   A. **IF YES**, How? _____

4. Has sarcoidosis affected the cost of your insurance? (1) Yes (2) No (3) Not Applicable (4) Don't Know

5. If you have health insurance, does your health insurance limit your ability to receive care for your sarcoidosis? (1) Yes (2) No (3) Not Applicable (4) Don't Know

   IF NO, NOT APPLICABLE OR DON'T KNOW, GO TO QUESTION 6.
   IF YES, ANSWER QUESTIONS 5A, 5B AND 5C.

   A. Has it limited your access to a specialist for sarcoidosis care? (1) Yes (2) No (3) Don't Know

      (1) **IF YES**, specify: _____

   B. Has it limited your receiving tests that your doctor thought should be done for your sarcoidosis? (1) Yes (2) No (3) Don't Know

      (1) **IF YES**, specify: _____

5. Continued

   C. Has it limited your receiving any medication that your doctor thought you should receive for sarcoidosis? (1) Yes (2) No (3) Don't Know

      (1) **IF YES**, specify: _____

6. During the past 6 months was there any time when you needed medical care specifically for sarcoidosis but could not get it? (1) Yes (2) No

   A. **IF YES**, about how many times? ____ ____

7. If your usual doctor is a specialist, does he or she also provide care for your sarcoidosis? (1) Yes (2) No (3) Not Applicable

8. In the last 6 months, how many times have you made appointments to see a doctor for your sarcoidosis? ____ ____

   A. How many of these appointments did you miss? ____ ____

   B. If you missed one or more appointments, what was the main reason for the last missed appointment?
   INTERVIEWER READ LIST

Cost	(1)
Lack of transportation	(2)
Weather	(3)
Other	(4)

IF OTHER, specify: _____

III. MEDICATIONS

9. I am going to read from a list of medications used for treatment of sarcoidosis. As I read each medication, please indicate if you have taken it for your sarcoidosis in the last 6 months.

USE THE BAG OF MEDICATIONS BROUGHT BY THE PARTICIPANT TO HELP IN ANSWERING THESE QUESTIONS

	(1) Generic Name of Medication	(2) Usage			(3) Duration in Months				(4) Frequency		(5) Average Total Daily Dose	(6) Response to Therapy		
		None	Not Current	Current	≤ 6	7 - 12	13 - 24	> 24	Continuous	Off - On		Improve	Same	Worse
A.	Corticosteroid Specify:_____	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
B.	Methotrexate	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
C.	Azathioprine	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
D.	Cyclosporine	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
E.	Immunosuppressives Specify:_____	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
F.	Anti-malarial Specify:_____	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
G.	Have you taken any other medications for your sarcoidosis within the last 6 months? **If YES, answer H - K. If NO, go to Question 10.**											Yes (1)	No (2)	
H.		(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
I.		(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
J.		(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
K.		(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)

ASK QUESTION 10 ONLY IF CURRENT USAGE OF A SARCOIDOSIS MEDICATION HAS BEEN CHECKED IN QUESTION 9.

10. I would like you to think about how you took your sarcoidosis medicines in the PAST WEEK; on how many days did you:

		Number of Days					
		0	**1**	**2**	**3**	**4**	**+5**
A.	forget to take some or all of it?	(1)	(2)	(3)	(4)	(5)	(6)
B.	not take some or all of it?	(1)	(2)	(3)	(4)	(5)	(6)
C.	take more of any of it than your doctor told you to?	(1)	(2)	(3)	(4)	(5)	(6)

ASK QUESTIONS 11 - 19 ONLY IF CURRENT OR NOT CURRENT USAGE OF A SARCOIDOSIS MEDICATION HAS BEEN CHECKED IN QUESTION 9.

11. Would you say that you take your sarcoidosis medicine just the way your doctor told you to take it? **INTERVIEWER READ LIST**.

All of the time	(1)
Almost all of the time	(2)
Most of the time	(3)
Some of the time	(4)
Almost never	(5)
Never	(6)

IF ALL OF THE TIME, GO TO QUESTION 14.

12. Was there any time you did not obtain your sarcoidosis medication because you could not afford it?

(1)	(2)
Yes	No

13. When you don't take all the medication that was prescribed, what is the most important reason for taking less?
INTERVIEWER READ LIST

Forgetful	(01)	
Too busy		(02)
Didn't need it		(03)
Side effects		(04)
Feeling pain, sick		(05)
Don't think medication works		(06)
Could not afford prescription/refill		(07)
Did not have transportation to get the prescription/refill		(08)
Other		(09)

IF OTHER, describe: _____]

14. Has your doctor ever directly asked you about how well you take your sarcoidosis medicine?

(1)	(2)
Yes	No

15. How confident are you that you can control your sarcoidosis by taking your medicine each day? **INTERVIEWER READ LIST**

Very confident	(1)
Somewhat confident	(2)
Not at all confident	(3)

16. If you don't take your sarcoidosis medicine what are the chances that something bad will happen to your health in the next year? **INTERVIEWER READ LIST**

Very little chance	(1)
Some chance	(2)
Fifty-fifty chance	(3)
Probably will happen	(4)
Almost surely will happen	(5)

17. If you don't take your sarcoidosis medicine what might happen?

    A. Don't know (1)

    B. Possibly: _____

18. How often do people in your daily life help you by reminding you to take your sarcoidosis medicines? **INTERVIEWER READ LIST**

All of the time	(1)
Some of the time	(2)
Never	(3)

19. Most people forget to take their medicine occasionally. How often does this happen to you? **INTERVIEWER READ LIST**

All of the time	(1)
Almost all of the time	(2)
Most of the time	(3)
Some of the time	(4)
Almost never	(5)
Never	(6)

20. I've asked you a lot of questions. The last question I want to ask is:
Do you think anything caused your sarcoidosis? (1) Yes (2) No

A. **IF YES**, what was it?

_____

_____

_____

_____

IV. ADMINISTRATIVE MATTERS

21. **Interviewer**:

A. **Signature**: _____

B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

22. **Research Coordinator**:

A. **Signature**: _____

B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

23. **Date form completed**: ____ ____ - ____ ____ - ____ ____
Month Day Year

TELEPHONE CONTACT SUMMARY

ID No.				-				
Form Type	**T**	**C**						

1. Initials of case: ____ ____ ____

2. Date of telephone contact: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. Was the case informed of the importance of his/her continued participation in the study? Yes (1) No (2)

4. Date of next scheduled Clinical Center visit: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

5. Has the case's address, employment or telephone number changed since the last contact? Yes (1) No (2)

   A. If **YES**, specify: _____

6. Did the case report any major medical problems related to sarcoidosis since the last telephone contact? Yes (1) No (2)

   A. If **YES**, specify: _____

7. Did the case volunteer any concerns or complaints about the study? Yes (1) No (2)

   A. If **YES**, describe: _____

8. Research Coordinator:

   A. Signature: _____

   B. ACCESS Staff No.: ____ ____ ____ - ____ ____

9. Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

AFFECTED RELATIVE REPORT FORM

ID No. of ACCESS Participant				-				
Form Type	**A**	**R**						

DO NOT CONTACT AFFECTED RELATIVE TO COMPLETE THIS FORM UNTIL CONSENT LETTER IS RECEIVED FROM THE AFFECTED RELATIVE

Instructions: This form is completed for every case or control with an affected relative. After completing ACCESS Forms 21, 22, and 23, complete Items 1, 2, 3 and 4. Complete a separate Form 29 for each affected first degree relative of the participant. Use sequential numbers for the form types of the Form 29s submitted for the affected relatives of each participant. If there is only one relative reported to be affected, the form type is AR01. If more than one affected relative is reported, assign the sequential numbers AR01, AR02, etc. in the following order: mother, father, children, as listed on Form 21s, Item 11, and siblings, as listed on Form 22s, Item 20, and Form 23s, Item 3.

I. IDENTIFYING INFORMATION

ACCESS Participant's name: (Do not enter into ACCESS database)

_____

1. Participant's initials: ____ ____ ____

2. Date letter for affected relative offered to participant: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. Relation of affected relative to ACCESS participant:

Mother	Father	Child	Sibling
(1)	(2)	(3)	(4)
		9	9
		ANSWER 3A	**ANSWER 3B**

A. FOR A CHILD, ENTER FORM TYPE AND LETTER FROM FORM 21:

(1) FORM TYPE OF FORM 21 ON WHICH THIS CHILD IS LISTED **R Q** ____ ____

(2) LETTER FROM FORM 21, ITEM 11 ____

3. (Continued)

B. FOR A SIBLING:

(1) CHECK FORM ON WHICH SIBLING IS LISTED **FORM 22 (1)**
FORM 23 (2)

IF FORM 23, GO TO (3).

(2) ENTER LETTER FROM FORM 22, ITEM 20 ____

GO TO ITEM 4

(3) ENTER FORM TYPE FROM FORM 23 ON WHICH SIBLING IS LISTED **F S** ____ ____

(4) ENTER LETTER FROM FORM 23, ITEM 3. ____

II. STATUS:

	Yes	No
4. Was the letter received at the Clinical Center, indicating the relative agreed to participate?	(1)	(2)

IF YES, ANSWER ITEM 4A.
IF NO, ANSWER ITEM 4B AND GO TO ITEM 26.

A. Was the relative contacted?	(1)	(2)

IF YES, ANSWER ITEM 5 AND COMPLETE BOX BELOW ITEM 5.
IF NO, ANSWER ITEM 4B AND GO TO ITEM 26 .

B. Which statement best describes the status of the relative's participation.

Letter received at Clinical Center indicating relative refused to participate	(1)
Letter received at Clinical Center, relative could not be located	(2)
Letter given to participant, but letter not received at Clinical Center	(3)
Relative deceased	(4)
Participant refused	(5)
Other	(6)

Specify: _____

III. INTERVIEW OF RELATIVE

5. Date of contact: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

INFORMATION OBTAINED FROM CONSENT TO PARTICIPATE LETTER. DO NOT ENTER INTO ACCESS DATABASE

A. Relative's name: _____

B. Relative's address: _____

_____

_____

C. Phone number of relative: (____ ___ ____) ____ ____ ____ - ____ ____ ____ ____
Area code

Introductory Script:

Your (relation to participant) recently participated in a study of sarcoidosis and listed you as a relative who might be willing to provide more information to us. The letter you returned to us indicated your willingness to participate. The following questions deal with your medical history as it relates to sarcoidosis and should take no more than five minutes to complete.

		Yes	No	Call Again
6.	Would you be willing to answer these questions at this time?	(1)	(2)	(3)

IF YES, GO TO QUESTION 7.

IF RELATIVE REQUESTS YOU CALL AGAIN, ASK WHEN A MORE APPROPRIATE TIME WOULD BE AND SCHEDULE TIME FOR ANOTHER CALL AND REVISE ITEM 5 TO RECORD DATE OF NEXT CONTACT.

IF NO, RELATIVE REFUSES, ASK REASON FOR REFUSAL AND GO TO ITEM 25.

A. **REASON FOR REFUSAL** _____
_____

Information Obtained from Relative

		Yes	No	Unknown
7.	Have you ever been told by a doctor that you had an abnormal chest X-ray?	(1)	(2)	(3)

8. Have you ever been told by a doctor that you have any type of lung disease? Yes (1) No (2) Unknown (3)

   A. **IF YES**, Specify: _____

9. Have you ever been told by a doctor that you have sarcoidosis? Yes (1) No (2) Unknown (3)

   IF YES, ASK QUESTIONS 10 THROUGH 15.

   IF NO OR UNKNOWN, THANK THE RELATIVE, END THE INTERVIEW AND GO TO ITEM 25.

10. How old were you when you got sarcoidosis? ____ ____ years

11. Did the doctor get a biopsy (take a piece of your lung or other part of your body) in order to know if you had sarcoidosis? Yes (1) No (2) Unknown (3)

12. Did health problems from your sarcoidosis cause you to see a doctor? Yes (1) No (2) Unknown (3)

13. I am going to read from a list of medications used for treatment of sarcoidosis. As I read each medication, please indicate if you have ever taken it for your sarcoidosis and whether you took it within two weeks of the time the doctor told you that you had sarcoidosis, more than two weeks but less than one year after the doctor told you that you had sarcoidosis or more than one year after the doctor told you that you had sarcoidosis.

    INTERVIEWER READ LIST ONE AT A TIME.

	(1) **Generic Name of Medication**	**Never**	**(2)** **Within two weeks**	**More than two weeks but less than one year**	**More than one year**	**Unknown**
A.	Corticosteriod (e.g. Prednisone)	(1)	(2)	(3)	(4)	(5)
	Specify: _____					
B.	Methotrexate	(1)	(2)	(3)	(4)	(5)
C.	Azathioprine	(1)	(2)	(3)	(4)	(5)
D.	Cyclosporine	(1)	(2)	(3)	(4)	(5)

13. (Continued)

	(1) Generic Name of Medication	Never	(2) Within two weeks	More than two weeks but less than one year	More than one year	Unknown
E.	Immunosuppressives Specify: _____	(1)	(2)	(3)	(4)	(5)
F.	Anti-malarial Specify: _____	(1)	(2)	(3)	(4)	(5)

		Yes	No	Unknown
G.	Have you ever taken any other medications for your sarcoidosis? **IF YES,** please list them. **IF NO OR UNKNOWN, GO TO QUESTION 14.**	(1)	(2)	(3)

		Within two weeks	More than two weeks but less than one year	More than one year
H.	_____	(1)	(2)	(3)
I.	_____	(1)	(2)	(3)
J.	_____	(1)	(2)	(3)

14. Did your doctor tell you that any of the following have been affected by sarcoidosis?

INTERVIEWER READ LIST ONE AT A TIME.

		Yes	No	Unknown
A.	Lungs	(1)	(2)	(3)
B.	Nervous system	(1)	(2)	(3)
C.	Heart	(1)	(2)	(3)
D.	Skin	(1)	(2)	(3)
E.	Eyes	(1)	(2)	(3)
F.	Liver	(1)	(2)	(3)
G.	Spleen	(1)	(2)	(3)

Thank you for the information you have provided us, it is very important to our study. We may need some additional information from your medical records. We would like to request your permission to read your medical records. Our request for use of your medical records is strictly for research purposes and the information will remain totally confidential.

		Yes	No
15A.	Would you be willing to sign a release for your medical records?	(1)	(2)

IF YES: Thank you, we will send you a medical release form that you should receive in a few days. When you get it, please fill in the information about where your sarcoidosis was diagnosed, sign the form and send it back to us. We would like to be sure we have your correct address.

CONFIRM THAT ADDRESS IS THE SAME AS WHAT IS WRITTEN IN THE BOX UNDER ITEM 5. MAKE CORRECTIONS AS NEEDED.

	Yes	**No**
(1) ADDRESS CONFIRMED?	**(1)**	**(2)**

IF NO: THANK RELATIVE, END INTERVIEW, AND GO TO ITEM 25.

15B.	**Has medical release form been received?**	(1)	(2)

IF AUTHORIZATION TO REVIEW MEDICAL RECORDS IS RECEIVED AT THE CLINICAL CENTER, COMPLETE SECTION IV. IF IT IS NOT RECEIVED, GO TO ITEM 25.

IV. VALIDATION REPORT

		Medical Record Information		
		Documented	**Ruled Out**	**Not Mentioned**
16.	Abnormal chest X-ray compatible with sarcoidosis	(1)	(2)	(3)
17.	Any lung disease	(1)	(2)	(3)
18.	Sarcoidosis	(1)	(2)	(3)
19.	Age when sarcoidosis diagnosed	(1)	(2)	(3)
20.	Biopsy confirmed sarcoidosis	(1)	(2)	(3)
21.	Symptoms compatible with sarcoidosis	(1)	(2)	(3)
22.	Treated after diagnosis	(1)	(2)	(3)

		Definite	**Probable**	**Possible**	**Ruled Out**	**Not Mentioned**
23.	Organs affected					
	A. Lungs	(1)	(2)	(3)	(4)	(5)
	B. Nervous system	(1)	(2)	(3)	(4)	(5)
	C. Heart	(1)	(2)	(3)	(4)	(5)
	D. Skin	(1)	(2)	(3)	(4)	(5)
	E. Eyes	(1)	(2)	(3)	(4)	(5)
	F. Liver	(1)	(2)	(3)	(4)	(5)
	G. Spleen	(1)	(2)	(3)	(4)	(5)
	H. Other	(1)	(2)	(3)	(4)	(5)

(1) Specify _____

V. ADMINISTRATIVE MATTERS

24. **PHYSICIAN REVIEWING MEDICAL RECORDS**

A. SIGNATURE: _____

B. ACCESS STAFF NO.: ____ ____ ____ - ____ ____

25. **INTERVIEWER:**

A. SIGNATURE: _____

B. ACCESS STAFF NO.: ____ ____ ____ **-** ____ ____

26. **RESEARCH COORDINATOR**

A. SIGNATURE: _____

B. ACCESS STAFF NO.: ____ ____ ____ **-** ____ ____

27. **DATE FORM COMPLETED:** ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

CHEST ROENTGENOGRAPHY INTERPRETATION FORM

ID No.				-				
Form Type	**C**	**R**						

1. Case's initials: ____ ____ ____

2. Date of x-ray: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. Film Quality: (1) Good (2) Acceptable (3) Poor (4) Unacceptable

IF FILM QUALITY IS UNACCEPTABLE, OBTAIN ANOTHER CHEST X-RAY. DO NOT COMPLETE THIS FORM FOR A FILM OF UNACCEPTABLE QUALITY.

4. Are there previous films available for comparison? Yes (1) No (2)

IF YES, ANSWER QUESTION 4A.
IF NO, GO TO QUESTION 5.

A. Date of most recent comparison film: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

5. Are the findings on the current film completely normal? Yes (1) No (2)

IF YES, GO TO QUESTION 17.
IF NO, ANSWER QUESTIONS 6 - 16.

6. Any <u>interstitial</u> infiltrates? (1) (2)

7. Any <u>alveolar</u> infiltrates? (1) (2)

8. Any adenopathy (hilar or mediastinal)? (1) (2)

9. Hilar retraction? (1) (2)

10. Bullae or blebs (cysts)? (1) (2)

		Yes	No
11.	Any cardiomegaly?	(1)	(2)
12.	Any pulmonary artery enlargement?	(1)	(2)
13.	Pulmonary fibrosis?	(1)	(2)
14.	Any pleural abnormalities? (Thickening, effusions, plaques)	(1)	(2)
15.	Other abnormalities?	(1)	(2)

IF YES, ANSWER QUESTION 15A.
IF NO, GO TO QUESTION 16.

A. Specify: _____

_____

16. Scadding Stage (Check one.)

Nodes and parenchyma normal (Stage 0)	(0)
Stage I	(1)
Stage II	(2)
Stage III	(3)
Stage IV	(4)

17. Date of reading: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

18. Reader

A. Signature: _____

B. ACCESS Staff No.: ____ ____ ____ - ____ ____

19. Research Coordinator:

A. Signature: _____

B. ACCESS Staff No.: ____ ____ ____ - ____ ____

20. Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

DIAGNOSTIC SPECIMEN REPORT

ID No.				-				
Form Type	**D**	**S**						

1. Patient's initials: ____ ____ ____

2. Date of examination of specimen by ACCESS pathologist: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. Results of examination:

   Presence of noncaseating granuloma consistent with diagnosis of sarcoidosis?

Definitely positive	(1)
Probable	(2)
Possible	(3)
Definitely negative	(4)

IF THE RESULT WAS <u>NOT</u> DEFINITELY POSITIVE, GO TO QUESTION 6.

4. If the result was **DEFINITELY POSITIVE**, was there a single site which provided the result? (1) Yes (2) No

IF YES, CHECK SITE (CHECK ONLY ONE) AND GO TO QUESTION 6.
IF NO, GO TO QUESTION 5.

A.

Skin	(01)
Lymph node	(02)
Parotid/salivary gland	(03)
Conjunctivae	(04)
Lacrimal gland	(05)
Sinus	(06)
Nasopharynx	(07)
Trachea and main bronchi	(08)
Lung	(09)
Heart	(10)
Liver	(11)
Spleen	(12)
Gastrointestinal tract	(13)
Muscle	(14)
Peripheral nervous system	(15)
Central nervous system	(16)
Kveim site	(17)
Other	(18)

Specify: _____

ANSWER QUESTION 5 ONLY IF THERE ARE MULTIPLE SITES WHICH PROVIDE A DEFINITELY POSITIVE DIAGNOSIS.

		Yes	No
5.	If there were multiple sites which provided a definitely positive diagnosis, which sites were involved?		
	A. Skin	(1)	(2)
	B. Lymph node	(1)	(2)
	C. Parotid/salivary gland	(1)	(2)
	D. Conjunctivae	(1)	(2)
	E. Lacrimal gland	(1)	(2)
	F. Sinus	(1)	(2)
	G. Nasopharynx	(1)	(2)
	H. Trachea and main bronchi	(1)	(2)
	I. Lung	(1)	(2)
	J. Heart	(1)	(2)
	K. Liver (1)	(2)	
	L. Spleen	(1)	(2)
	M. Gastrointestinal tract	(1)	(2)
	N. Muscle	(1)	(2)
	O. Peripheral nervous system	(1)	(2)
	P. Central nervous system	(1)	(2)
	Q. Kveim site	(1)	(2)
	R. Other	(1)	(2)
	Specify: _____		
6.	Was there a transbronchial biopsy?	(1)	(2)
	IF YES, ANSWER QUESTION 6A. **IF NO, GO TO QUESTION 7.**		
	A. How many transbronchial samples of lung tissue were taken at the time of biopsy?	____	____
		Yes	No
7.	Are the stains for histoplasmosis negative?	(1)	(2)
8.	Are the stains for other fungal diseases negative?	(1)	(2)
9.	Are the stains for tuberculosis negative?	(1)	(2)
10.	Is birefringent material present?	(1)	(2)
	A. If YES, describe _____		

11. Principal Investigator or Co-Principal Investigator

    A. Signature: _____

    B. ACCESS Staff No.: ____ ____ ____ - ____ ____

12. Signature of ACCESS Pathologist

    A. Signature: _____

13. Research Coordinator:

    A. Signature: _____

    B. ACCESS Staff No.: ____ ____ ____ - ____ ____

14. Date form completed: ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

BRONCHOALVEOLAR LAVAGE FORM

ID No.				-				
Form Type	**B**	**L**	**0**	**1**				

PART I: PARTICIPANT IDENTIFICATION

1. Case's initials: ____ ____ ____

2. Date of BAL: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

PART II: PROCEDURE PERFORMANCE

3. Area lavaged -- fluid from only one area should be sent to Central Repository (Check only one):

   Right upper lobe (1)
   Right middle lobe (2)
   Lingula (3)
   Left upper lobe (4)
   Other (5)

   Specify: _____

4. Volume of fluid instilled: ____ ____ ____ ml

5. Volume of fluid withdrawn: ____ ____ ____ ml

6. Technique for aspiration:

   Hand held syringe (1)
   Low pressure suction (2)

	Yes	No
7. First 20 ml included in total aspirated fluid:	(1)	(2)
8. Aspirated fluid passed through gauze:	(1)	(2)
9. Specimen sent for:		
A. Mycobacterial culture	(1)	(2)
B. Fungal culture	(1)	(2)
C. Bacterial culture	(1)	(2)
D. Cytology	(1)	(2)

10. Cytocentrifuge slide stain:

Wright-Giemsa	(1)
Diff-Quick	(2)
Other	(3)
Specify: _____	
Not Done	(4)

11. Method for cell count:

Hemocytometer	(1)
Coulter counter	(2)
Other	(3)
Specify: _____	
Not Done	(4)

12. Method for determining lymphocyte populations:

Flow activated cell sorter (FACS)	(1)
Immunohistochemistry	(2)
Other	(3)
Specify: _____	
Not Done	(4)

PART III: RESULTS

13. Cell count of neat fluid: ____ ____ ____ x 10^4/ml

14. Differential cell count from stained slide(s):

A. Macrophages ____ ____ ____ %

B. Neutrophils ____ ____ ____ %

C. Bronchial (epithelial) ____ ____ %

D. Lymphocytes ____ ____ %

E. Eosinophils ____ ____ %

F. Other ____ ____ %

Specify: _____

15. Lymphocytes subpopulations

    A. Mononuclear cells ____ ____ % Not Done (1)

    B. CD4+ ____ ____ % Not Done (1)

    C. CD8+ ____ ____ % Not Done (1)

16. Number of cell-free supernatant aliquots (2 ml) frozen for central repository (Four aliquots recommended): ____ ____

    A. Storage temperature (-80° C recommended) : + - ____ ____ °C

17. Number of cell pellets frozen for central repository (One recommended): ____ ____

    A. Storage temperature (-80° C recommended) : + - ____ ____ °C

18. Label sheet number:

    ____ ____ ____ ____

    Affix BAL Sheet Label Here

19. Participant has consented to the following use of his/her BAL specimens:

    Use in ACCESS or other research activities (1)
    Use only in ACCESS studies (2)
    Participant must be contacted before specimen is used in any study not currently part of the ACCESS studies (3)

PART IV: ADMINISTRATIVE MATTERS

20. Pulmonary Physician:

    Signature:_____

    ACCESS Staff No.: ____ ____ ____ - ____ ____

21. Research Coordinator:

    Signature:_____

    ACCESS Staff No.: ____ ____ ____ - ____ ____

22. Date form completed: ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

FOLLOW-UP QUESTIONNAIRE FOR CASES ONLY (PART I)

ID No.				-				
Form Type	**C**	**F**	**0**	**1**				

General Instructions: Complete this questionnaire for all cases completing two-year follow-up.

I. CASE IDENTIFICATION

1. **Case's initials**: ____ ____ ____

2. **Date of interview**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

II. ACCESS TO HEALTH CARE SERVICES

I would like to ask you some questions about your health insurance.

3. Currently, what is your main health insurance plan?
   INTERVIEWER READ LIST

Private	(1)
Medicare	(2)
Medicaid	(3)
Other public plan	(4)
None	(5)
Don't know/No answer	(6)

IF NONE OR DON'T KNOW, GO TO QUESTION 6.

	Yes	No
A. Does your insurance plan allow you to pay less money if you visit certain doctors?	(1)	(2)
B. Does your insurance plan allow you to pay less money if you visit a specific clinic or health center?	(1)	(2)
C. Does your insurance plan limit your ability to receive care from a medical specialist of your choice?	(1)	(2)

4. Does your health insurance limit your ability to receive care for your sarcoidosis? (1) Yes (2) No

IF YES, ANSWER QUESTIONS 4A, 4B AND 4C.
IF NO OR NOT APPLICABLE, GO TO QUESTION 5.

A. Has it limited your access to a specialist for sarcoidosis care? Yes (1) No (2)

(1) **IF YES**, specify: _____

B. Has it limited your receiving tests that your doctor thought should be done for your sarcoidosis? (1) (2)

(1) **IF YES**, specify: _____

C. Has it limited your receiving any medication that your doctor thought you should receive for sarcoidosis? (1) (2)

(1) **IF YES**, specify: _____

5. Has sarcoidosis affected the cost of your insurance? (1) (2)

6. Has sarcoidosis affected your ability to obtain health insurance? Yes (1) No (2) Not Applicable (3)

A. **IF YES**, How? _____

Now I would like to ask you about your usual source of health care, that is the place you go when you are sick or need medical advice.

7. Is there one particular clinic, health center, doctor's office, other place that you usually go to if you are sick or need advice about your health?

Yes	No
(1)	(2)

A. **IF YES**, What type of place is it? **INTERVIEWER READ LIST**

Doctor's private office	(1)
Hospital emergency room	(2)
Hospital out-patient clinic	(3)
Non-hospital clinical center	(4)
Public health clinic	(5)
Don't know	(6)
Other	(7)

Specify: _____

IF 7A IS ANSWERED, GO TO QUESTION 8.

B. **IF NO**, Is there one particular place where you would go if you were sick or needed advice about your health?

Yes	No
(1)	(2)

IF YES, ANSWER 7C.
IF NO, GO TO QUESTION 8.

C. What type of place is it? **INTERVIEWER READ LIST**

Doctor's private office	(1)
Hospital emergency room	(2)
Hospital out-patient clinic	(3)
Non-hospital clinical center	(4)
Public health clinic	(5)
Don't know	(6)
Other	(7)

Specify: _____

8. Is your regular doctor a general practitioner, internist, family doctor or doctor who treats a variety of illnesses and gives preventive care or is he or she a specialist (a doctor who mainly treats just one type of health problem)? **INTERVIEWER READ LIST.**

General practitioner/internist/family doctor/other doctor	(1)
Specialist	(2)
Don't have a regular doctor	(3)
Don't know	(4)

9. During the period since your ACCESS baseline interview, was there any time when you wanted to see a doctor but could not? Yes (1) No (2)

   A. **IF YES**, Why? **INTERVIEWER READ LIST**

		Yes	No
(1)	There was a lack of money or insurance to pay for the care	(1)	(2)
(2)	It was too far or too expensive to get to care	(1)	(2)
(3)	You were not able to get an appointment for care	(1)	(2)
(4)	Some other reason	(1)	(2)

   Specify: _____

10. During the period since your ACCESS baseline interview, have you delayed seeking medical care because of worry about the cost? Yes (1) No (2)

    A. **IF YES**, Approximately how many times? ____ ____

11. In the period since your ACCESS baseline interview, have you delayed or had difficulty getting medicine prescribed when you needed it? Yes (1) No (2)

    A. **IF YES**, Was it because of:

    INTERVIEWER READ LIST

		Yes	No
(1)	Cost	(1)	(2)
(2)	Did not feel it was needed/helpful	(1)	(2)
(3)	Could not get to a drug store or other place to fill the prescription	(1)	(2)
(4)	Other	(1)	(2)

    Specify: _____

12. During the period since your ACCESS baseline interview was there any time when you needed medical care specifically for sarcoidosis but could not get it? Yes (1) No (2)

    A. **IF YES**, about how many times? ____ ____

13. If your regular doctor at your usual source of health care is a specialist, does he or she also provide care for your sarcoidosis? Yes (1) No (2) Not Applicable (3)

14. In the period since your ACCESS baseline interview, how many times have you made appointments to see a doctor for your sarcoidosis? ____ ____

IF ZERO (00), GO TO QUESTION 15.
IF NOT ZERO, ANSWER QUESTIONS 14A AND 14B.

A. How many of these appointments did you miss? ____ ____

B. If you had to miss at least one appointment, what was the main reason?
INTERVIEWER READ LIST

Cost	(1)
Lack of transportation	(2)
Weather	(3)
Other	(4)

Specify: _____

15. During the period since your ACCESS baseline interview has your sarcoidosis affected any of your organs? (1) Yes (2) No (3) Don't Know

IF YES, ANSWER QUESTION 15A.
IF NO OR DON'T KNOW, GO TO QUESTION 16.

I will read slowly from a list of organs or problems. As I read each one, please tell me if that organ or problem has been affected by sarcoidosis during the period since the ACCESS baseline interview. If you don't know, please tell me that.

A. Were the major problems in your:

		Yes	No	Don't Know
1.	Lungs, with persistent cough or shortness of breath or abnormal chest x-ray	(1)	(2)	(3)
2.	Nervous system - your nerves or brain	(1)	(2)	(3)
3.	Lymph nodes outside the chest, such as easily felt lumps or nodes under your skin in your neck, under your arms, or in your groin	(1)	(2)	(3)
4.	Eyes, with significant pain, redness or blurred vision	(1)	(2)	(3)
5.	Skin, with small or large nodules or bumps or raised areas	(1)	(2)	(3)
6.	Heart with abnormal heart rhythm or other abnormal heart tests	(1)	(2)	(3)
7.	Liver, with enlarged liver, or abnormal blood tests of liver function	(1)	(2)	(3)
8.	Spleen with enlarged organ in left upper portion of abdomen	(1)	(2)	(3)

		Yes	No	Don't Know
9.	Bone-marrow or abnormal blood counts, with anemia, or low white cell counts or low platelet counts or bleeding	(1)	(2)	(3)
10.	Kidneys, with positive biopsy or bad kidney function	(1)	(2)	(3)
11.	Bones/joints with abnormal x-rays or swollen painful joints or arthritis	(1)	(2)	(3)
12.	Muscles with tenderness or weakness	(1)	(2)	(3)
13.	Ears/nose/throat/sinuses, with nasal obstruction or crusting or hoarseness	(1)	(2)	(3)
14.	Parotid salivary glands, with enlarged glands on the side of face, as with mumps	(1)	(2)	(3)
15.	Increased calcium in blood or urine or kidney stones	(1)	(2)	(3)
16.	Fever, fatigue and/or unintentional weight loss of more than ten pounds	(1)	(2)	(3)
17.	Other	(1)	(2)	(3)

Specify: _____

16. During the period since your ACCESS baseline interview have you needed treatment for your sarcoidosis? (1) Yes (2) No

IF YES, ANSWER QUESTION 16A.
IF NO, GO TO QUESTION 17.

I will read slowly from the same list of organs or problems. As I read each one, please tell me if you required treatment because of that organ or problem that was affected by sarcoidosis during the period since your ACCESS baseline interview. If you don't know, please tell me that.

		Yes	No	Don't Know
A.	Which were the major problems or organs affected that required treatment?			
1.	Lungs, with persistent cough or shortness of breath or abnormal chest x-ray	(1)	(2)	(3)
2.	Nervous system - your nerves or brain	(1)	(2)	(3)
3.	Lymph nodes outside the chest, such as easily felt lumps or nodes under your skin in your neck, under your arms, or in your groin	(1)	(2)	(3)
4.	Eyes, with significant pain, redness or blurred vision	(1)	(2)	(3)
5.	Skin, with small or large nodules or bumps or raised areas	(1)	(2)	(3)
6.	Heart with abnormal heart rhythm or other abnormal heart tests	(1)	(2)	(3)

		Yes	No	Don't Know
7.	Liver, with enlarged liver, or abnormal blood tests of liver function	(1)	(2)	(3)
8.	Spleen with enlarged organ in left upper portion of abdomen	(1)	(2)	(3)
9.	Bone-marrow or abnormal blood counts, with anemia, or low white cell counts or low platelet counts or bleeding	(1)	(2)	(3)
10.	Kidneys, with positive biopsy or bad kidney function	(1)	(2)	(3)
11.	Bones/joints with abnormal x-rays or swollen painful joints or arthritis	(1)	(2)	(3)
12.	Muscles with tenderness or weakness	(1)	(2)	(3)
13.	Ears/nose/throat/sinuses, with nasal obstruction or crusting or hoarseness	(1)	(2)	(3)
14.	Parotid salivary glands, with enlarged glands on the side of face, as with mumps	(1)	(2)	(3)
15.	Increased calcium in blood or urine or kidney stones	(1)	(2)	(3)
16.	Fever, fatigue and/or unintentional weight loss of more than ten pounds	(1)	(2)	(3)
17.	Other	(1)	(2)	(3)

Specify: _____

III. MEDICATIONS

17. I am going to read from a list of medications used for treatment of sarcoidosis. As I read each medication please indicate if you have taken it for your sarcoidosis during the period since your ACCESS baseline interview. We are not asking about any medication you stopped taking prior to your baseline interview.

USE THE BAG OF MEDICATIONS BROUGHT BY THE PARTICIPANT TO HELP IN ANSWERING THESE QUESTIONS

(1) Generic Name of Medication	(2) Usage in the Period Since the ACCESS Baseline Interview			(3) Duration in Months				(4) Frequency		(5) Average Total Daily Dose	(6) Response to Therapy		
	None	Not Current	Current	≤ 6	7 - 12	13 - 24	> 24	Continuous	Off - On		Improve	Same	Worse
A. Oral corticosteroid Specify:_____	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
B. Methotrexate	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
C. Azathioprine	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
D. Cyclosporine	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
E. Immunosuppressives (chlorambucil or cytoxan, etc. Specify:_____	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
F. Anti-malarial (chloroquine or hydroxy-chloraquine [plaquenil]) Specify:_____	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
G. Have you taken any other medications for your sarcoidosis in the period since the ACCESS baseline interview? If **YES**, answer H through K. If **NO**, answer L and go to Question 18.												Yes (1)	No (2)
H.	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
I.	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
J.	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
K.	(1)	(2)	(3)	(1)	(2)	(3)	(4)	(1)	(2)	_____	(1)	(2)	(3)
L. You indicated that you have been taking prednisone. Have you taken this medication in the last 12 months?											Yes (1)	No (2)	N/A (3)

If participant used any medication for sarcoidosis in the period since the ACCESS baseline interview, continue with Question 18.
If participant did not use any medication for sarcoidosis, go to Question 30.

ASK QUESTION 18 ONLY IF CURRENT OR NOT CURRENT USAGE OF A SARCOIDOSIS MEDICATION HAS BEEN CHECKED IN QUESTION 17.

18. We would like to know for what problem related to your sarcoidosis you were taking the medication(s) we just discussed.

I am going to read slowly from a list of organs or problems. As I read each one, please tell me if you were taking medication for that organ or problem since your ACCESS baseline interview. If you don't know, please tell me that.

		Yes	No	Don't Know
A.	Lungs, with persistent cough or shortness of breath or abnormal chest x-ray	(1)	(2)	(3)
B.	Nervous system - your nerves or brain	(1)	(2)	(3)
C.	Lymph nodes outside the chest, such as easily felt lumps or nodes under your skin in your neck, under your arms, or in your groin	(1)	(2)	(3)
D.	Eyes, with significant pain, redness or blurred vision	(1)	(2)	(3)
E.	Skin, with small or large nodules or bumps or raised areas	(1)	(2)	(3)
F.	Heart with abnormal heart rhythm or other abnormal heart tests	(1)	(2)	(3)
G.	Liver, with enlarged liver, or abnormal blood tests of liver function	(1)	(2)	(3)
H.	Spleen with enlarged organ in left upper portion of abdomen	(1)	(2)	(3)
I.	Bone-marrow or abnormal blood counts, with anemia, or low white cell counts or low platelet counts or bleeding	(1)	(2)	(3)
J.	Kidneys, with positive biopsy or bad kidney function	(1)	(2)	(3)
K.	Bones/joints with abnormal x-rays or swollen painful joints or arthritis	(1)	(2)	(3)
L.	Muscles with tenderness or weakness	(1)	(2)	(3)
M.	Ears/nose/throat/sinuses, with nasal obstruction or crusting or hoarseness	(1)	(2)	(3)
N.	Parotid salivary glands, with enlarged glands on the side of face, as with mumps	(1)	(2)	(3)
O.	Increased calcium in blood or urine or kidney stones	(1)	(2)	(3)
P.	Fever, fatigue and/or unintentional weight loss of more than ten pounds	(1)	(2)	(3)
Q.	Other	(1)	(2)	(3)

Specify: _____

19. When was the first time you began taking medication for your sarcoidosis?

____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

ASK QUESTION 20 ONLY IF CURRENT USAGE OF SARCOIDOSIS MEDICATION HAS BEEN CHECKED IN QUESTION 17.

20. I would like you to think about how you took your sarcoidosis medicines in the PAST WEEK:

		Number of Days					
		0	**1**	**2**	**3**	**4**	**+5**
A.	On how many days did you <u>forget</u> to take some or all of it?	(1)	(2)	(3)	(4)	(5)	(6)
B.	On how many days did you <u>not take</u> some or all of it?	(1)	(2)	(3)	(4)	(5)	(6)
C.	On how many days did you take <u>more</u> of any of it than your doctor told you to?	(1)	(2)	(3)	(4)	(5)	(6)

ASK QUESTIONS 21 THROUGH 29 ONLY IF THE CASE REPORTED TAKING MEDICATION FOR SARCOIDOSIS IN THE PERIOD SINCE THE BASELINE INTERVIEW IN RESPONSE TO QUESTION 17. IF THE CASE TOOK MEDICATION SOMETIME DURING THE PERIOD SINCE THE ACCESS BASELINE INTERVIEW, BUT IS NOT TAKING IT AT THE TIME OF THE INTERVIEW, TELL THE CASE HE/SHE SHOULD ANSWER THE QUESTION FOR THE TIME PERIOD THE MEDICATION WAS TAKEN.

21. Would you say that you take your sarcoidosis medicine just the way your doctor told you to take it? **INTERVIEWER READ LIST**

All of the time	(1)
Almost all of the time	(2)
Most of the time	(3)
Some of the time	(4)
Almost never	(5)
Never	(6)

IF ALL OF THE TIME, GO TO QUESTION 24.

22. Was there any time in the period since your ACCESS baseline interview, you did not obtain your sarcoidosis medication because you could not afford it?

Yes	No
(1)	(2)

23. When you don't take all the medication that was prescribed, what is the most important reason for taking less?
INTERVIEWER READ LIST

Forgetful	(01)
Too busy	(02)
Didn't need it	(03)
Side effects	(04)
Feeling pain, sick	(05)
Don't think medication works	(06)
Could not afford prescription/refill	(07)
Did not have transportation to get the prescription/refill	(08)
Other	(09)

IF OTHER, describe: _____

	Yes	No
24. Has your doctor ever directly asked you about how well you take your sarcoidosis medicine?	(1)	(2)

25. How confident are you that you can control your sarcoidosis by taking your medicine each day? **INTERVIEWER READ LIST**

Very confident	(1)
Somewhat confident	(2)
Not at all confident	(3)

26. If you don't take your sarcoidosis medicine what are the chances that something bad will happen to your health in the next year?
INTERVIEWER READ LIST

Very little chance	(1)
Some chance	(2)
Fifty-fifty chance	(3)
Probably will happen	(4)
Almost surely will happen	(5)

27. If you don't take your sarcoidosis medicine, what might happen?

    A. Don't know (1)

    B. Possibly: _____

28. How often do people in your daily life help you by reminding you to take your sarcoidosis medicines? **INTERVIEWER READ LIST**

All of the time	(1)
Some of the time	(2)
Never	(3)

29. Most people forget to take their medicine occasionally. How often does this happen to you? **INTERVIEWER READ LIST**

All of the time	(1)
Almost all of the time	(2)
Most of the time	(3)
Some of the time	(4)
Almost never	(5)
Never	(6)

III. ADMINISTRATIVE MATTERS

30. **Interviewer**:

    A. **Signature**: _____

    B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

31. **Research Coordinator**:

    A. **Signature**: _____

    B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

32. **Date form completed**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

FOLLOW-UP QUESTIONNAIRE FOR CASES ONLY (PART II)

ID No.				-				
Form Type	**S**	**F**	**0**	**1**				

General Instructions: Complete this questionnaire for all cases completing two-year follow-up.

I. CASE IDENTIFICATION

1. **Case's initials**: ____ ____ ____

2. **Date of interview**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

II. MEDICAL HISTORY

I am going to read you a list of health problems. For each problem, please tell me if you have ever had the problem. If you have had the problem, I will ask you to tell me your age when you first got it and whether you still have it. **IF RESPONSE IN COLUMN A IS DON'T KNOW, GO TO NEXT QUESTION.**

	A			**B**	**C**		
	Yes	No	Don't Know	Age?	Still Have It? Yes	No	Don't Know
3. Asthma	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
4. Chronic bronchitis	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
5. Emphysema	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
6. Sinus trouble	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
7. Allergies	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
8. Heart disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
9. High blood pressure	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
10. Kidney disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
11. Liver disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
12. Arthritis	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
13. Skin disease	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
14. Cancer	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
15. Lupus	(1)	(2)	(3)	____ ____	(1)	(2)	(3)
16. Diabetes	(1)	(2)	(3)	____ ____	(1)	(2)	(3)

17. Have you had any other health problems I have not asked you about? Yes (1) No (2)

IF YES, Please specify all the problems.

A. _____

B. _____

C. _____

D. _____

E. _____

18. Have you been pregnant at any time in the period since the ACCESS baseline interview? (1) Yes (2) No (3) Not Applicable

19. Have you been in the hospital as a patient in the period since the ACCESS baseline interview? Yes (1) No (2)

IF YES, ANSWER ITEMS A AND B.
IF NO, GO TO QUESTION 20.

A. How many times were you a patient in the hospital? ____ ____

B. Please give the following information for each time you were a patient in the hospital:

(1) Month Year	(2) Name of Hospital	(3) Reason
___ ___ ___-___ ___ ___ ___		
___ ___ ___-___ ___ ___ ___		
___ ___ ___-___ ___ ___ ___		
___ ___ ___-___ ___ ___ ___		
___ ___ ___-___ ___ ___ ___		
___ ___ ___-___ ___ ___ ___		

(Obtain signed release permission to obtain records)

20. During the past six weeks have you experienced any of the following?

		None	A Little	Some	Most of the Time	Always
A.	Increased appetite	(1)	(2)	(3)	(4)	(5)
B.	Difficulty sleeping	(1)	(2)	(3)	(4)	(5)
C.	Going to the bathroom more frequently	(1)	(2)	(3)	(4)	(5)
D.	Weight gain	(1)	(2)	(3)	(4)	(5)
E.	Swelling	(1)	(2)	(3)	(4)	(5)
F.	Heartburn or stomach pain	(1)	(2)	(3)	(4)	(5)
G.	Feeling “wired” or tense and hyperactive	(1)	(2)	(3)	(4)	(5)

21. Have you taken prednisone during the past six weeks? (1) Yes (2) No

III. PERSONAL HISTORY

22. Have you changed your job since your ACCESS baseline interview? (1) Yes (2) No

IF NO, GO TO QUESTION 23.

A. **IF YES**, Why?
- Sarcoidosis (1)
- Other physical condition (2)
- Other (3)
  Specify: _____

23. Have any of your brothers, sisters, spouse or mate, other relatives or friends or acquaintances been found to have sarcoidosis in the period since your ACCESS baseline interview? When you answer this question, you should think about old and new family members. (1) Yes (2) No (3) Don’t know

A. **IF YES**, Specify: _____

24. Do you have any children? (1) Yes (2) No

IF YES, ANSWER 24A.
IF NO, GO TO QUESTION 25.

A. Have any of your children been found to have sarcoidosis in the period since your ACCESS baseline interview? (1) Yes (2) No (3) Don't know

Smoking and Nicotine Use

25. Have you ever smoked any tobacco product? (1) Yes (2) No

IF NO, GO TO QUESTION 34.

26. Have you stopped smoking cigarettes in the period since your ACCESS baseline interview? (1) Yes (2) No (3) Never smoked cigarettes

27. Have you started smoking cigarettes in the period since your ACCESS baseline interview? (1) Yes (2) No

28. Have you stopped smoking cigarillos in the period since your ACCESS baseline interview? (1) Yes (2) No (3) Never smoked cigarillos

29. Have you started smoking cigarillos in the period since your ACCESS baseline interview? (1) Yes (2) No

30. Have you stopped smoking cigars in the period since your ACCESS baseline interview? (1) Yes (2) No (3) Never smoked cigars

31. Have you started smoking cigars in the period since your ACCESS baseline interview? (1) Yes (2) No

32. Have you stopped smoking a pipe in the period since your ACCESS baseline interview? (1) Yes (2) No (3) Never smoked a pipe

33. Have you started smoking a pipe in the period since your ACCESS baseline interview? (1) Yes (2) No

34. Do you spend more than three hours a week in rooms filled with smoke from other smokers? (1) Yes (2) No

IV. INCOME

GIVE THE PARTICIPANT CARDS I AND J NOW.

Income is important in analyzing the health information we collect. For example, this information helps us to learn whether persons in one income group use certain types of medical care services or have certain conditions more or less often than those in another group.

35. Was your total combined FAMILY income during the past 12 months more or less than $20,000 -- that is, yours as well as that of all the members of your household, including Armed Forces members living at home? Include money from jobs, social security, retirement income, unemployment payments, public assistance, and so forth. Also include income from interest, dividends, net income from business, farm, or rent, and any other money income received. **CHECK ONLY ONE.**

(1)	(2)
$20,000 or more (Card I)	Less than $20,000 (Card J)

36. Of these income groups, which number from the cards best represents your <u>total</u> combined FAMILY income during the past 12 months. Include wages, salaries, and other items we just talked about. **WRITE THE NUMBER IN THE BLANKS.** _____ _____

V. ADMINISTRATIVE MATTERS

37. **Interviewer**:

A. **Signature**: _____

B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

38. **Research Coordinator**:

A. **Signature**: _____

B. **ACCESS Staff No.**: ____ ____ ____ - ____ ____

39. **Date form completed**: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

CHANGE IN ORGAN INVOLVEMENT SINCE INITIAL EXAMINATION

ID No.				-				
Form Type	**C**	**I**	**0**	**1**				

1. Case's initials: ____ ____ ____

2. Date of follow-up examination: ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

ORGAN	**CHANGE [Check one response for each organ]**	
3. LUNGS	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
4. NEUROLOGIC	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
5. NON-THORACIC LYMPH NODE	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
6. RENAL	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
7. CARDIAC	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
8. SKIN	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
9. EYES	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
10. LIVER	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)
11. BONE MARROW	Better	($_1$)
	Worse	($_2$)
	Unchanged	($_3$)

ORGAN	**CHANGE [Check one response for each organ]**	
12. SPLEEN	Better	(1)
	Worse	(2)
	Unchanged	(3)
13. BONE/JOINTS	Better	(1)
	Worse	(2)
	Unchanged	(3)
14. EAR/NOSE/THROAT	Better	(1)
	Worse	(2)
	Unchanged	(3)
15. PARTOTID / SALIVARY GLANDS	Better	(1)
	Worse	(2)
	Unchanged	(3)
16. MUSCLES	Better	(1)
	Worse	(2)
	Unchanged	(3)
17. HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	Better	(1)
	Worse	(2)
	Unchanged	(3)

18. Principal Investigator or ACCESS Physician

    A. Signature: _____

    B. ACCESS Staff No.: ____ ____ ____ - ____ ____

19. Research Coordinator:

    A. Signature: _____

    B. ACCESS Staff No.: ____ ____ ____ - ____ ____

20. Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
    Month Day Year

TISSUE SAMPLE SHIPPING FORM

ID No.				-				
Form Type	**T**	**S**	**0**	**1**				

1. Case's initials: ____ ____ ____

2. Date of biopsy: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

3. Total number of slides included in this shipment: ____ ____

4. What tissues are included in this shipment?

Tissue	(1) Yes	(1) No	(2) If YES, Enter Number of Slides
A. Skin	(1)	(2)	____ ____
B. Lymph node	(1)	(2)	____ ____
C. Parotid/salivary gland	(1)	(2)	____ ____
D. Conjunctivae	(1)	(2)	____ ____
E. Lacrimal gland	(1)	(2)	____ ____
F. Sinus	(1)	(2)	____ ____
G. Nasopharynx	(1)	(2)	____ ____
H. Trachea and main bronchi	(1)	(2)	____ ____
I. Lung	(1)	(2)	____ ____
J. Heart	(1)	(2)	____ ____
K. Liver	(1)	(2)	____ ____
L. Spleen	(1)	(2)	____ ____
M. Gastrointestinal tract	(1)	(2)	____ ____
N. Muscle	(1)	(2)	____ ____
O. Peripheral nervous system	(1)	(2)	____ ____
P. Central nervous system	(1)	(2)	____ ____
Q. Kveim site	(1)	(2)	____ ____
R. Other	(1)	(2)	____ ____

Specify: _____

5. Research Coordinator:

   A. Signature: _____

   B. ACCESS Staff No.: ____ ____ ____ - ____ ____

6. Date form completed: ____ ____ ____ - ____ ____ - ____ ____ ____ ____
   Month Day Year

The original form should accompany the specimens to the Central Repository. A copy of this Transmittal List should be sent to the Clinical Coordinating Center and a copy kept at the Clinical Center. Send four 2 ml cryostat tubes containing supernatant, one 2 ml cryostat tube containing a cell pellet and one pair of slides for each case.

ACCESS BRONCHOALVEOLAR LAVAGE TRANSMITTAL LIST

	Specimen Number	No. Tubes	Case/Control Had Infectious Disease		In Good Condition Upon Receipt at Repository **(To be completed by Central Repository)**	
			Yes	No	Yes	No
A. Supernatant Aliquots	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Supernatant Aliquots	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Supernatant Aliquots	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Supernatant Aliquots	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Supernatant Aliquots	___ ___ ___ ___ ___	___	( )	( )	( )	( )
B. Cell Pellets	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Cell Pellets	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Cell Pellets	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Cell Pellets	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Cell Pellets	___ ___ ___ ___ ___	___	( )	( )	( )	( )
C. Slides	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Slides	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Slides	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Slides	___ ___ ___ ___ ___	___	( )	( )	( )	( )
Slides	___ ___ ___ ___ ___	___	( )	( )	( )	( )

Send specimens and forms to:

BBI-Biotech Research Laboratories
Attn: NHLBI epository
217 Perry Parkway
Gaithersburg, Maryland 20877

Date sent to the Central Repository:

___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

ACCESS staff member completing form and verifying contents of shipment:

Name _____

ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed at the Central Repository

Date shipment received:

___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

Individual reviewing contents:

Name _____

Please enter this information into your computer system inventory.

ACCESS DNA BLOOD SPECIMEN SHIPPING FORM

Send the original form with the blood specimens to the DNA Core Laboratory. Use one form for each case and one form for each control. Send a copy of this Transmittal List to the Clinical Coordinating Center and keep a copy at the Clinical Center. Send five large purple top tubes of blood for each case and each control. Send the specimens by Federal Express on the day of collection.

1. Specimen number: ____ ____ ____ ____ ____

2. Number of tubes: ____

Send specimens and form to:
Dr. Mary J. Maliarik
Pulmonary & Critical Care, Internal Medicine
Henry Ford Hospital
1 Ford Place, 5-D
Detroit, Michigan 48202

3. Did this case/control have a known infectious disease? ( ) Yes ( ) No

4. Date sent to the DNA Core Laboratory: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

5. ACCESS staff member completing form and verifying contents of shipment:

   A. Name: _____

   B. ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed by DNA Core Laboratory Staff

Date shipment received:
___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

All specimens in good condition: ( ) Yes ( ) No

Individual reviewing contents:

Name _____

Please enter this information into your computer system inventory.

ACCESS L-FORMS BLOOD SPECIMEN SHIPPING FORM

Send the original form with the blood specimens to Mr. Ian Brett. Use one form for each case and one form for each control. Send a copy of this Transmittal List to the Clinical Coordinating Center and keep a copy at the Clinical Center. Send one small, purple top tube of blood for each case and each control. Send the specimens by Federal Express on the day of collection.

1. Specimen number (Affix one of the Mt. Sinai blood specimen labels here):

2. Number of tubes: ____

Send specimens and form to: Mr. Ian Brett
Bronx VA Medical Center
130 West Kingsbridge Road, 4S-06
Bronx, New York 10468

3. Did this case/control have a known infectious disease? ( ) Yes ( ) No

4. Were skin and vial properly sterilized with iodine? ( ) Yes ( ) No

5. Date sent to Mr. Ian Brett: ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

6. ACCESS staff member completing form and verifying contents of shipment:

   A. Name: _____

   B. ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed by Dr. Lesser's Laboratory Staff

Date shipment received:
___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

All specimens in good condition: ( ) Yes ( ) No

Vial properly sterilized with iodine: ( ) Yes ( ) No

Individual reviewing contents:

Name _____

Please enter this information into your computer system inventory.

ACCESS GUANIDINIUM SUSPENDED CELL PELLET SHIPPING FORM

Send the original form with the specimens to the RNA Core Laboratory. Send a copy of this shipping form to the Clinical Coordinating Center. Send one cell pellet resuspended in solution D on dry ice for each case and each control. Send the specimens by Federal Express on the day of collection.

1. Specimen number: ____ ____ ____ ____ ____

2. Number of tubes: ____

Send specimens and form to: Patricia Finn, M.D.
Respiratory Division
Brigham & Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

3. Did this case/control have a known infectious disease? ( ) Yes ( ) No

4. Date sent to RNA Core Laboratory: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

5. ACCESS staff member completing form and verifying contents of shipment:

   A. Name: _____

   B. ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed by the RNA Core Laboratory

Date shipment received: ___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

All specimens in good condition: ( ) Yes ( ) No

Individual reviewing contents:

Name _____

Please enter this information into your computer system inventory.

ACCESS DNA TRANSMITTAL LIST

The original form should accompany the specimens to the Central Repository. Please enter the appropriate information in your computer system inventory. Please send this list to the Clinical Coordinating Center by FAX or by electronic transmission.

	Specimen Number	No. Tubes	Case/Control Had Infectious Disease		In Good Condition Upon Receipt at Repository **(To be completed by Central Repository)**	
			Yes	No	Yes	No
A. DNA	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
DNA	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
DNA	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
DNA	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
DNA	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
DNA	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
B. Plasma	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
Plasma	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
Plasma	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
Plasma	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
Plasma	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )
Plasma	___ ___ ___ ___ ___	___ ___	( )	( )	( )	( )

Send specimens and forms to:
Mark Cosentino, Ph.D.
BBI-Biotech Research Laboratories
Attn: NHLBI Repository
217 Perry Parkway
Gaithersburg, Maryland 20877

Date sent to the Central Repository:

___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

ACCESS staff member completing form and verifying contents of shipment:

Name _____

ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed at the Central Repository

Date shipment received:

___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

Individual reviewing contents:

Name _____

Please enter this information into your computer system inventory.

ACCESS BRONCHOALVEOLAR LAVAGE SLIDE TRANSMITTAL LIST

The original form should accompany the specimens to the BAL Core Laboratory. A copy of this Transmittal List should be sent to the Clinical Coordinating Center and a copy retained at the Clinical Center. Send one pair of slides for each case included in this shipment.

Specimen Number	No. Slides	Case/Control Had Infectious Disease		In Good Condition Upon Receipt at Laboratory **(To be completed by BAL Core Laboratory)**	
		Yes	No	Yes	No
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )

Send specimens and forms to:
Dr. Robert Baughman
University of Cincinnati Medical Center
231 Bethesda Avenue, Room 6004
Cincinnati, Ohio 45267-0564

Date sent to the BAL Laboratory:

___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

ACCESS staff member completing form and verifying contents of shipment:

Name ________________________________

ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed at the BAL Core Laboratory

Date shipment received:
___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

Individual reviewing contents:

Name ________________________________

Please enter this information into your computer system inventory.

ACCESS KVEIM BIOPSY SLIDE TRANSMITTAL LIST

The original form should accompany the specimens to Dr. Alvin Teirstein. A copy of this Transmittal List should be sent to the Clinical Coordinating Center and a copy retained at the Clinical Center. Send one pair of slides for each case included in this shipment.

Specimen Number	No. Slides	Case/Control Had Infectious Disease		In Good Condition Upon Receipt at Laboratory **(To be completed by Dr. Teirstein)**	
		Yes	No	Yes	No
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )
___ ___ ___ ___ ___	___	( )	( )	( )	( )

Send specimens and forms to:
Dr. Alvin Teirstein
Mount Sinai Medical Center
Division of Pulmonary and Critical Care Medicine
Box 1232
1 Gustave L. Levy Place
New York, New York 10029

Date sent to Dr. Teirstein

___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

ACCESS staff member completing form and verifying contents of shipment:

Name
____

ACCESS Staff No.: ___ ___ ___ - ___ ___

This section should be completed by Dr. Teirstein

Date shipment received:
___ ___ ___ - ___ ___ - ___ ___ ___ ___
Month Day Year

Individual reviewing contents:

Name ________________________________

Please FAX this form to the Clinical Coordinating Center (410-435-0689)

A CASE CONTROL ETIOLOGIC STUDY OF SARCOIDOSIS

ACCESS

PROCEDURES MANUAL

VOLUME IIB

November 1998*

NOTICE: **The contents of this Procedures Manual are confidential and are not to be cited or discussed except with individuals to whom it has been distributed on behalf of the ACCESS Steering Committee.**

Prepared by:

Clinical Trials & Surveys Corp.
The Village of Cross Keys
350 West Quadrangle
Baltimore, Maryland 21210

*** Selected pages revised.**

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IIB

SCRIPTS FOR STUDY FORMS

* Revised November, 1998

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IIB

SCRIPTS FOR STUDY FORMS
(Continued)

*Added - July, 1998
**Added - November 1998

A Case Control Etiologic Study of Sarcoidosis

General Instructions for All Forms

1.	ID Number:	As soon as a potential new case is identified from hospital records or a potential control is identified by notification from the RDD Interview Group, the potential new case or control should be assigned the next available number on the ID Log provided by the Clinical Coordinating Center. In order to avoid issuing the same ID number to two different persons, cross off ID numbers as they are used.
2.	Initials:	Item 1 on all forms is for the participant's initials. The initials should always be in this order: first, middle, last. The same combination of ID number and initials must always be used for a given participant. If a participant lacks any of the three names, an "X" should be used for the initial. For example, if the participant has no middle name, "X" should be used for the middle initial. A person identifying himself or herself by only his/her first name would have "Xs" for both the middle and last initials.
3.	Dates:	Item 2 on all forms is the date of interview or procedure. The last item on all forms is the date the form was completed. Other dates appear in the body of some forms. All dates on ACCESS forms (except ATRS Worksheets) are to be recorded as a three-letter abbreviation of the month (first three letters), two-digit date (a leading zero is to be used for dates 1-9) and the complete four-digit year. Thus, September 6, 1996 would be SEP-06-1996, November 10, 1945 would be NOV-10-1945. See Appendix B for a list of standard month abbreviations.
4.	Boldface Items:	Items or questions in boldface capitals are to be answered by the Research Coordinator/Interviewer and are not to be asked of the participant.
5.	Instructions to interviewer:	All instructions in boldface capital letters on the forms are instructions to the interviewer and are not to be read to the participant.
6.	Research Coordinator Signature/ACCESS Staff Number:	The Research Coordinator signs all forms and records his/her staff number which will be assigned by the Clinical Coordinating Center. The Research Coordinator is not responsible for collecting all data but is responsible for reviewing all forms for completeness and legibility.
7.	Instructions in scripts:	Not all items have instructions in the scripts for each form. Either it is an item discussed in the general instructions or the item is considered self-explanatory.

A Case Control Etiologic Study of Sarcoidosis
Log for RDD Controls

1. As soon as the Research Coordinator receives notification from the RDD Interview Group of a potential control, the potential control should be listed on the log by his/her ID number and initials.

2. The Research Coordinator contacts the potential control by letter as soon as possible. The letter should tell the potential control that the Research Coordinator will contact the potential control by telephone within three days after the letter arrives. The date of the telephone call is the date of initial contact.

3. If, during this initial contact, information is obtained concerning conditions that would make the potential control ineligible, a "Y" is written in the "Exclusions" column and the reason code (see code sheet) written in the "Reasons for Ineligibility" column.

4. If no exclusion criteria are discovered and the potential control is wiling to have a face-to-face interview, the Research Coordinator completes Forms 01 and 05 at the start of the interview. The interview should proceed using the scripts for Forms 01 and 05. All pertinent information is added to the log until it is definitely known that the potential control is enrolled or not enrolled. If the control is enrolled, all appropriate study forms should be completed and information about health care coverage should be collected from Form 10. If the control is not enrolled, the Research Coordinator should request information from the control on his/her health care coverage and this should be recorded in the proper column on the log.

A Case Control Etiologic Study of Sarcoidosis
Participant Information Form
(Form 01)

PURPOSE The purpose of the Participant Information Form is to provide information which will help the Research Coordinator locate and maintain contact with study participants. The information on this form is strictly confidential and is not transmitted to the Clinical Coordinating Center.

7.	Name of spouse/partner:	This should be the name of the person with whom the participant is currently living.
10. 11.	Names and address of persons knowing participant's whereabouts:	These should be persons not residing with participant, so both these names should be different from the name of the spouse/partner. If case/control refuses to answer these questions, leave blank.
12.	Name of referring physician (Cases Only):	The case's personal physician may be able to provide information on the case's whereabouts.

A Case Control Etiologic Study of Sarcoidosis
Confirmation of Eligibility (Cases)
(Form 02)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of this form is to confirm that all eligibility criteria have been met. The form should be begun for all potential new cases if review of the medical records indicates no ineligible conditions and the case agrees to come to the Clinical Center for an initial interview. If any **STOP** responses are encountered, the Research Coordinator should stop completing the form for that potential case and record the reason for ineligibility on the Case Screening Log. If no **STOP** responses are encountered, the form is completed and the case is registered using the Automated Telephone Response System (ATRS) and the Case Registration Worksheet (Form 03). Registration of a case can occur before the diagnosis of sarcoidosis from tissue specimens is confirmed. As soon as the pathology report is complete, the potential case is either enrolled in the study or determined to be ineligible for enrollment and the enrollment/non-enrollment status confirmed on the ATRS using the Case Enrollment/Non-Enrollment Worksheet (Form 04).

2. Date of confirmation of eligibility:	This date cannot be earlier than Item 9, date of biopsy. Complete date according to General instruction for dates.
3. Has case agreed to be in this study:	Either verbal or written consent should be obtained from the potential case before proceeding with the completion of this form. Written consent must be obtained before the case can be definitely enrolled.
4. Case's gender:	From Form 01.
5. Age:	Potential cases's stated age should be compared with birthdate on Form 01.
6. Race:	Read list of responses. Do not suggest an answer or category to the respondent and do not try to explain or define any of the groups. The concept of race does not reflect classification of biological characteristics nor does it conform to any scientific definition. Rather, it reflects self-identification by the respondent; that is the race with which the person most closely identifies. If the respondent says he or she is biracial or multiracial (e.g., Asian-American, Chinese-American), check "Other." If the answer is not one from the list of responses (White, Black, or African-American, Asian/Pacific Islander, American Indian or Alaska Native) but is unclassifiable (e.g., Mexican, Puerto Rican) ask the respondent whether he or she is a white Mexican or Puerto Rican or a black Mexican or Puerto Rican. The potential case should be classified according to whichever of these two designations the potential case specifies. If both designations are rejected, check the response "Other" and write the verbatim response on the "Specify" line.
7. Hispanic:	Do not suggest an answer to the respondent.

8. Exclusion Criteria:

Although the Research Coordinator reviews the medical records of each potential case before arranging for a face-to-face interview, it may become apparent during the face-to-face interview that the potential case has ineligibility conditions that were not noted in the medical records. If any **STOP** responses are encountered, the Research Coordinator should stop completing the form. If the potential case does not recognize one or more of these conditions, the potential case has probably not had that condition. Further prompting should be avoided.

9. Has tissue specimen been obtained for diagnosis?

10. Where were the diagnostic biopsies performed?

11. Has pathology report (ACCESS Form 31) been completed?

The tissue specimen(s) may have been obtained after the potential case was referred to the Clinical Center or up to six months before the expected date of enrollment. If the tissue specimen was obtained prior to the potential case being considered for ACCESS, please be sure that the slides from the previously obtained specimens are provided to the pathologist who has agreed to review all the pathology specimens for ACCESS in your Clinical Center. If the biopsy specimens have been obtained in the course of evaluation of the patient for ACCESS, be sure that the pathology department in your Clinical Center arranges for the pathologist designated for ACCESS to read these slides.

In all cases a Diagnostic Specimen Report (Form 31) must eventually be completed. However, if the Form 31 is completed after the completion of the Form 02, the Form 02 is not revised to reflect the Form 31 data.

If the Form 02 has been entered into the local data management system and the potential case is later determined to be ineligible because the pathology report is not consistent with a positive diagnosis of sarcoidosis, a Form D1 (Form Deletion -- Participant Identification Correction Form) should be submitted to the Clinical Coordinating Center, requesting deletion of the Form 02.

12. Were specimens sent for culture?

13. Was the culture positive for acid fast bacilli, fungus or other excluded infectious agent in any of the specimens?

All potential cases should have acid-fast bacillus and fungal cultures of all available tissue performed and appropriately stained. In potential cases undergoing bronchoscopy, bronchial washings should always be obtained specifically for fungal and acid-fast bacilli cultures. Potential cases who live in areas where histoplasmosis is endemic or who have risk factors for tuberculosis should have appropriate tests performed on tissue specimens (cultures of biopsy specimens required) to exclude tuberculosis and fungal infections, especially histoplasmosis.

14.	Have any stop responses been checked?	If the answer is Yes, do not complete the form or enter it into the local data management system. Record the reason for ineligibility on the Case Screening Log, but do not register the potential case on the ATRS.

A Case Control Etiologic Study of Sarcoidosis

Case Registration Worksheet (ATRS)
(Form 03)

PURPOSE The purpose of the Form 03 is to register a potential case with the Clinical Coordinating Center as soon as possible using the Automated Telephone Response System(ATRS).

GENERAL INSTRUCTIONS This form is to be completed as soon as the Form 02 has been completed. All of the information comes from Form 01 and Form 02. If any **STOP** response has been encountered on Form 02, Form 03 is not completed and the potential case is not registered on the ATRS.

If the tissue specimen(s) for diagnosis are still being examined either by the local pathologist or as part of the Tissue Sample Reading Program, then the response for Item 11 should be "Pending". The tissue specimen(s) may have been obtained after the potential case was referred to the Clinical Center or up to six months before the expected date of enrollment. If the tissue specimen was obtained prior to the potential case being considered for ACCESS, please be sure that the slides from the previously obtained specimen(s) are provided to the pathologist who has agreed to review all the pathology specimens for ACCESS in your Clinical Center. If the biopsy specimens have been obtained in the course of evaluation of the patient for ACCESS, be sure that the pathology department in your Clinical Center arranges for the pathologist designated for ACCESS to read these slides.

A Case Control Etiologic Study of Sarcoidosis

Case Enrollment / Non-Enrollment Worksheet (ATRS)
(Form 04)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of the Form 04 is to notify the Clinical Coordinating Center as quickly as possible, using the ATRS, of the final enrollment status of all potential cases. This worksheet is completed and the ATRS notified after all pathology reports (local and/or Tissue Sample Reading Program) have been completed. If the report indicates a positive diagnosis of sarcoidosis, the potential case is asked to sign the informed consent form. If the potential case signs the informed consent, he/she is enrolled in ACCESS. The Clinical Coordinating Center needs the information on Form 04 in order to begin the procedures required for selecting a Random Digit Dialing (RDD) Control in conjunction with the RDD Interview Group.

A Case Control Etiologic Study of Sarcoidosis

Confirmation of Eligibility (Controls)
(Form 05)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of this form is to confirm that all eligibility criteria have been met. As soon as the Research Coordinator receives notification from the RDD Interview Group of the name and telephone number of a potential control, he/she should call the potential control. The Research Coordinator should complete as much of this form as possible over the telephone. If no **STOP** responses are encountered, the Research Coordinator should make an appointment for a face-to-face interview with the potential control. If any **STOP** responses are encountered, the Research Coordinator does not complete the Form 05, but the eligibility status of the potential control must be reported to the Clinical Coordinating Center using the ATRS and the Control Status Worksheet (Form 06).

4.	Has the control agreed to be in this study?	This item should not be answered "Yes" until the informed consent form has been signed.
5.	Control's gender:	Self-designated gender.
7.	Race:	Read list of responses. Do not suggest an answer or category to the respondent and do not try to explain or define any of the groups. The concept of race does not reflect classification of biological characteristics nor does it conform to any scientific definition. Rather, it reflects self-identification by the respondent; that is the race with which the person most closely identifies. If the respondent says he or she is biracial or multiracial (e.g., Asian-American, Chinese-American), check "Other." If the answer is not one from the list of responses (White, Black, or African-American, Asian/Pacific Islander, American Indian or Alaska Native) but is unclassifiable (e.g., Mexican, Puerto Rican) ask the respondent whether he or she is a white Mexican or Puerto Rican or a black Mexican or Puerto Rican. The potential case should be classified according to whichever of these two designations the potential case specifies. If both designations are rejected, check the response "Other" and write the verbatim response on the "Specify" line.
8.	Hispanic:	Do not suggest an answer to the respondent.
9.	Exclusion Criteria:	The Research Coordinator should ask these questions during the telephone interview. However, during the face-to-face interview, it may become apparent that the potential control has ineligibility conditions that were not noted during the telephone interview. If any **STOP** responses are encountered during either the telephone or the face-to-face interviews, the Research Coordinator should stop completing the form and notify the Clinical Coordinating Center of the status of the potential control as soon as possible using the ATRS (Form 06). If the potential control does not recognize one or more of these conditions, the potential control has probably not had that condition. Further prompting should be avoided.

A Case Control Etiologic Study of Sarcoidosis

Control Status Worksheet (ATRS)
(Form 06)

PURPOSE AND GENERAL INSTRUCTIONS This form is completed and the ATRS notified after the control has been interviewed or it is definitely known that the control will not be interviewed. (The control should fail to keep at least three appointments for interviews before the Clinical Center "drops" the control.) It is essential that the Clinical Coordinating Center be notified by means of the ATRS as soon as a potential control is known to refuse or be ineligible so that the process for identifying another control can be initiated.

8. Linked to Case: As part of the procedures for linking RDD controls to cases, the RDD Interview Group will FAX information for a potential control specifically linking the information for a potential control to a specific case. This faxed information should be kept in an accessible place. When the control is enrolled, this document should be filed with the control's other ACCESS forms. When it is known that a potential control will not be enrolled, the document should be destroyed.

A Case Control Etiologic Study of Sarcoidosis

Enrollment Confirmation Form (from ATRS)
(Form 09)

PURPOSE AND GENERAL INSTRUCTIONS: The purpose of this form is to confirm that the information entered on the ATRS concerning the ID Number and initials of the case/control are the same as the information that was entered on the Form 02 (cases) or Form 05 (controls). At the time the Form 09 is entered into the local data management system the computer system will check to make sure that the eligibility criteria have been entered correctly. The date of enrollment on this form sets the time windows for completion of any other forms that will be required in ACCESS. Only patient identification number, form type, initials, enrollment date and confirmation number are entered into the local data management system.

Demographic items printed on the Form 09 for cases should be checked visually and any discrepancies immediately reported to the Clinical Coordinating Center. Confirmation of these data is very important for the cases since this information will be used to enroll an age-gender-race matched control.

This form will be sent by FAX to you immediately after contacting the ATRS and enrolling the case/control. This form should be entered into your local data management system as soon as possible after you receive it.

A Case Control Etiologic Study of Sarcoidosis

Demographics and Medical History Questionnaire
(Form 10)

PURPOSE The purpose of this questionnaire is to obtain information about the participant's social status and access to medical care. This information is used to compare cases and controls with respect to marital status, race, education, the kinds of places people go to receive medical care, from whom they receive care, and why they seek care. Some of the questions may be considered sensitive, and care must be taken to ask questions and record responses in a nonjudgmental manner.

II. DEMOGRAPHICS

2A. Reference Date:

The reference date is the date of diagnosis of sarcoidosis for a case. For controls the reference date must be calculated using the date of diagnosis for the case and the date the case was interviewed. The difference (in days) between these two dates is subtracted from the date of interview of the control and this yields the control reference date.

For instance suppose a matched control is being interviewed on November 11, 1996 and the case was diagnosed on July 19, 1996 and interviewed on September 16, 1996. To calculate the reference date for the control convert each date to the corresponding day of the year. July 19, 1996 is day 201 and September 16, 1996 is day 260; the difference is 59 days. November 11, 1996 is day 316 and 59 days prior to day 316 is day 257 or September 13, 1996. September 13, 1996 is the reference date for the control.

2B. Reference Period:

The reference period is the three-year period prior to the reference date. The second date in Question 2B is the reference date as determined in Question 2A. The first date is the date three years prior to the reference date. These dates should be determined by the Research Coordinator so the interviewer can remain blinded as to whether the person being interviewed is a case or a control.

3. What is your birth date?

Enter the date on which the participant was born using the general guidelines for recording dates.

4. Where were you born?

Enter the full city name. If unknown, write "unknown". Enter the two letter postal code for the state. Enter the three-digit country code. See Appendix C for standard two-letter postal codes for states. See Appendix D for standard three-digit country codes.

5. Are you now married, widowed, divorced, separated, or have you never been married?	Read response list. This question refers to the most recent marriage. A person whose first marriage ended in divorce, but whose most recent spouse died is considered "Widowed". Mark "Married" for a married person who is not legally separated and whose spouse is temporarily absent (e.g. an Armed Forces member currently not living at home). Mark "Living in a marriage-like relationship" for a person who states he/she has a common-law marriage or is living with another person (as husband and wife) or lives with a steady partner. Accept a respondent's statement that a person is separated. If, however, the respondent raises a question as to the meaning of "Separated," explain that the term refers to married persons who have a legal separation or who are living in different places because of marital discord or disagreement. Consider a legally annulled marriage as never having taken place. For example, mark "Never married" for persons whose only marriage has been legally annulled. Individuals whose marriage has been annulled only by religious decree but not by a legal procedure are to be marked according to their legal marital status (e.g., divorced). Probe for clarification if there is any doubt about whether an annulment was granted through the courts or through religious decree.

6. Including yourself, how many people are now living in your home?

The number living in the home is considered the entire group of persons who live in one housing unit with the respondent. It may be several persons living together or one person living alone in a house or apartment. It includes the respondent, any relatives living in the unit, and may also include roomers, servants, or other persons not related to the respondent. Consider the following two categories of persons as members of the home: (1) Persons, whether present or temporarily absent, whose usual place of residence at the time of interview is the respondent's unit; and (2) Persons staying in the respondent's unit who have no usual place of residence elsewhere. "Usual place of residence"is ordinarily the place where a person usually lives and sleeps. A usual place of residence must be specific living quarters held by the person to which he/she is free to return at any time. Living quarters which a persons rents or lends to someone else cannot be considered his/her usual place of residence during the time these quarters are occupied by someone else.

There may be special situations regarding home membership. Below are guidelines for handling these situations.

(1) Students and student nurses - Students away at school, college, trade or commercial school in another locality are eligible to be interviewed in the locality where they are attending school. That is, even if a student considers his/her parents' home to be the usual residence, consider him/her to be a household member where presently residing. Consider a student to be a household member of his/her parents' home only if he/she is at home for the summer vacation and has no usual residence at the school.

(2) Seamen - Consider crew members of a vessel to be household members at their homes rather than on the vessel, regardless of the length of their trips and regardless of whether they are at home or on the vessel at the time of this interview (assuming they have no usual place of residence elsewhere).

(3) Members of Armed Forces - Consider members of the Armed Forces (either men or women) as household members if they are stationed in the locality and usually sleep in the respondent's unit.

(4) Inmates of specified institutions - Persons who are inmates of certain types of institutions at the time of this interview are not household members of the respondent's unit.

6A. Check here if homeless.

Consider the respondent "homeless" if he/she does not have a usual place of residence.

7. What grade of schooling have you completed?

Interviewer should read the list of responses, the intent of which is to identify the highest level of formal education attained. Definition - For this question include regular schooling in graded public, private, or parochial schools, or in colleges, universities, or professional schools, whether day school or night school. Regular schooling is that which advances a person toward an elementary or high school diploma, or a college, university, or professional school degree. Count schooling in other than regular schools only if the credits obtained are acceptable in the regular school system.

Do NOT include:

(1) Education obtained at vocational schools, business schools or colleges, and other trade and specialized schools unless such schools are part of a regular school system.
(2) Training received by mail from "correspondence" schools, unless the correspondence course counted toward promotion in a regular school.
(3) Any kind of "on-the-job" training.
(4) Adult education classes unless such schooling is being counted for credit in a regular school system. If a person is taking adult education classes but not for credit, he/she should not be regarded as enrolled in a regular school. Adult education courses given in a public school building are part of regular schooling only if their completion can advance a person toward an elementary school certificate, a high school diploma, or college degree.
(5) Government sponsored training under the Comprehensive Employment and Training Act (CETA) or the Job Training Partnership Act (JTPA). Most of this training more than likely will be courses obtained at private vocational or trade schools or possibly will be in the nature of on-the-job training. In any event, it will not be obtained at a regular school. There may be a few isolated cases where such schooling is given for credit at a regular school; ask to be sure.
(6) Any type of military basic training.

The highest level of education should be checked for grade school and high school. This has been divided into three categories. Check 1-8 if the highest grade completed is in that range. Check 9-12 if person completed some, but not all of high school. Check "High School Graduate" if the person actually received a diploma or General Educational Development (GED). For students who entered college, check the "College Graduate" or "Post Graduate" codes only if they actually received a degree. Persons who have completed professional schools (law, medical, dental, etc.) after completing college are considered to have post graduate degrees.

III. ACCESS TO HEALTH CARE SERVICES

8. Currently, what is your main health insurance plan?

Interviewer should read list of responses. The focus of this question deals with the source of funding (private, self or government source) for insurance coverage for health care. A response of "I have a HMO" describes the type of health care plan, but does not identify who pays for the insurance. The following is a list of definitions:

(1) Private health insurance differs from public plans by who pays for the insurance. Private health insurance refers to any type of health insurance paid for all or in part by a family member out of pocket or all or in part by an employer. Coverage could be by fee-for-service, single- or multiple-provider HMO plans, or combination plans - e.g., plans with a single provider in which the patient can go elsewhere/anywhere for an additional payment. It does not include publicly paid programs listed below. Public plans are those in which the government pays for most or all of the cost of care for some people - e.g., those 65 years of age or older on Medicare.

(2) Medicare refers to the Federal health insurance coverage most common for persons 65 years and over. In certain situations people under 65 may be covered.

(3) Medicaid refers to a medical assistance program that provides health care coverage to low income and disabled persons. The Medicaid program is a joint federal-state program which is administered by the States.

(4) Other public plans refer to other state or federal health insurance programs not listed above and can include:

(a) Military health care refers to health care available to active duty personnel and their dependents; in addition, the VA provides medical assistance to veterans of the Armed Forces, particularly those with service-connected ailments.

(b) CHAMPUS (Comprehensive Health and Medical Plans for the Uniformed Services) provides health care in private facilities for dependents of military personnel on active duty or retired for reasons other than disability.

(c) CHAMPVA (pronounced CHAMP V-A) (Comprehensive Health and Medical Plan of the Veterans Administration) provides health care for the spouse, dependents, or survivors of a veteran who has a total, permanent service-connected disability.

If the respondent answers with "None" or "Don't Know", go to Question 9. Otherwise, ask Questions 8A -8C.

9. Is there one particular clinic, health center, doctor's office, or other place that you usually go to if you are sick or need advice about your health?

This question is intended to find out if the respondent has a usual source of health care. "Usual source of health care" refers to a place one would usually go if he/she were sick or in need of advice about his/her health. If respondent answers "Yes" to Question 9, interviewer should read Question 9A and response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. Skip Questions 9B and 9C and proceed to Question 10. If the answer to Question 9 is "No", interviewer should skip to Question 9B.

9A. What type of place is it?

Read the response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. The following definitions may be helpful:

(1) A "doctor's private office" refers to an individual office in a freestanding or office building or a suite of offices occupied by several doctors. Do not consider a suite of individual, private, or unrelated group of doctors' offices as a clinic.

(2) A "Hospital emergency room" is the unit of a hospital where persons may receive medical care, often of an urgent nature, without or before being admitted. Emergency rooms are usually open 24 hours a day.

(3) A "Hospital outpatient clinic" is the unit of a hospital where persons may go for medical care without being admitted. Outpatient clinics usually provide routine, non-emergency medical care and are usually open only during specific hours.

(4) A "Non-hospital clinical center" refers to a private clinical facility that provides ambulatory care and is freestanding in the community. This includes not-for-profit, non-government owned, "free" health clinics which may operate on a sliding scale. Examples include: urgent care centers; private walk-in care centers; Planned Parenthood centers; hospital-related centers not located within the hospital; and commercial (e.g., health care system, HMO-owned) centers employed by the HMO, commercial company or University.

(5) A "Public health clinic" refers to a publicly - i.e., locally, state, or federally - supported facility where one or more physicians provide walk-in or ambulatory medical care. This also includes community health clinics which accept insurance but are federally sponsored clinics in under served areas.

9B.	If no, is there one particular place where you <u>would</u> go if you were sick or needed advice about your health?	This question is intended to find out where the respondent would prefer to go if he/she did have a usual source of health care. If the answer to Question 9B is "No", skip Question 9C and proceed to Question 10. If the answer to Question 9B is "Yes", ask Question 9C.
9C.	What type of place is it?	Read the response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. See Question 9A for definitions.
10.	Is your regular doctor a general practitioner, internist, family doctor or doctor who treats a variety of illnesses and gives preventive care or is he or she a specialist (a doctor who mainly treats just one type of health problem)?	Interviewer should read response list. The following definitions may be helpful: (a) "Regular doctor" refers to the usual doctor the respondent usually visits when in need of medical care or advice for either preventive, curative, or continuing health care. This is the doctor you would go to for a new complaint or who coordinates your care. (b) The central concept is to differentiate whether the respondent's regular doctor is a primary physician or a specialist physician. In addition, some primary care doctors limit their care to people of particular ages - e.g., children for pediatricians or adults for internal medicine doctors (internists). A "general practitioner" or "family physician" refers to a generalist medical doctor who provides comprehensive medical care on a continuing basis to patients of any age or sex regardless of the specific nature of the patient's health problems. (c) A "specialist" refers to a medical doctor whose practice is limited to a particular type of medicine or surgery such as reproductive or urinary problems, or who is a pediatric or internal medicine physician who treats one organ system or category of disease. A specialist has advanced training and is certified by a specialty board as being qualified to limit his/her practice to that field. Examples of specialists are surgeons, internists specializing in pulmonary (lung) diseases, pediatricians specializing in heart problems, psychiatrists, obstetricians, proctologists, ophthalmologists, and so forth.
11.	During the last 12 months, was there any time when you wanted to see a doctor but could not?	This question is intended to find out if the respondent could not get health care when he/she thought it was necessary. The question refers to <u>any</u> reason the respondent could not see a doctor. A "doctor" means <u>any</u> doctor, not just participant's personal physician. If the respondent answers "Yes" to Question 11, ask Question 11A. If the respondent answers "No", skip Question 11A and proceed to Question 12. If respondent says he/she could have seen some doctor but not his/her own doctor, check "No".

11A.	If Yes, Why?	This question is intended to find out why the respondent could not get health care. Read the response list. Mark all appropriate answers. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
12.	During the past 12 months, have you delayed seeking medical care because of worry about the costs?	This question is intended to find out if the respondent put off or delayed seeking medical care because he/she was worried about the costs involved. It refers to the respondent's wanting to see or be referred to a doctor but not being able to afford to see the desired doctor. If the respondent answers "Yes" to Question 12, ask Question 12A. If the respondent answers "No" to Question 12, skip Question 12A and proceed to Question 13.
12A.	If yes, approximately how many times?	If the respondent answers Question 12A with a range of numbers (e.g. 10-12 times), ask the respondent for a single number. If the person persists with a range, put down a number at the middle of this range - e.g., 11.
13.	In the past 12 months have you delayed or had difficulty getting medicine prescribed when you needed it?	This question is intended to find out if the respondent was not able to get medication prescribed by a doctor even when he/she thought it was necessary. It means that the respondent had been prescribed medicine but delayed in getting or did not get the medicine initially, or when he/she ran out of the medication but was supposed to continue to use the medicine. If the respondent answers "Yes", ask Question 13A. If the respondent answers "No" to Question 13, proceed to Question 14.
13A.	If yes, was it because of:	This question is intended to find out why the respondent could not get medication prescribed by a doctor even though he/she thought it was necessary. Read the response list. Mark all appropriate answers. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.

IV. MEDICAL HISTORY

14. to 27.	I am going to read you a list of health problems. For each health problem, please tell me if you have ever had the problem. If you have had the problem, I will ask you to tell me your age when you first got it and whether you still have it.	For each condition, the response should be coded as "Yes" if a doctor indicated that the condition was present. For instance, sinus trouble should be checked "No" if the respondent reports a stuffy nose, but should be checked "Yes" if a doctor told the respondent that he/she had sinus problems. Likewise, allergies should be determined from a skin test or some other form of verifying the presence of an allergy. In Part B, respondent should indicate the age at which the symptoms were first present regardless of when the problem was diagnosed.
28.	Have you had any other health problems I have not asked you about?	This addresses other health problems not previously specified. Make sure you do not write any health problem that is listed in Questions 14-27. If the participant has no other health problems, check No and go to Question 29.

30.	Date blood drawn.	Blood should be drawn from all cases and controls and sent to designated Core Laboratories for future analysis.
32.	Label sheet number:	Copy the label sheet number from the sheet of labels provided by the Clinical Coordinating Center. Please affix the Blood Specimen Sheet Label (the label with the label sheet number and the case/control's ACCESS ID number) to the form in the space provided.
33.	Where was blood shipped?	Please check Yes for those Core Laboratories to which blood is being shipped. Use the appropriate labels on the tubes and send the appropriate shipping form with the specimens.
34.	Participant has consented to the following use of his/her blood specimens	Check the appropriate response based on the participant's consent form. The ACCESS Clinical Coordinating Center will notify the Central Repository of specimen numbers which have restricted use.
39.	When were the blood specimens obtained?	Report timing of blood specimen collection as before or after the ACCESS interview.

A Case Control Etiologic Study of Sarcoidosis

Occupational History Worksheet
(Form 11)

GENERAL INSTRUCTIONS: Form 11 is copied and the copy kept at the Clinical Center. The original is forwarded to the Clinical Coordinating Center for Standard Industrial Classification/Standard Occupational Classification (SIC/SOC) coding. Only pages 1, 2 and 10 of the form are entered into the local data management system.

2A. Reference date:	The reference date is the date of diagnosis of sarcoidosis for a case. For controls the reference date must be calculated using the date of diagnosis for the case and the date the case was interviewed. The difference (in days) between these two dates is subtracted from the date of interview of the control and this yields the control reference date. For instance suppose a control is being interviewed on November 11, 1996 and the matched case was diagnosed on July 19, 1996 and interviewed on September 16, 1996. To calculate the reference date for the control, convert each date to the corresponding day of the year. July 19, 1996 is day 201 and September 16, 1996 is day 260; the difference is 59 days. November 11, 1996 is day 316 and 59 days prior to day 316 is day 257 or September 13, 1996. September 13, 1996 is the reference date for the control. This date should be determined by the Research Coordinator so the interviewer can remain blinded as to whether the person being interviewed is a case or control.
3A. Has the case been selected to give complete job history?	The ACCESS Clinical Coordinating Center will provide a list of cases from whom a complete job history should be obtained.
4. What was your job status as of the reference date?	This question is asked of all cases and controls at baseline and of selected cases at follow-up. It is designed to collect chronological information about jobs that people have held beginning with the reference date. If this is the baseline interview and the interviewee indicates that he/she has either been a full-time homemaker who never held a full-time job or part-time job for as long as six months (response 03), or reports that he/she is unemployed and has never worked (response 08), or is disabled without any prior work (response 11), the only items remaining to be completed are Questions 12 through 14.

5.	What is your current job status?	This question is asked of all cases at follow-up. The case should be asked about jobs held between the ACCESS baseline interview and the current date unless the case has been selected to give a complete job history. If the case has been selected to give a complete job history, he or she should be asked about jobs beginning with current one (at the time of the follow-up interview) and working back through his entire employment history.
6A. to 11.	General Instructions:	In completing the occupational history worksheet, please note that each row should consist of any full-time or part-time job that's been held for six months or more beginning with the job held just prior to the reference date (baseline interview) or at the time of the ACCESS follow-up interview. Job changes held for six months or more within the same company should be considered as a new job and written on a new line.

It is important for interviewers to recognize that the information that they write in for Questions 4 through 9 will be reviewed and the information coded using so-called standardized industrial codes and standardized occupational codes. Only by obtaining detailed job descriptions can we do accurate coding.

Occupational data can be very hard to code. Probe to obtain a job title which reflects as accurately as possible the <u>type</u> of work performed. Be as specific as possible. "Restaurant worker" is not sufficient. Probe to see if he or she was a waiter/waitress, cook, manager, maintenance person, cashier, or something else. The following are examples of adequate and inadequate entries.

<u>Inadequate</u>	<u>Adequate</u>
Adjuster	Claims, brake, machine, complaints, or insurance adjuster.
Agent	Freight, insurance, sales, advertising, or purchasing agent.
Caretaker or Custodian	Servant, janitor, guard, building superintendent, gardener, grounds keeper, sexton, property clerk, locker attendant.
Clerk	Stock, shipping, or sales clerk, i.e., a person who sells goods in a store is a salesman or sales clerk.
Data Processor	Computer programmer, keypunch operator, computer operator, coding clerk.
Doctor	Physician, dentist, veterinarian, osteopath, chiropractor.
Engineer	Civil, locomotive, mechanical or aeronautical engineer.
Entertainer	Singer, dancer, acrobat, musician.

Inadequate	Adequate
Equipment Operator	Road grade, bulldozer, or trench operator.
Factory Worker	Electric motor assembler, forge heater, turret lathe operator, weaver, loom fixer, knitter, stitcher, punch press operator, spray painter, riveter.
Firefighter	Locomotive, city, or stationary fire fighter.
Foreperson/Foreman	Specify the craft or activity involved, as foreman carpenter, foreman truck driver.
Helper	Baker's, carpenters or janitor's helper.
Laborer	Sweeper, charwoman, porter, janitor, stevedore, window washer, car cleaner, section hand, hand trucker.
Layout Person	Pattern maker, sheet metal worker, compositor, commercial artist, structural steel worker, boiler maker, draftsman, cooper smith.
Mechanic or Technician	Auto, dental, radio, airplane, or office machine mechanic.
Nun	Specify the type of work done, such as grammar school teacher, housekeeper, art teacher, organist, cook, laundress, registered nurse.
Research Worker	Microbiologist, virologist, chemist, statistician.
Trainee vs. Skilled Worker	Professional, technical, and skilled occupations usually require periods of training or education which a young person normally has not had. Upon further inquiry you may find that the young person is really only a trainee, apprenticed, or helper (for example, accountant trainee, electrician trainee, apprentice plumber, electrician's helper).
Teacher	Elementary, secondary, college, vocational.
Secretary vs. Official Secretary	The title "Secretary" should be used for secretarial work in an office. A secretary who is elected or appointed an officer of a business, lodge, or other organization should be reported as an "Official secretary."
Names of Departments or Places of Work	Occupation entries which give only the name of the department or a place of work are unsatisfactory. Examples of such are "Works in warehouse," "Works in shipping department," "Works in cost control". The occupation must tell what the worker does, not what the department of the company does.

SCRIPT FOR DEVELOPING ANCHOR DATES

Insert the reference date in the blank space below before starting the interview and the script.

I'm going to ask you about events, hobbies, and jobs that you have had in the past. I will also ask you about your family, friends and co-workers. As I ask you about some of these events or contacts you will instantly know you never had the event or contact of interest. For other events and contacts, you will have a very good memory of the event or contact and the timing of the event or contact because it is a major event in your life. However, there will be some information that is not easy to remember, and it will be even harder to answer questions about how recently the event happened. We are very interested in events that happened for three years prior to _____(**reference date**), so if you remember that you had an event or contact, I will then ask you whether it happened within the reference period which is defined as that three-year period of time.

Sometimes special events occur during people's lives. Examples of these special events are: births (and pregnancy period), deaths, marriages (divorce), hospitalizations or severe illnesses, accidents, son or daughter leaving, foreclosure of mortgage or loan, retirement, jail terms, Bar-mitzvahs/Confirmations, child entering school, graduations, memorable vacations, changing residences (moves), dates of new jobs or losing a job, buying a car, spouse begins or stops work, major sporting events. Did you have any of these special dates in the past year?

(**List any dates and the activities for those dates as special dates during the year. To the best of your ability, place the dates in reverse chronological order. Thus if the participant talks about a special date that is almost one year ago, place this date and event at the bottom of the list, and leave a blank line above and below the date).**

CONTINUE THIS PROCESS FOR EACH 12-MONTH PERIOD OF THE REFERENCE PERIOD. WHEN YOU ARE FINISHED, GIVE THE COMPLETED CARD TO THE PARTICIPANT.

I would like you to take a look at the dates I have given you and see if you can remember what your lifestyle was like around each of those dates--that is: where you lived, what your hobbies were, your basic day to day routine etc. (**The dates that the participant can remember the most are the best anchor dates and should be used as time point refreshers during the interview. For instance if a person remembers working with unusual chemicals, you would ask if any special dates were close to that time, or you could suggest some of the special dates and ask if the exposure came close to those dates)**.

Recall Dates for the Reference Period

Year 1 Date	Special Dates Event

Year 2 Date	Special Dates Event

Year 3 Date	Special Dates Event

A Case Control Etiologic Study of Sarcoidosis

Occupational and Recreational Questionnaire
(Form 12)

2A.	Reference date.	See the Instructions for Form 10 for directions for completing the reference date and reference period. These dates should be determined by the Research Coordinator so the Interviewer can remain blinded as to whether the person being interviewed is a case or control.
2B.	Reference period.	
3.	Was participant unemployed with no work experience or disabled without previous work experience?	Note that if the response on Form 11, Question 3 showed the person to be a homemaker who never held a full-time or part-time job for as long as six months (response 03), unemployed with no work experience (response 08), or disabled without previous work experience (response 11) then skip to Question 80 of Form 12. Otherwise continue with script as written.

Questions 4 through 77: Most of these are self-explanatory. In general, avoid embellishing on these categories. Several points of clarification may be provided by the interviewer as follows:

5.	U.S. Army	Civilian employees of the Armed Forces are <u>not</u> included. Only consider it a "Yes" if referring to enlisted or drafted service in one of these branches of the Armed Forces, not civil servants.
6.	U.S. Navy	
7.	U.S. Air Force	
8.	U.S. Marine	
9.	Other branch of armed forces	
16.	Raising birds	Note that some individuals may raise birds as a hobby. However, this question is explicitly about raising birds as a form of <u>employment</u>.
19.	Child care worker (i.e., children under the age of 18)	This category includes day care workers, self-employed or employed outside of their home; including live-in or live-out nannies. It does <u>not</u> include men or women who are caring exclusively for their own children.
30.	Fire fighter	Firefighter may be either full-time or part-time employed; volunteer fighters are <u>not</u> included.
42.	Meat packing	Meat packing deals with direct contact with the meat being processed.
43.	Meat wrapping	Meat wrapping deals with the person who is using plastics to wrap the meat.

45.	In a nursing home or long-term care facility	There is potential for overlap. For example, people may work in a nursing home or long-term care facility and be a nurses' aide, a registered nurse, or a licensed practical nurse. In such circumstance they would respond "Yes" to <u>both</u> Questions 45 and 46 or to <u>both</u> Questions 45 and 47.
46.	Nurses' aide	
47.	Registered nurse or licensed practical nurse.	
54.	A motor vehicle operator (truck, bus, car driver)	This does <u>not</u> include people who only operate a motor vehicle for personal use.
78.	In your office or indoor working environment, have you ever noticed any of the following conditions?	Questions about obvious mold or mildew should be marked "Yes" only if the mold or mildew occurs in locations other than the workplace bathrooms.
79.	Were you ever around any animals in your work?	Animals should <u>not</u> be included if the animals spend all of their time outdoors and the respondent spent all of his/her work time indoors. Conversely, animals should be included if they spent any of their time sharing the same space as the person at work whether indoors or out. If the respondent states that he/she had contact with animals alive or dead, this should be entered and the type of animal designated in Question 79C.
79C.	What type or types of animal was that?	Be as complete and specific as possible. For example, "Pigeons" is a preferred answer over the term "Birds." Four spaces are provided. Additional spaces may be required in some instances and should be added as needed after the fourth entry.
80. to 108.	Now I want to ask about some activities that you may have been involved in <u>which were not related to your work,</u> either at home or elsewhere. Once again, I am going to read slowly from a long list of activities. For each activity, please tell me whether you ever did the activity, whether you did it between [reference period start date] and [reference period end date] and whether you continued the activity for more or less than one year .	General Comment: Emphasize in reading the script that these questions are now about activities that people may have performed which were <u>not</u> related to their work. These are not questions about cumulative time spent in the activity; rather they are questions about the time intervals over which the case/control participated in the activity.
88.	Firefighting	Category firefighting in this portion of the questionnaire includes volunteer firefighters.
105.	Swimming in an indoor pool	Emphasize, if necessary, that this concerns swimming in an <u>indoor</u> pool only; it does not include outdoor swimming pools.

Environmental Questionnaire
(Form 13)

2A. Reference date. 2B. Reference period.	See the Instructions for Form 10 for directions for completing the reference date and reference period. These dates should be determined by the Research Coordinator so the Interviewer can remain blinded as to whether the person being interviewed is a case or control.
3. Have you ever used a wood or coal stove to heat your home?	Record code “2" or “3" in Column A if respondent ever used a wood or coal stove for heat during the reference period, whether or not it was the primary source of heat.
4. Have you ever used a wood or coal fireplace with an open flame in your home?	In this question we are interested in wood or coal burning fireplace use, whether or not is was specifically for heat. Do not count a gas fireplace. This question deals with use ever, even infrequent or seasonal use.
General Comment Questions 10 through 14:	After respondent lists one type of cooling equipment, you should probe to find out about the use of other types. More than one of the answers here may be checked.
10. Central air conditioning	Central air conditioning is usually operated by thermostats and the temperature of the whole house or large parts is controlled from a single location.
11. Window air conditioners	In the absence of central air conditioning, individual window units may be used to cool a house. They are installed in the window, and each is operated individually. These may be removed during the winter.
13. Evaporative (swamp cooler)	Evaporative or swamp coolers are used in dry climates. They usually contain a roof unit in which water is dripped over mats. A fan cools the air by blowing it across the wet mats, and then blows it out into the house through a system of ducts.
17. Did your home or basement ever have a problem with leaks or water damage?	This question is not restricted to basement problems. Any problem resulting in serious water leakage should be coded as “(2)” or “(3)” in Column A.
19. Did you ever vent your clothes dryer exhaust into the house or basement?	It is fairly common practice for clothes dryers to not have their vents extend to the outside but into the house or basement.

22. to 37.	I'm going to read a list of animals. Please tell me if you, or anyone living in your house, ever had any of these animals that stayed <u>inside</u> your home. I will also ask if you had these animals during the reference period and if you had them for more than one year.	Pets should be included if they spend any of their time in the home. They do not need to be entirely indoor pets to be coded as "Yes" (code "2" or "3" in Column A).
38.	Have you every raised any <u>other</u> animals?	Please emphasize the word "Other". Do not list animals that have been specifically asked about in the preceding Questions 22 through 37.
42.	Foam	Foam is also referred to as urethane or polyurethane foam. It may be known to some individuals as synthetic.
Questions 44 through 59:		Please make clear that we are interested here in exposures to substances that could have been inhaled as dust fumes or vapors associated with <u>either</u> jobs <u>or</u> hobbies.
44.	Aluminum	Aluminum is a metal. Do not code such common non-occupational exposures as aluminum cans, window frames or siding, unless a dust or fume is generated by heating, cutting, grinding or otherwise matching.
45.	Beryllium	Beryllium is a metal used in many high-tech alloys and in the past in fluorescent lights.
46.	Chromium	Chromium is another metal used as a coating over other metals in electroplating, as well as in many chemical and high-tech metal production processes.
47.	Cobalt	Cobalt is a metal used in many high-tech alloys.
48.	Gold	It is appropriate to include jewelry making but not the wearing of gold jewelry.
49.	Nickel	Nickel is a metal used in the manufacture of various forms of steel and in jewelry making.
50.	Platinum	Platinum is a metal used in jewelry manufacture, high-tech industries and as an additive in chemical manufacture.
51.	Titanium	Titanium is a metal and is frequently used as a pigment to color paints as well as an additive to high-tech metal alloys.
52.	Zirconium	Zirconium is a metal used in manufacture of metal alloys.
53.	Other metals	If participant gives the name of more than one metal record exposure data only for the one to which he/she was exposed most recently.

54. Talc	Talc is a fibrous mineral used commercially for coating and as an ingredient in body care products. Code use of "Talcum powder" as non-occupational.
55. Silica	Silica is sand. Exposures may take place in mining, sandblasting, foundries and many other types of work.
56. Insecticides or Pesticides	Record all occupational and non-occupational use.
57. Vegetable dust	If participant give the name of more than one vegetable dust, record exposure data only for the one to which he/she was exposed most recently.
58. Animal dust	If participant gives the name of more than one vegetable dust, record exposure data only for the one to which he/she was exposed most recently.
59. Hair spray	Check for all occupational and non-occupational use. This includes both aerosols that come from spray cans that contain propellants as well as those that require hand pumping to produce a mist. Code "Both" if respondent holds a job that requires administration of hair spray to other people's hair and also uses it on his/her own hair.
Questions 60 through 63:	The focus of these questions is to measure the participant's lifetime cigarette and other tobacco smoking habits, i.e., "Have you ever?". Note that smoking less than one cigarette per week is coded as a "No".
61. Have you ever smoked cigarillos?	Cigarillos are cigar-like tobacco products in the size and shape of cigarettes. It does not include the smoking of cigars (see Question 62).
64. Are there now smokers (not including yourself) in your household?	This question is designed to provide some estimate of passive smoking. It is to be administered to all participants regardless of their own smoking status. In responding, the individual should not include themselves but consider only the other people in their household who may or may not smoke.

After completing all of the occupational and environmental exposure forms (Forms 11, 12 and 13), the interviewer should check over these forms for obvious inconsistencies while the case/control is still in the Clinical Center. If there are inconsistencies (for example, on Form 11 the case/control says he/she worked in a pet shop, but later says he/she was not exposed to animals at work), the interviewer should re-read the question(s) to be sure the participant understood/heard the question correctly and the interviewer understood/heard the answer correctly.

A Case Control Etiologic Study of Sarcoidosis

Medications Questionnaire
(Form 14)

PURPOSE AND GENERAL INSTRUCTIONS The Medication Questionnaire form collects information on the participant's use of prescription and non-prescription medications. The exact wording and order of the questions should be followed to ensure standardization. Questions should not be skipped unless indicated by the skip pattern instructions. Because there are many skip patterns, the interviewer should be very familiar with the flow of questions to insure smooth administration with a conversational tone. Many of the questions on alternative drugs may puzzle the respondent and care must be taken to ask each question slowly, allowing enough time for a clear response. Read the questions clearly using the exact wording on the form.

See the instructions for Item 10 for directions for completing reference date and reference period. These dates should be completed by the Research Coordinator so the Interviewer can remain blinded as to whether the person being interviewed is a case or control.

Questions 3-32, A and B, ask about non-prescription and alternative medications. In Section A, if the respondent did not use medication at any time, check off the "Never" box. If the substance was used before the reference period, check off the second box, "Ended Before Reference Period". If the respondent is still using the medication, or used it during the reference period, check off the third box, "Current or Ended in the Reference Period". If the respondent does not know or remember use, check off Box 4 (unknown). If the respondent replies that they take a specific medicine, the interviewer should confirm that the medicine is being taken for the stated condition.

Section B should be completed for each drug that was ever used. The “Yes” box should be checked off if the medication was used for ONE YEAR OR MORE. Question 33 asks about coffee and tea consumption. Complete columns A and B as for medications. Questions 34-62 ask about medications requiring a physician's prescription.

A separate list of medications is provided to show the participant in case the participant does not recognize the medication when the interviewer reads the list from the form.

34.	Have you ever taken any heart or blood pressure medication?	Heart or blood pressure medication refers to medicine taken for heart disease of any kind and medicine to lower blood pressure, respectively. If the answer is “Yes”, ask Questions 35-43 and record the answers as outlined for Questions 3-33. If the answer is “No” to Question 34, go to Question 44.
44.	Did you ever take medicines to fight infections?	This question asks about the use of antibiotics for any kind of infection, including infections in the lung (pneumonia), kidney (urinary tract infection), skin (abscess), etc. If the answer is “Yes”, record responses to Questions 45 and 46 as outlined for Questions 3-33.
47.	Did you ever take birth control pills?	This question asks about birth control pills to prevent pregnancy. Record responses as for Questions 3-33.

48.	Did you ever take any anti-inflammatory medicine?	Question 48 asks about medication used to treat inflammation of the body, such as arthritis. If the respondent answers "Yes", record responses to Questions 50-58 as for Questions 3-33.
49.	Did you ever take cancer treatment?	Question 49 asks about medications used to treat cancer. If the respondent's answer is "Yes," record responses to Questions 50-58 as for Questions 3-33.
59.	Have you ever taken any seizure or tranquilizer medicine?	This question asks about medicines used to prevent seizures of any type or to help relax or calm an individual. If the respondent answers "Yes", record the responses to Questions 59-61 as for Questions 3-33. If "No", skip to Question 63.
63.	Have you had a joint (knee or hip) replacement?	Question 63 asks about artificial joint replacements, at anytime. If the answer is "Yes", ask Question 63A.
63A.	What year did you receive the replacement?	Fill in the estimated year.
64.	Do you have or have you ever had silicone implants or injections?	Question 64 asks about silicon implants or injections, for example, in the lips, breasts, or hips. If the respondent answers "Yes", complete Questions 64A and B.

MEDICATIONS LIST

Amiodarone (Cordarone)

Atenolol (Tenoretic, Tenormin)

Diltiazem (Cardiazem, Delacor)

Hydralazine (Apresazide, Apresaline, Serapes, Hydrazide)

Methyldopa (Aldomet, Aldoclor, Aldocil)

Procainamide (Procan SR)

Propranolol (Inderal, Inderide)

Quinidine (Cardiioquin, Quinidex)

Thiazide diuretics (Moduretic, Diazide, Hydrodiuril)

Nitrofurantoin (Macrobid, Macrodantin)

Penicillin

Allopurinol (Zyloprim)

Alpha-Interferon (Alferon-N, Intron-A, Roferon-A)

Azathioprine (Imuran)

Bleomycin (Blenoxane)

D-Penicillamine (Cuprimine, Depen)

Gold salts (Myochrysine, Gold Sodium Thiomalate)

Methotrexate (Rheumatrex)

Minocycline (Dynacin, Minocin)

Vincristine (Oncovin)

Carbamazepine (Tegretol)

Diazepam (Libirium, Valium)

Phenytoin (Dilantin)

A Case Control Etiologic Study of Sarcoidosis

Questionnaires 15 - 19

PURPOSE Questions on Questionnaires 15 - 19 are designed to measure the participant's self-reported mood, overall well-being, functional status and family support. These questions are personal and may be upsetting to some participants, therefore the interviewer must display both respect and concern for the participant's feeling and privacy during this phase of the interview. These questionnaires are designed to be read and completed by the participant privately, however, some participants may require assistance in reading or completing the forms.

SCRIPT "The next group of questions will be personal questions about how family support, health and illness can affect your mood and well-being. Some questions will be repeated. Try not to let your answer to one question influence your answer to other questions. There are no right or wrong answers. I can read each question to you and you can answer verbally, or you may read and answer the questions by yourself. Which would you prefer?"

If participant wishes to complete the questionnaires by him/herself, hand the participant Questionnaires 15 - 19 and a sharp pencil with an eraser, and provide an appropriate private, quiet area for completion.

"If you have any questions or need any help, I will be here [*your location*] to help you."

If participant wishes to have the questionnaires read to him/her, read the script for each questionnaire and provide scales as instructed. If a participant refuses to respond for personal reasons, make a notation on the form for each refusal.

Review each form for completeness. Ask participant to complete any missing items. If participant refuses to complete an item for personal reasons, make a notation near each refused item. Sign administrative sheet for Questionnaires 15 - 19.

A Case Control Etiologic Study of Sarcoidosis

Questionnaire 15
(Form 15)

GENERAL INSTRUCTIONS AND SCRIPT Provide the participant with Scale A. Instruct the participant, "The following questions ask about your feelings during the past week. For each statement that I read, please use this card for your answer. Please indicate for each statement if you felt that way *rarely or never*, *some of the time*, *a moderate amount of time* or *most of the time*. Tell me the number next to your answer for each statement that I read.".

COMPLETION INSTRUCTIONS Review each form for completeness. Ask participant to complete any missing items. If participant refuses to complete an item for personal reasons, make a notation near each refused item. The data entry code for refusal to answer will be 8. Sign administrative page.

A Case Control Etiologic Study of Sarcoidosis

Questionnaire 16
(Form 16)

GENERAL INSTRUCTIONS AND SCRIPT Instruct the participant, "The following questions ask about the support from other people that is available to you.".

Read Question 3 and complete.

Provide the participant with Scale B. Instruct the participant, "People sometimes look to others for companionship, assistance, or other types of support. For each statement that I read, please use this card for your answer. Please indicate if each of the following kinds of support is available to you *none of the time*, *a little of the time*, *some of the time*, *most of the time* or *all of the time*. Tell me the number next to your answer for each statement that I read.".

COMPLETION INSTRUCTIONS Review each form for completeness. Ask participant to complete any missing items. If participant refuses to complete an item for personal reasons, make a notation near each refused item. The data entry code for refusal to answer will be 8 or 98. Sign administrative page.

A Case Control Etiologic Study of Sarcoidosis

Questionnaire 17
(Form 17)

GENERAL INSTRUCTIONS AND SCRIPT Provide the participant with Scale C. Instruct the participant "The following questions ask about your mood and attitudes most of the time. Remember, there are no right or wrong answers. For each statement that I read, please use this card for your answer. Please indicate if you *strongly agree*, *agree, are neutral* (neither agree or disagree), *disagree* or *strongly disagree*. Tell me the number next to your answer for each statement that I read.".

COMPLETION INSTRUCTIONS Review each form for completeness. Ask participant to complete any missing items. If participant refuses to complete an item for personal reasons, make a notation near each refused item. The data entry code for refusal to answer will be 8. Sign administrative page.

A Case Control Etiologic Study of Sarcoidosis

Questionnaire 18
(Form 18)

GENERAL INSTRUCTIONS AND SCRIPT Instruct the participant "The following questions ask about your health.". Read Questions 3 and 4 along with the responses and complete.

For items 5A - 5J, provide the participant with Scale D. Instruct the participant "The following items are about activities you might do during a typical day. For each activity, please indicate if your health now limits your doing this activity *a lot*, *a little*, *not at all*, or if this activity is *not applicable* to you (that is, an activity you wouldn't normally do). Tell me the number next to your answer for each statement that I read.".

For items 11A - 11I, provide the participant with Scale E. "The following questions are about how you feel and how things have been with you during the past four weeks. For each question, please select the answer that comes closest to the way you have been feeling. Tell me the number next to your answer for each question I ask. How much of the time during the past four weeks...." (continue with items A - I).

Read Question 12 and responses and complete.

For items 13A - 13D, provide the participant with Scale F. Instruct the participant "The following statements are descriptions of health. As I read each statement, please indicate how true the statement is of you. Tell me the number next to your answer for each statement I read.".

COMPLETION INSTRUCTIONS Review each form for completeness. Ask participant to complete any missing items. If participant refuses to complete an item for personal reasons, make a notation near each refused item. The data entry code for refusal to answer will be 8. Sign administrative page.

A Case Control Etiologic Study of Sarcoidosis

Questionnaire 19
(Form 19)

GENERAL INSTRUCTIONS AND SCRIPT Instruct the participant "The following questions ask about places you have lived, your well-being and your income." Provide the participant with Cards I and J. Tell the participant these cards will be used to answer Questions 11 and 12.

COMPLETION INSTRUCTIONS Review each form for completeness. Ask participant to complete any missing items. If participant refuses to complete an item for personal reasons, make a notation near each refused item. The data entry code for refusal to answer will be 8 or 98. Sign administrative page.

Script Describing Sarcoidosis

READ THIS SCRIPT AFTER THE RESPONDENT HAS COMPLETED FORMS 15-19 AND BEFORE YOU BEGIN ASKING QUESTIONS ABOUT THEIR FAMILY AND RELATIONSHIPS.

Script

I would now like to ask you questions about your family and friends and whether any of your family and friends have had a disease called sarcoidosis.

Sarcoidosis is a disease that affects many parts of an individual's body, but its major effects are in the lungs. The cause of this disease is not known, and patients of all races and ages can get the disease.

There are thousands of new cases in the U.S. every year. Most sarcoidosis patients have no symptoms at all. Patients with more severe disease can have symptoms of cough and shortness of breath, when the lung is involved. Other symptoms can include skin rash, fever, painful eyes, weakness, tiredness and weight loss. Two-thirds of the patients who have sarcoidosis recover completely. The remainder have varying amounts of chronic scarring in the lungs which can interfere with breathing, and, in a small percent, cause premature death.

The disease is diagnosed by chest X-ray, breathing tests, blood tests and tissue samples from the lungs. Patients who require therapy usually receive drugs that reduce the inflammation in the body. These drugs may have to be taken for a year or more, under the care of a physician.

A Case Control Etiologic Study of Sarcoidosis

Relationship Questionnaire A
(Form 20)

PURPOSE AND GENERAL INSTRUCTIONS The knowledge of family history varies greatly from person to person. Some people can give a thorough and accurate family history at a moment's notice, others possess little knowledge of family members and can only provide a scant family history. When asking questions, first introduce each section and allow ample time for respondent to think about questions. Often, knowledge of family history will come after some time for thought. Do not force the subject into responses, make sure they know that "Don't Know" is an acceptable response to all questions.

3.	Number of spouse(s)/mate(s) with whom respondent has had children	Make sure respondent is aware that the correct response is only those spouse(s)/mate(s) with whom they have had children. DO NOT INCLUDE SPOUSE(S)/MATE(S) WITH WHOM NO CHILDREN WERE BORN. DO NOT LIMIT TO SPOUSES ONLY. Make sure respondent knows this answer requires ALL spouse(s)/mate(s), not just most recent one or one with most children.
4.	Total number of birth children	Include all live born children. Do not include children who died at birth or conceived children that did not result in a live birth. Do include live born children who have since died.

A Case Control Etiologic Study of Sarcoidosis

Relationship Questionnaire B
(Form 21)

PURPOSE AND GENERAL INSTRUCTIONS The knowledge of family history varies greatly from person to person. Some people can give a thorough and accurate family history at a moment's notice, others possess little knowledge of family members and can only provide a scant family history. When asking questions, first introduce each section and allow ample time for respondent to think about questions. Often, knowledge of family history will come after some time for thought. Do not force subject into responses, make sure they know that "Don't Know" is an acceptable response to all questions.

There is a core set of questions for each type of relative (spouse, child, sibling, parent). The following instructions apply to these questions. Make an effort to ask these questions in a consistent manner for each different family member.

	Form Type	Give each form a sequential Form Type number starting with 01.
3.	Spouse/Mate's Initials	Initials for first, middle and last names. If an initial is not known, use an X. Make sure that the form type for each new spouse/mate is incremented by one.
4.	Race	Allow the respondent to designate his/her spouse/mate's race. Read list of responses. Do not suggest an answer or category to the respondent and do not try to explain or define any of the groups. The concept of race does not reflect classification of biological characteristics or conform to any scientific definition. If the respondent cannot answer, do not re-ask and do not pursue the matter any further. Enter "Don't Know" in the answer space. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
5.	Hispanic	Do not suggest an answer to the respondent.
6.	Is this person now alive?	Make sure respondent does not answer "Yes", when the more correct reply may be "Don't Know". If the respondent answers a tentative "Yes", you can also ask when was the last time respondent saw or talked with person. If more than a year since last contact, probe further to establish the family member's vital status. For example, do they keep in touch with the same people, therefore respondent knows through mutual contact that family member is alive. If respondent cannot give a satisfactory answer, then record "Don't Know".

7.	How old is this person? (If dead, how old was this person when he/she died?)	Record age at death or age when last contact was made for "Don't Know" response to previous question. Use 98 for "Don't Know."
8.	About how many years have you lived (did you live) with this person?	Include total years in same household. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together. Use 98 for "Don't Know."
9.	Has this person ever had sarcoidosis?	A "Yes" response should only include cases of confirmed sarcoidosis, i.e. a physician told the individual, parent or guardian that the individual had sarcoidosis.
10A.	Age when he/she got sarcoidosis	Age when family member was told by a physician that he/she had sarcoidosis, not when first symptoms appeared. Leave blank, if only suspected sarcoidosis with no known diagnosis date. Use 98 for "Don't Know."
10B.	How many years did you live with this person after he/she got sarcoidosis?	Count the number of years lived together from the time of physician's diagnosis to the last date lived together. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together for that period. Use 98 for "Don't Know."
11.	Child's Initials	Initials for first, middle and last names. If an initial is not known, use an X. Make sure that the form type for each new spouse/mate is incremented by one.
13.	Is this child still alive?	Make sure respondent does not answer "Yes", when the more correct reply may be "Don't Know". If the respondent answers a tentative "Yes", you can also ask when was the last time respondent saw or talked with person. If more than a year since last contact, probe further to establish the family member's vital status. For example, do they keep in touch with the same people, therefore respondent knows through mutual contact that family member is alive. If respondent cannot give a satisfactory answer, then record "Don't Know".
14.	What is [was] this child's current age?	If child is no longer living, record age of death. For infants under the age of one year use 00. If answer to Question 13 was "Don't Know" record age of child when last contact was made. Use 98 if none of these ages are known.
15.	About how many years did you live in the same household with this child?	Include total years in same household. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together. Use 98 for "Don't Know."

16.	Did this child ever have sarcoidosis?	A "Yes" response should only include cases of confirmed sarcoidosis, i.e. a physician told the individual, parent or guardian that the individual had sarcoidosis.
17.	How old was this child when he/she got sarcoidosis?	Age when family member was told by a physician that he/she had sarcoidosis, not when first symptoms appeared. Leave blank, if only suspected sarcoidosis with no known diagnosis date. Use 98 for "Don't Know."
18.	How many years did you live with this child after he/she got sarcoidosis?	Count the number of years lived together from the time of physician's diagnosis to the last date lived together. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together for that period. Use 98 for "Don't Know."
19.	Were any of these children twins, triplets, quadruplets, etc.?	Refer to Questionnaire for instructions.

A Case Control Etiologic Study of Sarcoidosis

Family History Questionnaire
(Form 22)

PURPOSE AND GENERAL INSTRUCTIONS The knowledge of family history varies greatly from person to person. Some people can give a thorough and accurate family history at a moment's notice, others possess little knowledge of family members and can only provide a scant family history. When asking questions, first introduce each section and allow ample time for respondent to think about questions. Often, knowledge of family history will come after some time for thought. Do not force subject into responses, make sure they know that "Don't Know" is an acceptable response to all questions.

There is a core set of questions for each type of relative (spouse, child, sibling, parent). The following instructions apply to these questions. Make an effort to ask these questions in a consistent manner for each different family member.

3. Do you know who at least one of your birth parents are?	If respondent is unclear about this question, you can also ask: 1) Were you adopted? 2) Do you know who your real parents are? If respondent only knows one parent, still make an attempt to collect as much information as possible about the other parent. However, make sure respondent is not guessing about information for lesser known parent.
4. What best describes your mother's race?	Allow the respondent to designate his/her family member's race. Read list of responses. Do not suggest an answer or category to the respondent and do not try to explain or define any of the groups. The concept of race does not reflect classification of biological characteristics or conform to any scientific definition. If the respondent cannot answer, do not re-ask and do not pursue the matter any further. Enter "Don't Know" in the answer space. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
5. Is/was your mother Hispanic?	Do not suggest an answer to the respondent.
6. Is your mother now alive?	Make sure respondent does not answer "Yes", when the more correct reply may be "Don't Know". If the respondent answers a tentative "Yes", you can also ask when was the last time respondent saw or talked with person. If more than a year since last contact, probe further to establish the family member's vital status. For example, do they keep in touch with the same people, therefore respondent knows through mutual contact that family member is alive. If respondent cannot give a satisfactory answer, then record "Don't Know".

7.	How old is your mother? (If dead, how old was she when she died?)	Record age at death or age when last contact was made for "Don't Know" response to previous question. Use 98 for "Don't Know."
8.	About how many years did you live with your mother?	Include total years in same household. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together. Use 98 for "Don't Know."
9.	Has(did) your mother ever had(have) sarcoidosis?	A "Yes" response should only include confirmed sarcoidosis (i.e., a physician told the family member he/she had sarcoidosis).
10A.	Age when she got sarcoidosis	Age when family member was told by a physician that he/she had sarcoidosis, not when first symptoms appeared. Leave blank, if only suspected sarcoidosis with no known diagnosis date. Use 98 for "Don't Know."
10B.	How many years did you live with your mother after she got sarcoidosis?	Count the number of years lived together from the time of physician's diagnosis to the last date lived together. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together for that period. Use 98 for "Don't Know."
11.	What best describes your father's race?	Allow the respondent to designate his/her family member's race. Read list of responses. Do not suggest an answer or category to the respondent and do not try to explain or define any of the groups. The concept of race does not reflect classification of biological characteristics or conform to any scientific definition. If the respondent cannot answer, do not re-ask and do not pursue the matter any further. Enter "Don't Know" in the answer space. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
12.	Is/was your father Hispanic?	Do not suggest an answer to the respondent.
13.	Is your father now alive?	Make sure respondent does not answer "Yes", when the more correct reply may be "Don't Know". If the respondent answers a tentative "Yes", you can also ask when was the last time respondent saw or talked with person. If more than a year since last contact, probe further to establish the family member's vital status. For example, do they keep in touch with the same people, therefore respondent knows through mutual contact that family member is alive. If respondent cannot give a satisfactory answer, then record "Don't Know".
14.	How old is your father? (If dead, how old was he when he died?)	Record age at death or age when last contact was made for "Don't Know" response to previous question. Use 98 for "Don't Know."

15.	About how many years did you live with your father?	Include total years in same household. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together. Use 98 for "Don't Know."
16.	Has(did) your father ever had(have) sarcoidosis?	A "Yes" response should only include confirmed sarcoidosis (i.e., a physician told the family member he/she had sarcoidosis).
17A.	Age when he got sarcoidosis	Age when family member was told by a physician that he/she had sarcoidosis, not when first symptoms appeared. Leave blank, if only suspected sarcoidosis with no known diagnosis date. Use 98 for "Don't Know."
17B.	How many years did you live with your father after he got sarcoidosis?	Count the number of years lived together from the time of physician's diagnosis to the last date lived together. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together for that period. Use 98 for "Don't Know."
18.	How many full and half brothers and sisters do you have living and deceased? This does not include adopted, foster or step bothers and sisters.	Tell respondent NOT to include himself in this count. If respondent does not know what half brother or sister is, say: those brothers and sisters who only have the same mother or father as you. If respondent is unsure of total number, ask for the number for which they can give age and vital status information. Do not include siblings who were stillborn.
19.	What number were you in the birth order of your brothers and sisters?	1 = first child; 2 = second; etc. Put a star or some other mark in sibling table where respondent should fall in the birth order. When the last question is asked about the sibling directly before the respondent and before the first question is asked about the sibling directly after the respondent, ask the question: To confirm your earlier response, you were born after sibling (sibling's initials) and before sibling (sibling's initials).
20.	Brother's / sister's initials	Initials for first, middle and last names. If an initial is not known, use an X.
22.	Did this brother/ sister have: a. The same mother as you? b. The same father as you?	Make sure respondent knows this question refers to birth mother and father.
23.	Is this brother/ sister still alive?	Make sure respondent does not answer "Yes", when the more correct reply may be "Don't Know". If the respondent answers a tentative "Yes", you can also ask when was the last time respondent saw or talked with person. If more than a year since last contact, probe further to establish the family member's vital status. For example, do they keep in touch with the same people, therefore respondent knows through mutual contact that family member is alive. If respondent cannot give a satisfactory answer, then record "Don't Know".

24.	What is (was) the current age (age at death) of this brother/ sister?	Record age at death or age when last contact was made for "Don't Know" response to previous question. If sibling died under the age of one year, record 00. Use 98 for "Don't Know."
25.	About how many years did you live in the same household with this brother/sister?	Include total years in same household. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together. Use 98 for "Don't Know." If the respondent says he or she lived with a sibling as long as or longer than with either parent, the interviewer should ask if the respondent has considered the age difference between the respondent and a younger sibling or the time when an older sibling may have left home. For example, if both the respondent and a sibling two years older left home when they were 18, the respondent was only 16 when the older sibling left. It is unusual to live exactly the same number of years with your parents and all of your siblings.
26.	Did this brother/sister ever have sarcoidosis?	A "Yes" response should only include confirmed sarcoidosis (i.e., a physician told the family member he/she had sarcoidosis).
27.	How old was this brother/sister when he/she got sarcoidosis?	Age when family member was told by a physician that he/she had sarcoidosis, not when first symptoms appeared. Leave blank, if only suspected sarcoidosis with no known diagnosis date. Use 98 for "Don't Know."
28.	About how many years did you live in the same house with this brother/ sister after he/she got sarcoidosis?	Count the number of years lived together from the time of physician's diagnosis to the last date lived together. Make sure that respondent knows to subtract any long periods of separation (6 months or more) from total time lived together for that period. Use 98 for "Don't Know."
29.	Were any of your brothers and sisters twins, triplets, quadruplets, etc.?	Refer to Questionnaire for instructions.
30.	How many full brothers and sisters living and deceased do your parents have, that is, brothers and sisters with the same parents?	Use synonyms when asking about each type, i.e., paternal aunts = father's sisters. To verify numbers, after obtaining data ask follow-up question for paternal and maternal siblings: e.g. So, your father came from a family with 4 children (if 2 paternal aunts and 1 paternal uncle)
32.	Which of your relatives had sarcoidosis?	Respondent may immediately say something like: "My paternal grandmother had sarcoidosis.". Even so, ask about sarcoidosis for each type of relative to give respondent the opportunity to say "Yes" or "No". After recording number of sarcoidosis cases in second degree relatives, can finish by saying something like the following (if, for instance, 2 affected second degree relatives are reported): "So, among your grandparents, uncles and aunts, two persons have had sarcoidosis.".

33.	Not counting spouses/mates with whom you had children, your children and other blood relatives, how many other persons (neighbors, co-workers, friends, etc.) have you known (before [reference date]) who have had sarcoidosis? This includes spouses / mates with whom you did not have children.	If respondent replies with a positive number, ask who were these people before proceeding, to make sure they do not include relatives already listed. If they include a relative reported as unaffected in forms 20-22, go back and reconcile the inconsistency. Do not count sarcoidosis patients the respondent may have had contact with in the course of obtaining medical care to procure a diagnosis (i.e., somebody he sat next to in a waiting room before his chest X-ray). Note that the question mentions reference date. Refer to Item 2A on Form 10 to obtain reference date.
33A.	How many of these people did you actually have contact with? 1. at home 2. at work 3. other places	Can have more than one contact place with the same person. "Other places" should only include the clinic or hospital if respondent was there for reasons unrelated to his sarcoidosis diagnosis or care.
33B.	How old were you when you first met any of these people with sarcoidosis?	Make sure respondent knows that "Age when first met" can be prior to the time when the person in question had sarcoidosis. Make sure respondent does not try to frame these responses around the disease periods of either himself or his sarcoidosis contacts.
33C.	How old were you when you last saw any of these people?	Age at last contact would be current age if respondent still has contact with these people. Make sure respondent does not try to frame these responses around the disease periods of either himself or his sarcoidosis contacts.
33D.	How often did you generally see these people?	If more than one contact, tell respondent to answer for total contacts with all people known to have sarcoidosis. If respondent has difficulty picking a frequency, have them try to recreate instances of contact and time periods between each contact.
33E.	Did you (or do you) live in the same house as any of these people?	Should include anyone who respondent shares(d) primary living quarters with (i.e. bathroom, kitchen, living room). A "Yes" response should not include living in the same apartment building or neighbors.
33F.	Did you (or do you) work in the same building as any of these people?	"Building" should be an easily defined structure, i.e. office building, factory, store. If buildings are part of the same complex but physically separated, then response should be "No".
33G.	Are you a close friend or co-worker with any of these people?	Can clarify this category as someone the respondent has physical contact with on a daily or weekly basis. DO NOT include close friends that live apart and only have sporadic contact. DO include neighbors or persons living close to the respondent with whom he/she regularly (once a week) comes in contact with.

A Case Control Etiologic Study of Sarcoidosis

Family History Supplement
(Form 23)

GENERAL INSTRUCTIONS Use definitions for Questions 20 - 28 on Form 22 (Family History Questionnaire). Give each form a sequential form type number starting with 01.

A Case Control Etiologic Study of Sarcoidosis

Physical Examination Form
(Form 24)

GENERAL INSTRUCTIONS: Complete this form for cases as part of the baseline evaluation (form type PE01) and for those cases who have a two-year follow-up evaluation (form type PE02).

II. PHYSICAL EXAMINATION

3.	Height (cm) (999.8 if not measured):	Height and weight should be measured with case's shoes off and dressed in light clothing (e.g., no coat) using a good statiometer.
4.	Weight (kg) (999.8 if not measured):	Should be measured in kilograms using a balance scale that has been calibrated.
5.	Heart rate (beats/min) (998 if not measured):	Heart rate and respiratory rate should be measured over 30 seconds. Heart rate, respiratory rate and blood pressure should be measured while the case is in a sitting position. There should be a minimum of five minutes in this resting state before these measurements are taken.
6.	Respiratory rate (breaths/min) (98 if not measured):	
7.	Blood pressure:	Blood pressure should be measured using a standard sphygmomanometer.
8.	Is there lung involvement?	This question should be answered with a positive response only if there is a positive response to any of the following Questions: 10A - 10G, 11A - 11C, or 12A - 12B. If the answer is "Yes", Questions 9-12 should be completed. If there are no positive responses to any of these questions, then there is no lung involvement, the answer should be "No" and the interviewer should go to Question 13.
9.	Extent of involvement?	Definitions: "Definite" involvement exists if there is any positive response to Questions 10A - 10G. "Probable" involvement exists if there is any positive response to Questions 11A - 11C **and** there are no positive responses to Questions 10A - 10G. If there is also a positive response to any of Questions 10A - 10G, the extent of involvement is "Definite". Extent of involvement is "Possible" if there is a positive response to Questions 12A - 12B **and** there is no positive response to 11A - 11C **or** 10A - 10G. If there is a positive response to any of Questions 10A - 10G, the extent of involvement is "Definite"; and if there is a positive response to any of Questions 11A - 11C without a positive response to any of Questions 10A - 10G, the extent of involvement is "Probable".

10.	Is there definite involvement?	If “Yes”, answer items A - G, otherwise go to Question 11.
10A.	Positive lung biopsy	Any lung biopsy including endobronchial biopsy (or transbronchial biopsy) in which noncaseating granulomas are identified and no other etiology besides sarcoidosis is thought to explain the histologic findings.
10B.	Positive mediastinal/hilar lymph node biopsy	Any biopsy of a mediastinal or hilar node that reveals noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
10C.	Positive pleura biopsy	Any biopsy of pleural tissue (closed or open pleural biopsy) which reveals noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
10D.	Chest roentgenogram with bilateral hilar adenopathy	Includes any such roentgenogram without a clinical explanation other than sarcoidosis.
10E.	Chest roentgenogram with diffuse infiltrates	Includes any such roentgenogram without a clinical explanation other than sarcoidosis.
10F.	Chest roentgenogram with upper lobe fibrosis	Includes any such roentgenogram without a clinical explanation other than sarcoidosis.
10G.	Restriction of PFTs	(1) TLC of less than 80% of predicted, **OR** (2) FVC less than 80% of predicted **AND** FEV_1/FVC ratio greater than or equal to 70% of predicted.
11.	Is there probable involvement?	If “Yes”, answer items A - C, otherwise go to Question 12.
11A.	Lymphocytic alveolitis by BAL	Greater than 10% lymphocytes in the cell differential obtained from a bronchoalveolar lavage.
11B.	Any pulmonary infiltrates	Any pulmonary infiltrates seen on a chest roentgenogram without a clinical explanation other than sarcoidosis.
11C.	Isolated reduced DLCO	A DLCO of less than 80% of predicted.
12.	Is there possible involvement?	If “Yes”, answer items A - B, otherwise go to Question 13.
12A.	Any adenopathy	Any adenopathy seen on a chest roentgenogram without a clinical explanation other than sarcoidosis.
12B.	Obstructive PFTs	A FEV_1/FVC ratio of less than 70%.
13.	Is there definite, probable or possible non-thoracic involvement?	A positive response to this question should be made if there is a positive response to at least one of Questions 14 - 79. A negative response to this question should be made if there are no positive responses to Questions 14 - 79 and the examiner should go to Question 80.

14.	Is there neurological involvement?	A positive response to this question should be made if there is any positive response to Questions 15 - 18. A negative response should be made if there are no positive responses to Questions 15 - 18 and the examiner should go to Question 19.
15.	Extent of involvement:	"Definite" involvement is indicated by any positive response to Questions 16A - 16H. "Probable" involvement is indicated by any positive response to Questions 17A - 17C **and** all responses to Questions 16A - 16H are negative. Involvement is "Possible" if there is a positive response to either Question 18A or 18B **and** there are only negative responses to Questions 16A - 17C.
16.	Is there definite involvement?	If "Yes", answer items A - H, otherwise go to Question 17.
16A.	Positive MRI with uptake in meninges or brainstem	Sarcoidosis may cause a basilar meningitis which may be revealed by MRI scanning. MRI with contrast may show enhancement of the basal meninges or in the region of the brainstem.
16B.	CSF with increased lymphocytes and/or protein	Patients with neurosarcoidosis may show evidence of inflammation in the cerebrospinal fluid (CSF) such as increased WBCs (primarily lymphocytes) and/or protein.
16C. 16D. 16E.	Diabetes insipidus Bell's palsy Cranial nerve dysfunction (other than Bell's palsy)	Granulomatous involvement of the basal regions of the brain may lead to diabetes insipidus from hypothalamic/pituitary involvement, (Bell's palsy (peripheral seventh nerve dysfunction manifested by ipsilateral facial weakness including the forehead) or cranial nerve dysfunction other than Bell's palsy.
16F.	Positive brain biopsy	A biopsy of the brain showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
16G.	Positive dura biopsy	A biopsy of the dura showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
16H.	Positive peripheral nerve biopsy	A biopsy of peripheral nerve noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
17.	Is there probable involvement?	If "Yes", answer items A - C, otherwise go to Question 18.
17A.	Other abnormalities on MRI	MRI scanning may show hyperintense signal abnormalities in the brain parenchyma or other abnormalities which could be consistent with neurosarcoidosis. Review of the scan with a neuroradiologist may be useful in determining if abnormalities noted are consistent with sarcoidosis.

17B.	Unexplained neuropathy	May represent granulomatous involvement of peripheral nerves in patients with sarcoidosis.
17C.	Positive EMG	May show evidence of myopathy or provide objective documentation of neuropathy.
18.	Is there positive involvement?	If “Yes”, answer items A - B, otherwise go to Question 19.
18A.	Unexplained headaches	Headaches that cannot be explained due to any other clinical reason. While certainly a non-specific symptom, otherwise unexplained headaches in a patient with sarcoidosis could possibly represent neurological involvement.
18B.	Peripheral nerve radiculopathy	Symptoms of radiculopathy (pain, dematomal sensory loss, weakness of muscles supplied by a single nerve root) could possibly represent nerve root involvement in a patient with sarcoidosis.
19.	Is there non-thoracic lymph node involvement?	Non-thoracic lymph node involvement: a positive response to this question should be made if there is any positive response to Question 21 through Question 23. A negative response should be made if there are no positive responses to Question 21 through Question 23.
20.	Extent of involvement?	Involvement should be listed as “Definite” if there is a positive response to Question 21. Extent of involvement is “Probable”if there is a positive response to Question 22A or 22B and response to Question 21 is negative. Involvement is “Possible”if there is a positive response to Question 23 and there are negative responses to all Questions 21 and 22A-22C.
21.	Is there definite involvement (positive lymph node biopsy)?	Biopsy of lymph node showing noncaseating granulomas and no other etiology besides sarcoidosis is through to explain the histologic findings.
22.	Is there probable involvement?	If “Yes,” answer Items A-B, otherwise got to Question 23.
22A.	New palpable node above the waist	This includes any lymph node 1 cm or greater above the waist either noted by the patient for the first time or discovered by the physician without previous record of a positive lymph node.
22B.	Lymph node > 2 cm by CT scan	The lymph node must have an axial diameter greater than 2 cm in a CT scan slice taken in the axial dimension.
23.	Is there possible involvement (new palpable femoral lymph node)?	This is a lymph node either newly discovered by the patient or physician.

24.	Is there renal involvement?	A positive response to this question should be made if there is any positive response to Question 26 through Question 28. A negative response should be made if there are no positive responses to Question 26 through Question 28.
25.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to Question 26A or Question 26B. Extent of involvement is "Probable" if there is a positive response to Question 27 and responses to Questions 26A and 26B are negative. Involvement is "Possible" if there is a positive response to Question 28 and there are negative responses to all Questions 26A, 26B and 27.
26.	Is there definite involvement?	If "Yes," answer Items A-B, otherwise go to Question 27.
26A.	Positive kidney biopsy	Biopsy of a kidney revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
26B.	Treatment responsive renal failure	Steroid-responsive renal failure is defined as a decrease in serum creatinine of $\geq$ 1.0 mg/dL if the peak creatinine is $\geq$ 1.5 mg/dL **OR** a decrease in serum creatinine of > 0.5 mg/dL if the peak serum creatinine is < 1.5 mg/dL, and if the patient is not hypercalcemic. Treatment is defined in the instructions for Question 84.
27.	Is there probable involvement (steroid responsive renal failure in patient with diabetes and/or hypertension)?	Same criteria for steroid responsive renal failure as for 26B.
28.	Is there possible involvement (renal failure in absence of other disease)?	A positive response should be made if the serum creatinine is $\geq$ 1.5 mg/dL with no other clinical cause for the elevated serum creatinine having been identified.
29.	Is there cardiac involvement?	A positive response to this question should be made if there is any positive response to Question 31A through Question 33. A negative response should be made if there are no positive responses to Question 31 through Question 33.
30.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to Question 31A through Question 31E. Extent of involvement is "Probable" if there is a positive response to Question 32A or 32B and all responses to Questions 31A through Question 31E are negative. Involvement is "Possible" if there is a positive response to Question 33A or 33B and there are negative responses to all Questions 31A and 32A.
31.	Is there definite involvement?	If "Yes," answer Items A-E, otherwise go to Question 32.

31A	Positive heart biopsy	Biopsy of the heart revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
31B.	Positive pericardium biopsy	Biopsy of the pericardium revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
31C.	Treatment responsive cardiomyopathy	Documented improvement of congestive heart failure symptoms, echocardiographic systolic function, or restrictive hemodynamics after treatment. Treatment is defined in the instructions for Question 84.
31D.	EKG showing IVCD or nodal block	The presence of first, second, or third degree AV block **OR** a QRS duration of greater than or equal to 0.12 seconds.
31E.	Positive gallium scan of the heart	Positive gallium scan of the heart showing multiple areas of increased uptake in the absence of other known heart disease.
32.	Is there probable involvement?	If "Yes," answer Items A-B, otherwise go to Question 33.
32A.	No other cardiac problem and either ventricular arrhythmias or cardiomyopathy	Ventricular arrhythmias or echocardiographic findings of cardiomyopathy in the absence of other possible etiologies.
32B.	Positive nuclear medicine scan other than gallium scan	Uptake on any nuclear medicine scan other than gallium which is not likely to be the result of a disease other than sarcoidosis based on the clinical data.
33.	Is there possible involvement?	If "Yes," answer Items A-B, otherwise go to Question 34.
33A.	Cardiomyopathy in patient with diabetes and/or hypertension	Echocardiographic evidence of cardiomyopathy in a patient with diabetes mellitus and/or hypertension in the absence of any other possible etiology.
33B.	Ventricular arrhythmias in patient with diabetes and/or hypertension	Ventricular arrhythmias in patient with diabetes and/or hypertension in the absence of other known structural heart disease, history of myocardial infarction, or primary valvular disease.
34.	Is there skin involvement?	A positive response to this question should be made if there is any positive response to Question 36A through Question 38. A negative response should be made if there are no positive responses to Question 36A through Question 38.

35.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to Question 36A-36D. Extent of involvement is "Probable" if there is a positive response to Question 37A or Question 37B and all responses to Question 36A-36D are negative. Involvement is "Possible" if there is a positive response to Question 38A-38C and there are negative responses to all Questions 36A-36D and Question 37A-37B.
36.	Is there definite involvement?	If "Yes," answer Itesm A-D, otherwise go to Question 37.
36A.	Positive skin biopsy	Biopsy of the skin revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
36B.	Lupus pernio	Bluish-red to violaceous, indurated papules usually distributed symmetrically on the nose, cheeks, ears, and lips. Surface of lesions may be shiny with large, dilated pores on surface. Rarely ulcerate.
36C.	Erythema nodosum	Tender, warm, erythematous nodules up to several centimeters in diameter, usually located on the anterior legs. Lesions resolve over 3-6 weeks without scarring or atrophy; may leave some pigmentary alteration.
36D.	Annular lesion	Purple-red, annular, indurated shiny skin lesions which spread peripherally with central clearing. Central area may be pigmented or pale, and may be atrophic.
37.	Is thre probable involvement?	If "Yes," answer Itesm A-B, otherwise go to Question 38.
37A.	Macular papular lesions	Waxy, translucent, flat-topped, red-brown to orange to purple papules; 2-6 mm in diameter; may see few to hundreds of papules; often develop in crops. Most common on the face, neck, upper back, extensor aspects of limbs. Flatter, macular lesions $\pm$ scale may occur.
37B.	New nodules	Red to reddish-brown to violaceous nodules, soft or firm, larger than 5 mm in diameter; usually single to a few lesions. Present on face, extremities, trunk. May see telangiectasias on surface. Center of nodule may become depressed as lesions involute.
38.	Is there possible involvement?	If "Yes," answer Items A-C, otherwise go to Question 39.
38A.	Keloids	Purple to hyperpigmented nodules of varied sizes, occurring in sites of scars or other skin trauma.
38B.	Hypopigmentation	Should be self-explanatory. May see hypopigmentation as a sole finding or around central indurated lesions.

38C.	Hyperpigmentation	Increase pigmentation in skin; particularly common in darkly pigmented skin.
39.	Is there eye involvement?	A positive response to this question should be made if there is any positive response to Question 41A through Question 43C. A negative response should be made if there are no positive responses to Question 41A through Question 43C.
40.	Extent of involvement:	Involvement should be listed as “Definite” if there is a positive response to Question 41A through Question 41E. Extent of involvement is “Probable” if there is a positive response to Question 42 and all responses to Question 41A through Question 41E are negative. Involvement is “Possible” if there is a positive response to Question 43A through Question 43C and there are negative responses to all Questions 41A through Question 42.
41.	Is there definite involvement?	If “Yes,” answer Items A-E, otherwise go tto Question 42.
41A.	Positive conjunctiva biopsy	Biopsy of the conjunctiva revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
41B.	Positive sclera biopsy	Biopsy of the sclera revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain this histologic findings.
41C.	Lacrimal gland swelling	The palpebral lobes of the lacrimal gland are normally not palpable in the superior lateral quadrant of the eye socket. Patients with sarcoidosis frequently have firm, non-tender mass in the superior lateral quadrant of the eye socket. This can be palpated by pressing the thumb gently along the inside of the eye socket at the lateral aspect of the eyebrow. If a mass is felt, this is consistent with the swelling noted in sarcoidosis.
41D.	Uveitis	Uveitis describes a broad category of ocular inflammation. Patients with uveitis may have red, inflamed appearing eyes. They may complain of photophobia and acute onset visual loss. Slit lamp examination reveals mutton-fat or greasy keratic precipitates on the endothelium of the cornea, or nodules on the iris.
41E.	Optic neuritis	Decreased vision and decreased peripheral vision with appropriate ophthalmologic findings.
42.	Is there probable involvement (blindness)?	Visual acuity less than 20/200.
43.	Is thre possible involvement?	If “Yes,” answer Items A-C, otherwise go to Question 47.

43A.	Glaucoma	Diagnosed by the combination of elevated intraocular pressure and changes in the patient's central and peripheral vision. Intraocular pressure should be determined by tonometry.
43B.	Cataract	Progressive diffuse vision loss from opacification of the intraocular lens.
43C.	Sicca (dry eyes)	The patient is unable to produce adequate tear film to moisturize the eye. Requires a positive Schirmer's test.
44.	Is there liver involvement?	A positive response to this question should be made if there is any positive response to Question 46A through Question 47B. A negative response should be made if there are no positive responses to Question 46A through 47B.
45.	Extent of involvement	Involvement should be listed as "Definite" if there is a positive response to Question 46A and Question 46B. Extent of involvement is "Probable" if there is a positive response to Question 47A or Question 47B and all responses to Question 46A and Question 46B are negative.
46.	Is there definite involvement?	If "Yes," answer Itesm A-E, otherwise go to Question 47.
46A.	Positive liver biopsy	A biopsy of the liver showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
46B.	Serum alkaline phosphatase greater than three times the upper limit of normal	The upper limit of normal means the upper limit of normal for the laboratory where these tests were performed. These tests must have been performed wihtin six months of study entry.
46C.	Serum total bilirubin greater than three times the upper limit of normal	
46D.	Serum AST or ALT greater than three times the upper limit of normal	
46E.	Serum albumin less than 3.0 mg/dl	
47.	Is there possible involvement?	If "Yes," answer Items A-B, otherwise go to Question 48.
47A.	Compatible CT scan	CT scan compatible with liver involvement. Hepatic masses or hepatic enlargement seen on CT scan that is thought to be related to sarcoidosis with no alternative clinical diagnosis present which would explain the radiographic findings.
47B.	Elevated alkaline phosphatase	Serum alkaline phosphatase greater than the upper limits of the laboratory normal.

48.	Is there bone marrow involvement?	A positive response to this question should be made if there is any positive response to Question 50A and Question 51. A negative response should be made if there are no positive responses to Question 50 and Question 51.
49.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to any of Questions 50A-50D. Involvement is "Possible" if there is a positive response to Question 51 and there are negative responses to all Questions 50A through 50D.
50.	Is there definite involvement?	If "Yes," answer Itesm A-D, otherwise go tot Question 51.
50A.	Granulomas in bone marrow	Biopsy of the bone marrow revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
50B.	Unexplained anemia	Hemoglobin less than the lower limits of normal without any likely alternative explanation than sarcoidosis based on the clinical data, including no evidence of iron deficiency anemia (e.g., normal iron studies, reticulocyte count).
50C.	Leukopenia	White blood cell count less than 3500/cu. mm^3 without any likely alternative explanation than sarcoidosis based on the clinical data.
50D.	Thrombocytopenia	Platelet count less than 100,000/cu. mm^3 without any likely alternative explanation than sarcoidosis based on the clinical data.
51.	Is there possible involvement (anemia with low MCV)?	Hemoglobin less than the lower limits of normal with a low MCV.
52.	Is there spleen involvement?	A positive response to this question should be made if there is any positive response to Question 54 through 55. A negative response should be made if there are no positive responses to Question 54 through Question 55.
53.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to Question 54. Extent of involvement is "Probable" if there is any positive response to Questions 55A-55C and response to Question 54 is negative.
54.	Is there definite involvement (spleen biopsy)?	Biopsy of the spleen (including splenectomy) revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
55.	Is there probable involvement?	If "Yes," answer Itesm A-L, otherwise go to Question 56.
55A.	Enlargement by examination.	If the spleen is palpable on physical examination.

55B.	Enlargement by CT scan	The spleen is enlarged if it is visible on 12 centimeters of contiguous CT slices (15 8mm spiral slices) or if the splenic index (length times width times depth) is greater than 480 mm^3.
55C.	Enlargement by radioisotope scan	Spleen length on the posterior image is greater than 13 centimeters.
56.	Is there bone/joint involvement?	A positive response to this question should be made if there is any positive response to Question 58 through Question 60. A negative response should be made if there are no positive responses to Question 58 through Question 60.
57.	Extent of involvement:	Involvement should be listed as "Definite" if there is any positive response to Question 58A-58C. Extent of involvement is "Probable" if there is a positive response to Question 59 and all responses to Question 58A-58C are negative. Involvement is "Possible" if there is a positive response to Question 60 and there are negative responses to all Questions 58A -58C and Question 60.
58.	Is there definite involvement?	If "Yes," answer Items A-C, otherwise go to Question 59.
58A.	Granulomas in bone biopsy	Biopsy of bone revealing noncaseating granulomas and other etiology besides sarcoidosis is thought to explain the histologic findings.
58B.	Granulomas in synovium biopsy	Biopsy of synovium revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
58C.	Cystic changes on hand or feet phalanges	A positive radiologic change for sarcoidosis in the hand is present when focal trabecular pattern is coarsened because of adjacent bone resorption, cysts (oval, circular, or irregular) more than 1 millimeter in diameter surrounded by trabeculae are present, or when focal destructive bone lesions are present. Some, but not all, of the cystic change may involve the articular surface.
59.	Is there probable involvement (asymmetric, painful clubbing)?	Asymmetric clubbing of the fingers or toes that is thought to be the result of sarcoidosis with no alternative cause likely on the basis of the clinical data.
60.	Is there possible involvement (arthritis with no other cause)?	Arthritis that is thought to be the result of sarcoidosis with no alternative cause likely on the basis of the clinical data.
61.	Is there ear/nose/throat involvement?	A positive response to this question should be made if there is any positive response to Question 63 through Question 65. A negative response should be made if there are no positive responses to Question 63 through 65.

62.	Extent of involvement:	Involvement should be listed as “Definite” if there is a positive response to Question 63. Extent of involvement is “Probable” if there is a positive response to Question 64 and response to Question 63 is negative. Involvement is “Possible” if there is a positive response to Question 65A or 65B and there are negative responses to Question 63 and Question 64.
63.	Is there definite involvement (granulomas in ear, nose or throat)?	Biopsy of ears, nose, or throat revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
64.	Is there probable involvement (unexplained hoarseness with examination consistent with granulomatous involvement)?	Granulomatous changes can be observed by inspection of the tympanic membranes, nasal septum and turbinates and oral cavity. The tympanic membranes will appear thickened and granular. The nasal and oral mucosa will appear dry, red, and granular. If examination is equivocal, nasal biopsy may be needed. In absence of positive physical examination, inspection of the true vocal cords by fiberoptic laryngoscopy may be necessary. Inspection of the true vocal cords will show dry, granular changes. A history of hoarseness in the presence of positive physical examination of the nose, ears, or oropharynx is sufficient.
65.	Is there possible involvement?	If “Yes,” answer Items A and B, otherwise go to Question 66.
65A.	New onset sinusitis	Should be confirmed by radiographic findings: either screening CT or plain radiographs.
65B.	New onset dizziness	Can be ascertained by history.
66.	Is there parotid/salivary gland involvement?	A positive response to this question should be made if there is any positive response to Question 68A. through Question 69. A negative response should be made if there are not positive responses to Questions 68A through Question 69.
67.	Extent of involvement:	Involvement should be listed as “Definite” if there is a positive response to Question 68A through Question 68D. Involvement is “Possible” if there is a positive response to Question 69 and there are negative responses to all Questions 68A through Question 68D.
68.	Is there definite involvement?	If “Yes,” answer Items A-D, otherwise go to Question 69.
68A.	Positive parotid biopsy	Biopsy of the parotid gland revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
68B.	Positive salivary gland biopsy	Biopsy of a salivary gland revealing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.

68C.	Symmetrical parotitis with syndrome of mumps	Symmetrical parotitis can be ascertained by inspection and palpation of the parotid gland. Glands will be firm and diffusely enlarged.
68D.	Positive gallium scan ("Panda sign")?	A gallium scan showing uptake in both the lacrimal and salivary glands.
69.	Is there possible involvement (dry mouth)?	The oral mucosa will appear dry, red, and granular.
70.	Is there muscle involvement?	A positive response to this question should be made if there is any positive response to Question 72 through Question 74. A negative response should be made if there are no positive responses to Question 72 through Question 74.
71.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to Question 72A and 72B. Extent of involvement is "Probable" if there is a positive response to Question 73 and response to Questions 72 and 72B are negative. Involvement is "Possible" if there is a positive response to Question 74 and there are negative responses to all Questions 72A -72B and Question 73.
72.	Is there definite involvement?	If "Yes," answer Items A and B, otherwise got to Question 73.
72A.	Granulomas in muscle	A biopsy of muscle showing noncaseating granulomas and no other etiology besides sarcoidosis is thought to explain the histologic findings.
72B.	Increased CPK/aldolase which decreases with treatment	Serum CPK or aldolase greater than the upper limits of normal which decreases into the normal range or is halved on treatment for sarcoidosis. Treatment is defined in the instructions for Question 84. Other clinical causes of elevations of CPK or aldolase (e.g., drugs, muscle trauma, recent seizure) need to be excluded.
73.	Is there probable involvement (increased CPK/aldolase)?	Serum CPK or aldolase greater than the upper limits of normal. Treatment is defined in the instructions of this form.
74.	Is there possible involvement (myalgias responding to treatment)?	Myalgias that cannot be explained by any other cause that resolve completely on treatment for sarcoidosis.
75.	Is there calcium metabolism (hypercalcemia / hypercalcuria / nephrolithiasis) involvement?	A positive response to this question should be made if there is any positive response to Question 77 through Question 79. A negative response should be made if there are no positive responses to Question 77 through Question 79.

76.	Extent of involvement:	Involvement should be listed as "Definite" if there is a positive response to Question 77. Extent of involvement is "Probable" if there is a positive response to Question 78A or 78B and response to Question 77 is negative. Involvement is "Possible" if there is a positive response to Question 79A or 79B and there are negative responses to Questions 77 and Question 78A and 78B.
77.	Is there definite involvement (increased serum calcium) with no other cause?	Hypercalcemia. Serum calcium concentration greater than the upper limits of normal **OR** a serum ionized calcium greater than the upper limits of normal.
78.	Is there probable involvement?	If "Yes," answer Items A and B, otherwise go to Question 79.
78A.	Increased urine calcium	Hypercalcuria. Twenty-four hour calcium greater than 4 mg/kg.
78B.	Nephrolithiasis analysis showing calcium	Nephrolithiasis analysis showing calcium.
79.	Is there possible involvement?	If "Yes," answer Item A and B, otherwise go to Question 80.
79A.	Nephrolithiasis -- no stone analysis	Nephrolithiasis without stone analysis.
79B.	Nephrolithiasis with negative family history for stones	Nephrolithiasis without a family history for stones.
80.	What is the patient's level of dyspnea?	The most appropriate choice should be selected based on the level of dyspnea on the day of the physical examination.
81.	Radiographic findings	Each item should be assessed based on review of the chest x-ray by an ACCESS certified physician.
81A.	Hilar adenopathy	Enlarged hilar structures, usually oblong, often not compressing the airways significantly, that are thought to represent hilar adenopathy.
81B.	Alveolar infiltration	Alveolar infiltration present in the lung parenchyma. It may be diffuse, patchy, nodular, or localized to a particular lung zone (e.g., upper lung fields) or lobe.
81C.	Interstitial infiltrates.	Interstitial infiltration of the lung parenchyma. May be diffuse or localized to a particular lung zone.
81D.	Pulmonary hypertension.	Enlarged main pulmonary arteries **OR** right ventricular enlargement present.
81E.	Stage 4 disease	Fibronodular disease present with significant lung distortion. May be diffuse or localized to a particular lung zone (usually upper lobes).

81F.	Mycetoma	Round or ovoid water density structure present in an air density structure. An air-crescent sign may be present.
81G.	Other	Identify other radiographic abnormalities that are thought to be the result of pulmonary sarcoidosis.
82.	Evidence of involvement (ever)	The appropriate responses are defined by the responses to Questions 8 through 79 above.
83.	Severity of current involvement (evaluation at time of ACCESS physical examination only)	**Not clinically involved** implies no involvement of that organ (see Question 82). **Organ failure** is defined as follows: Lung: acute respiratory failure requiring mechanical ventilation or status-post lung transplantation. Kidney: on dialysis or status-post transplantation. Cardiac: status-post heart transplantation. Eyes: blindness. Liver: fulminant hepatic failure or status-post liver transplantation. Bone Marrow: status-post bone marrow transplantation. Spleen: status-post splenectomy. Organ failure also requires that the cause of the organ failure is thought to be the result of sarcoidosis. All other organ systems not mentioned above cannot be associated with organ failure. **Clinically involved but functioning** is defined as organ involvement (see Question 82) but not organ failure (see above).
84.	Is the patient currently on treatment for sarcoidosis?	Treatment is defined on the use of oral or intravenous corticosteroids, methotrexate, azathioprine, cyclosporine, and/or another immunosuppressive medication or anti-malarials at any dose. Treatment does NOT incude topical immunosuppressive medications such as inhaled corticosteroids. It also does NOT include medications used for control of symptoms usch as inhaled beta agonists or nonsteroidal anti-inflammatory agents. It DOES include ophthalmic steroids used for treatment of cases with eye involvement.
88.	When was the physical examination performed?	Report performance of ACCESS physical examination as before or after ACCESS interview.

TABLE FOR ACCESS FORM 24

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy is of the organ or is one of the clinical conditions in Table 6.1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
NEUROLOGIC	1. Positive MRI with uptake in meninges or brainstem 2. CSF with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's Palsy 5. Cranial nerve dysfunction 6. Positive peripheral nerve, brain or dura biopsy	1. Other abnormalities on MRI 2. Unexplained neuropathy 3. Positive EMG	1. Unexplained headaches 2. Peripheral nerve radiculopathy
NON-THORACIC LYMPH NODE	1. Positive biopsy	1. New palpable node above waist 2. Lymph node > 2 cm by CT scan	1. New palpable femoral lymph node
RENAL	1. Treatment responsive renal failure 2. Positive kidney biopsy	1. Steroid responsive renal failure in patient with diabetes and/or hyper tension	1. Renal failure in absence of other disease
LUNGS	1. Chest roentgenogram with one of the following: -Bilateral hilar adenopathy -Diffuse infiltrates -Upper lobe fibrosis 2. Restriction on PFTs 3. Positive lung, mediastinal/hilar lymph node or pleura biopsy	1. Lymphocytic alveolitis by BAL 2. Any pulmonary infiltrates 3. Isolated reduced DLCO	1. Any adenopathy 2. Obstructive PFTs
CARDIAC	1. Treatment responsive cardiomyopathy 2. EKG showing IVCD or nodal block 3. Positive gallium scan of heart 4. Positive heart or pericardium biopsy	1. No other cardiac problem and either: -Ventricular arrhythmias -Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: -Cardiomyopathy -Ventricular arrhythmias

TABLE FOR ACCESS FORM 24 (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy is of the organ or is one of the clinical conditions in Table 6.1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
SKIN	1. Lupus pernio 2. Annular lesion 3. Erythema nodosum 4. Positive skin biopsy	1. Macular papular lesions 2. New nodules	1. Keloids 2. Hypopigmentation 3. Hyperpigmentation
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis 4. Positive sclera or conjunctiva biopsy	1. Blindness	1. Glaucoma 2. Cataract 3. Sicca
LIVER	1. Serum alk phos > 3 x ULN 2. Serum total bilirubin > 3 x ULN 3. Serum AST/ALT > 3 x ULN 4. Serum albumin < 3.0 mg/dL 5. Positive liver biopsy	1. Compatible CT scan 2. Elevated alkaline phosphatase	
BONE MARROW	1. Granulomas in bone marrow 2. Unexplained anemia 3. Leukopenia 4. Thrombocytopenia		1. Anemia with low MCV
SPLEEN	1. Positive spleen biopsy	1. Enlargement by: -Exam -CT scan -Radioisotope scan	

TABLE FOR ACCESS FORM 24 (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy is of the organ or is one of the clinical conditions in Table 6.1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
BONE / JOINTS	1. Granulomas in bone or synovium biopsy 2. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR / NOSE / THROAT	1. Granulomas in ear, nose or throat	1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness
PAROTID / SALIVARY GLANDS	1. Positive parotid biopsy 2. Positive salivary gland biopsy 3. Symmetrical parotitis with syndrome of mumps 4. Positive gallium scan (“Panda sign”)		1. Dry mouth
MUSCLES	1. Granulomas in muscle 2. Increased CPK/aldolase which decreases with treatment	1. Increased CPK/aldolase	1. Myalgias responding to treatment
HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis - no stone analysis 2. Nephrolithiasis with negative family history for stones

MRI = magnetic resonance image; CSF = cerebrospinal fluid; EMG = Electromyogram; CT = computed tomography;
PFT = pulmonary function tests; D_LCO = diffusing capacity of the lungs for carbon monoxide; BAL = bronchoalveolar lavage;
EKG = electrocardiogram; IVCDs = interventricular conductor defect ; LFT = liver function test; MCV = mean corpuscular volume

A Case Control Etiologic Study of Sarcoidosis

Laboratory Data Form
(Form 25)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of Form 25 is to collect basic laboratory information that should be part of the initial clinically indicated work-up of patients with sarcoidosis. Complete this form for all cases as part of the baseline evaluation (Form Type LD01) and for those cases that have a two-year follow-up evaluation (Form Type LD02). The form is designed to collect laboratory information for the case as close to the time of enrollment as possible. In some cases the laboratory tests requested for the designated categories may actually be done on different dates. For instance, the calcium measurement may not be done as part of the standard work-up of the case, and a special request is made for the measurement. If there is more than one date on which the data for the measurements are collected, the date that is most distant from the date of enrollment should be used as the date for the group of tests being reported.

Example: A standard lab work-up was done for the case on February 14, 1997. The lab work-up did not include a calcium test which was subsequently done on February 20, 1997. The case was enrolled on March 1, 1997. The date recorded in Item 19 should be February 14, 1997, since this is more distant from the date of enrollment than the date of the calcium test.

3.	Date of most recent (spirometry) test:	This date should be within six months prior to study entry.
4. to 8.	Spirometry results:	Spirometry should be performed only in pulmonary function laboratories that have been certified by the Principal Investigator. ACCESS Form 103 must be signed by the Principal Investigator. Such laboratories must adhere to the requirements outlined in the ACCESS Procedures Manual and must be able to print out the spirogram and flow volume loop curves for distribution to other ACCESS investigators for review.
9.	Date of CBC:	If CBC results are used from multiple laboratory tests on different dates, use the date most distant from the date of enrollment. All dates are expected to be within six months prior to study entry.
10. to 18.	CBC results	Complete blood counts may be performed in laboratories outside of the ACCESS Clinical Center if their standards for quality of laboratory performance are acceptable to the ACCESS Clinical Center Principal Investigator.
19.	Date of lab chemistries	If laboratory chemistry results are used from multiple tests on different dates, use the date most distant from the date of enrollment. All dates are expected to be within six months prior to study entry.

20. to 33.	Lab chemistry results	Laboratory chemistry evaluations may be performed in laboratories outside of the ACCESS Clinical Center if their standards for quality of laboratory performance are acceptable to the ACCESS Clinical Center Principal Investigator.
34.	Pulmonary physician	ACCESS Principal Investigator or designee (e.g., co-investigator) verifies that pulmonary function testing meets standards required in ACCESS and all laboratory data are being reported accurately.

A Case Control Etiologic Study of Sarcoidosis

Baseline Questionnaire for Cases Only
(Form 26)

PURPOSE The purpose of this questionnaire is to obtain information about the patient's ability to assess, use, and adhere to medical care specifically for sarcoidosis. This information is used to produce estimates on the types of insurance people have, the kinds of places people go to receive medical care, from whom they receive medical care, and why they seek care. Some of the questions may be considered sensitive, and care must be taken to ask questions and record responses in a nonjudgmental manner.

II. ACCESS TO, USE OF, AND ADHERENCE WITH MEDICAL CARE FOR SARCOIDOSIS

3.	Has sarcoidosis affected your ability to obtain health insurance?	The intent is to ascertain if the patient has or has not been denied all or some health insurance coverage because of this disease. If the respondent answers "Yes," ask Question 3A. Not applicable should be used only if the case did not have health insurance at the time of diagnosis of sarcoidosis and did not apply for health insurance after the date of diagnosis. Health insurance includes private insurance, Medicare, Medicaid or other public plan.
3A.	If yes, how?	Write the verbatim response on the line provided.
4.	Has sarcoidosis affected the cost of your insurance?	The question relates to increased insurance premiums charged to the patient because of having this disease. If the respondent doesn't have health insurance, check "Not Applicable".
5.	If you have health insurance, does your health insurance limit your ability to receive care for your sarcoidosis?	"Limit one's ability to receive care" means having to pay additional money for a visit or being restricted in the doctors or places where care can be provided paid for by the insurance. Include those that can go anywhere if they pay additional money out-of-pocket. If the respondent doesn't have health insurance, check "Not Applicable". If the answer to Question 5 is "No" or "Not Applicable", skip Questions 5A, 5B, and 5C and proceed to Question 6. If the response to Question 5 is "Yes", ask Questions 5A - 5C.
5A.	Has it limited your access to a specialist for sarcoidosis care?	If the respondent answers "Yes" to Question 5A, ask him/her to specify and write the verbatim response on the line provided.
5B.	Has it limited your receiving tests that your doctor thought should be done for your sarcoidosis?	"Tests" refers to both types and frequency of medical tests. If the respondent answers "Yes" to Question 5B, ask him/her to specify and write the verbatim response on the line provided.
5C.	Has it limited your receiving any medication that your doctor thought your should receive for sarcoidosis?	"Medications" refers to medications prescribed by a doctor which the patient believes are for his/her sarcoidosis. If the respondent answers "Yes" to Question 5C, ask him/her to specify and write the verbatim response on the line provided.

6.	During the past 6 months, was there any time when you needed medical care specifically for sarcoidosis but could not get it?	"Needing medical care" means any time either you or the doctor thought you should have a visit but either you or the doctor thought the visit could not be paid for by insurance. If the answer is "Yes", ask Question 6A.
6A.	If yes, how many times?	If the respondent gives a range of numbers for Question 6A (e.g., 3 or 4), ask the respondent for a single number.
7.	If your usual doctor is a specialist, does he or she also provide care for your sarcoidosis?	If the respondent's usual doctor is not a specialist, mark "Not Applicable". If the patient usually goes to a doctor - e.g., an Ob/Gyn specialist - for usual care, does that doctor also care for the sarcoidosis symptoms, or does the person go to another specialist for sarcoidosis care?
8.	In the last 6 months, how many times have you made appointments to see a doctor for your sarcoidosis?	If the answer is zero (0), skip Questions 8A and 8B and proceed to Question 9. If the answer to Question 8 is at least one (1), ask Question 8A.
8A.	How many of these appointments did you miss?	A "missed appointment" is an appointment that was scheduled or requested by the doctor but not made or not kept. A scheduled appointment that is canceled but rescheduled and kept would <u>not</u> be missed. If the respondent answers Question 8A with more than one number (e.g., 2 or 3), ask the respondent for a single number. If the answer to Question 8A is zero (0), skip Question 8B and proceed to Question 9. If the answer to Question 8A is at least one (1), ask Question 8B.
8B.	If you missed one or more appointments, what was the main reason for the last missed appointment?	Read the response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
9.	I am going to read from a list of medications used for treatment of sarcoidosis. As I read each medication, please indicate if you have taken it for your sarcoidosis in the last 6 months.	Answer Questions 3, 4, 5, and 6 if usage was Current or Not Current. "Not Current" means the case took the medication sometime during the past six months but is not taking it as of the interview date. "Off and On" (Column 4) means sometimes off medication and sometimes on medication, or intermittently on medication over months. "Response to Therapy" (Column 6) is the cases's subjective evaluation of his/her symptoms. "Improve" would be lessening of symptoms, "Same" would be no change in symptoms, and "Worse" would be an increase in the number or intensity of symptoms.
10.	I would like you to think about how you took your sarcoidosis medicines in the past week; on how many days did you:	For Questions 10A, 10B, and 10C, read the words "On how many days did you" before each question. If the person does not provide a definite number of days, say "<u>about</u> how many days or your best estimate." If the respondent gives more than one number (e.g., 3 or 4), ask the respondent for a single number.

10A.	forget to take some or all of it?	"Forget" refers to not taking the medication at all. This does not refer to taking the dose later in the day.
10B.	not take some or all of it?	"Not take some" indicates the patient consciously decided not to take the medication.
10C.	take more of any of it than your doctor told you to?	"Take more" indicates the patient consciously decided to take more than the prescribed dose.

Questions 11-19 refer to medications taken anytime during the past 6 months. If the case took medication sometime during the past six months, but is not taking it at the time of the interview, tell the case he/she should answer the question for the time period the medication was taken.

11.	Would you say that you take your sarcoidosis medicine just the way your doctor told you to take it?	Interviewer should read the response list. If the response to Question 11 is "All of the time", skip Questions 12 and 13 and proceed to Question 14. If the answer to Question 11 is any other response, proceed to Question 12.
12.	Was there any time you did not obtain your sarcoidosis medication because you could not afford it?	This means the patient did not purchase and have the medication as the doctor indicated and/or did not take the medication in the amount and at the times indicated. Include persons who were getting free medication but could not afford to travel to obtain medication.
13.	When you don't take all the medication that was prescribed, what is the most important reason for taking less?	Interviewer should read list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. If more than one reason is given, ask the respondent to specify the most important or most usual reason.
14.	Has your doctor ever directly asked you about how well you take your sarcoidosis medicine?	Include any inquiries by the doctor as to the frequency or regularity of taking the medications.
15.	How confident are you that you can control your sarcoidosis by taking your medication each day?	This question refers to the patient's belief that his/her medication can improve his/her health or slow down the course of the disease. Interviewer should read response list.
16.	If you don't take your sarcoidosis medicine, what are the chances that something bad will happen to your health in the next year?	This question investigates the patient's belief that without the medication the sarcoidosis will progress to new places in the body or worsen in places already affected. Interviewer should read response list. Do not accept "Don't know". Encourage patient to make a choice from the responses listed.
17.	If you don't take your sarcoidosis medicine, what might happen?	If the case says, "I don't know," check the "Don't Know" response. If the case provides an answer, the Interviewer should record the respondent's answer verbatim.
17B.	Possibly	

18.	How often do people in your daily life help you by reminding you to take your sarcoidosis medicines?	This question investigates whether there is someone who inquires about the patient and his/her medication. Interviewer should read response list.
19.	Most people forget to take their medicine occasionally. How often does this happen to you?	If the person says “Don’t know” or “Not sure”, have them estimate which category is most likely. Interviewer should read response list.
20.	I’ve asked you a lot of questions. The last question I want to ask is: Do you think anything caused your sarcoidosis?	If answer is “Yes”, ask Question 20A.
20A.	If yes, what was it?	Record the respondent’s answer verbatim.

A Case Control Etiologic Study of Sarcoidosis

Telephone Contact Summary
(Form 28)

PURPOSE The purpose of this telephone contact is to encourage continued participation in ACCESS of patients enrolled in the clinical course study. Additionally, major medical problems that the patient has developed should be recorded. The emphasis is on tracking subjects, not on data collection.

The interviewer should have the following information available before he/she calls the participant:

1. Participant 's address, phone number, place of employment and occupations;
2. Date, time, and place of participant's next Clinical Center visit;
3. Name of Project Coordinator and Principal Investigators; and
4. ACCESS Clinical Center telephone number.

In order to have the greatest chance of retaining patients in ACCESS, efforts should be made to be as cordial as possible during this telephone contact. This usually will not be difficult as most telephone contacts will be made by study coordinators who have already developed rapport with the ACCESS cases. Rigid adherence to a script may detract from the personal approach of this telephone contact, and this may impair retaining cases in the study. However, it is essential that certain points be made during this telephone contact. For this reason, a checklist is provided below of items which should all be discussed during the telephone contact. A suggested script is provided for each item in the checklist, not as a requirement, but as an option to be used if the interviewer prefers this approach.

It is important that the interviewer not answer questions from a patient that specifically relate to medical conditions, symptoms, or clinical state of sarcoidosis. All such questions should be referred to the patient's physician. The checklist and optional script are provided below. Efforts should be made to go through items in the order listed on the checklist although, again, this is not mandatory.

Since this form will be completed at three different times for each case enrolled in the clinical course study, the form type in the upper right portion of the first page should be completed. Use TC01 for the six-month contact, TC02 for the 12-month contact and TC03 for the 18-month contact.

1.	Initials of case	The interviewer should identify himself/herself as calling from ACCESS and ensure that he/she is talking to the right person. *Suggested script: I am (interviewer) from (Clinical Center) calling about the National Heart, Lung, and Blood Institute sarcoidosis study, called ACCESS which (case) participated in. Is (case) on the phone with me now or is he/she at home? I want to remind you that you participated in ACCESS on (date of participation) and I want to thank you for your participation.* Record initials of case and date of contact.
3.	Was the case informed of the importance of his/her continued participation in the study?	Explain the reasons for this phone call: (a) ability to contact the case and (b) identification of major medical problems. *Suggested script: I am calling for two reasons; first, we want to make sure we don't lose contact with you since you will have one future visit as part of the sarcoidosis study. Second, we want to find out if you have had any major medical problems since (date of last contact)*
4.	Date of next Clinical Center visit.	Give the case the date of future participation. *Suggested script: Your future visit as part of ACCESS will be (date of follow-up visit).* Describe the future participation. *Suggested script: During that visit, you will participate in a very short interview, much shorter than the first interview that you had. There will be no blood sample collected during this visit, (or if a blood specimen collection planned, "a blood sample will be collected at this visit to add to the sample collected at your first visit") and you will receive an additional (supply clinic payment) for your participation.*
5.	Has the case's address, employment or telephone number changes since the last contact?	Obtain contact information. *Suggested script: We show your home phone number to be (case's listed home phone number) and your home address to be (case's listed home address). Is that correct? We show your work phone number to be (case's listed work phone number) and your work address to be (case's listed work address). Is that correct?*

6.	Did the case report any major medical problems related to sarcoidosis since the last contact?	Identify major medical problems related to sarcoidosis. *Suggested script: Have you developed any major medical problems because of your sarcoidosis since our last phone conversation (or clinic visit if this is the first telephone contact) give date __ __ __-__ __-__ __ __ __? These would include any hospitalizations, emergency room visits, or unscheduled visits to a physician because of your sarcoidosis.* If the case describes medical problems and asks for medical advice, refer the case to his/her personal physician.
7.	Did the case volunteer any concerns or complaints about the study?	We are not going to ask for concerns or complaints, but if the case volunteers any, they should be recorded.

Before closing the conversation, give the case the Clinical Center phone number, tell the case to call the medical center if there is a change in his/her work or home address and inform the case that another telephone contact will be made in six months or a clinic visit will be scheduled.

Suggested script: Our phone number is (Clinical Center phone number). If you change your home phone number or address or your work phone number or address, please call us at (Clinical Center phone number) to make sure we know of those changes. I or someone else at (Clinical Center) will be calling you (in six months or two weeks prior to your scheduled visit) to remind you again of your future participation. Thank you again for participating in the sarcoidosis study, ACCESS.

A Case Control Etiologic Study of Sarcoidosis

Affected Relative Report Form
(Form 29)

PURPOSE

The purpose of this form is to collect first hand information about the presence of sarcoidosis in relatives of cases and controls. The case or control should be provided with a letter of consent to give to any relative 18 years old or older who is reported as having definite or probable sarcoidosis. This information should be documented using the medical record of the affected relative if the relative provides authorization to review his/her medical records.

You should not contact the relative or begin data collection until you have received permission from the relative; that is, the relative has signed and returned the letter of consent that the case or control has delivered to the affected relative. The letter from the affected relative should be filed with this form after the form is completed. If the letter has not been received within three months of the time it was offered to the participant, the Clinical Coordinating Center will notify the Clinical Center of incomplete Form 29s. The Research Coordinator at the Clinical Center should mail the Affected Relative Reminder Letter (page 96) to the appropriate case/control and enclose with the letter another permission letter to be given to the affected relative. If the participant could not or would not give the letter to the relative, complete Items 1-4, 26 and 27 and enter the form into the local data management system. If the letter is received after three months and the relative gives consent to be interviewed, you should contact the relative, conduct the interview, correct Item 4, complete the remainder of the form, and enter the revised form in the local data management system.

The questions should be asked as stated in the form. If the affected relative does not understand the question, the scripts below should be used.

ACCESS Participant's name	Self-explanatory. This item is not to be data entered or sent to the Clinical Coordinating Center.

3.	Relation to ACCESS participant:	The purpose of this question is to link the information on this form with the information from the participant recorded on the Relationship Questionnaire B (Form 21), the Family History Questionnaire (Form 22) and the Family History Supplement (Form 23). Item 11 on the Form 21, Item 20 on the Form 22 and Item 3 on the Form 23 list the affected relative's initials. There is one relative per line of data. Each line is indexed by the letters A, B, C, etc. It is the appropriate line index letter, (A, B, C, etc.), not the affected relative's initials, which should be recorded for Items 3A or 3B on the Affected Relative Form. Since an ACCESS participant can have children listed on more than one Form 21 or siblings listed on more than one Form 23, please write in the form type of the form on which the given affected relative is listed. (There is only one Form 22 for each participant, so it is not necessary to list form type for Form 22.) Remember that this information is to be collected only from first degree relatives of the participant. Do not include step-parents, step-brothers, etc.
4.	Status	Check the appropriate response. If you receive the letter after two months, make a correction to Item 4 on the original form for this relative, and conduct the interview.
5.	Date of contact:	Self-explanatory.

		INFORMATION OBTAINED FROM CONSENT TO PARTICIPATE LETTER
A.	Relative's name	Self-explanatory. Get this information from the letter of consent from the affected relative. You should not ask the participant the name of the relative. This item is not to be data entered or sent to the Clinical Coordinating Center.
B.	Relative's address	Self-explanatory. Get this information from the letter of consent from the affected relative. This item is not to be data entered or sent to the Clinical Coordinating Cener.
C.	Phone number of relative	Self-explanatory. Get this information from the letter of consent from the affected relative. This item is not to be data entered or sent to the Clinical Coordinating Center.

	Would you be willing to answer these questions at this time?	If the relative does not want to be interviewed at the time of the initial call, but agrees to be interviewed at a later time, use the same form you already started to conduct the actual interview. Make corrections to Questions 5 and 6 as needed.
7.	Have you ever been told by a doctor that you had an abnormal chest X-ray?	Self-explanatory.

8.	Have you ever been told by a doctor that you have any type of lung disease?	These should be conditions that have been verified by a doctor. If the relative reports symptoms such as a chest cold or volunteers lung diseases that were not reported by a doctor (e.g. "I think I have emphysema"), the response should be "no". You should check unknown if the affected relative states he/she cannot remember. If "yes", Question 8A should be completed.
8A.		Record the information exactly as the relative gives it to you.
9.	Have you ever been told by a doctor that you have sarcoidosis?	Self-explanatory. If the affected relative asks what sarcoidosis is, he/she probably does not have it. If "yes", ask Questions 10-15.
10.	How old were you when you got sarcoidosis?	Age when relative was told by a physician that he/she had sarcoidosis, not when first symptoms appeared. Use 98 for "Don't Know."
11.	Did the doctor get a biopsy in order to know if you had sarcoidosis?	Again, if the relative does not know what a biopsy is, he/she probably did not have one.
12.	Did health problems from your sarcoidosis cause you to see a doctor?	Note that symptoms can come before or after the actual diagnosis of sarcoidosis.
13.	I am going to read from a list of medications used for treatment of sarcoidosis. As I read each medication, please indicate if you have ever taken it for your sarcoidosis and whether you took it within two weeks of the time the doctor told you that you had sarcoidosis, more than two weeks but less than one year after the doctor told you that you had sarcoidosis or more than one year after the doctor told you that you had sarcoidosis.	Check the appropriate response for each medication.
14.	Did your doctor tell you that any of the following have been affected by sarcoidosis?	Read the list one at a time. "Yes" should be checked only if a doctor has verified that the organ or system has been affected by sarcoidosis. If the relative reports system involvement that has not been verified by a doctor, the response should be "no". You should check "Unknown" if the affected relative states he/she cannot remember.

15.	A. Would you be willing to sign a release for your medical records?	Self-explanatory.
	A(1). Affected relative's mailing address confirmed.:	Self-explanatory.
	B. Has medical release form been received?	Self-explanatory.
16.	Abnormal chest X-ray	Information for Items 16-23 should be obtained from review of the medical record and not based on the interview with the affected relative. The responses are: documented -- stated as being present in the medical record, ruled out -- an entry in the medical record indicating that the condition/physical state was considered and determined not to be present, not mentioned -- there was no entry in the medical record about the condition/physical state.
17.	Any lung disease	
18.	Sarcoidosis	
19.	Age when sarcoidosis diagnosed	
20.	Biopsy confirmed sarcoidosis	
21.	Symptoms compatible with sarcoidosis	
22.	Treated after diagnosis	
23.	Organs affected	See definitions in Table of Multi-Organ Involvement on pages 92-94.
24.	Physician reviewing medical records	Items 24 - 27 are self-explanatory.
25.	Interviewer	
26.	Research coordinator	
27.	Date form completed	

TABLE FOR ACCESS FORM 29

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy is of the organ or is one of the clinical conditions in Table 6.1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
LUNGS	1. Chest roentgenogram with one of the following: -Bilateral hilar adenopathy -Diffuse infiltrates -Upper lobe fibrosis 2. Restriction on PFTs 3. Positive lung, mediastinal/hilar lymph node or pleura biopsy	1. Lymphocytic alveolitis by BAL 2. Any pulmonary infiltrates 3. Isolated reduced DLCO	1. Any adenopathy 2. Obstructive PFTs
NEUROLOGIC	1. Positive MRI with uptake in meninges or brainstem 2. CSF with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's Palsy 5. Cranial nerve dysfunction 6. Positive peripheral nerve, brain or dura biopsy	1. Other abnormalities on MRI 2. Unexplained neuropathy 3. Positive EMG	1. Unexplained headaches 2. Peripheral nerve radiculopathy
CARDIAC	1. Treatment responsive cardiomyopathy 2. EKG showing IVCD or nodal block 3. Positive gallium scan of heart 4. Positive heart or pericardium biopsy	1. No other cardiac problem and either: -Ventricular arrhythmias -Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: -Cardiomyopathy -Ventricular arrhythmias
SKIN	1. Lupus pernio 2. Annular lesion 3. Erythema nodosum 4. Positive skin biopsy	1. Macular papular lesions 2. New nodules	1. Keloids 2. Hypopigmentation 3. Hyperpigmentation

TABLE FOR ACCESS FORM 29 (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy is of the organ or is one of the clinical conditions in Table 6.1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
EYES	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis 4. Positive sclera or conjunctiva biopsy	1. Blindness	1. Glaucoma 2. Cataract 3. Sicca
LIVER	1. Serum alk phos > 3 x ULN 2. Serum total bilirubin > 3 x ULN 3. Serum AST/ALT > 3 x ULN 4. Serum albumin < 3.0 mg/dL 5. Positive liver biopsy	1. Compatible CT scan 2. Elevated alkaline phosphatase	
SPLEEN	1. Positive spleen biopsy	1. Enlargement by: -Exam -CT scan -Radioisotope scan	
BONE / JOINTS	1. Granulomas in bone or synovium biopsy 2. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
EAR / NOSE / THROAT	1. Granulomas in ear, nose or throat	1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness

TABLE FOR ACCESS FORM 29 (Continued)

MULTI-ORGAN INVOLVEMENT IN PATIENTS WITH BIOPSY–CONFIRMED SARCOIDOSIS

DEFINITION OF ORGAN INVOLVEMENT: 1) Positive biopsy is of the organ or is one of the clinical conditions in Table 6.1. 2) No other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

ORGAN	DEFINITE	PROBABLE	POSSIBLE
PAROTID / SALIVARY GLANDS	1. Positive parotid biopsy 2. Positive salivary gland biopsy 3. Symmetrical parotitis with syndrome of mumps 4. Positive gallium scan (“Panda sign”)		1. Dry mouth
MUSCLES	1. Granulomas in muscle 2. Increased CPK/aldolase which decreases with treatment	1. Increased CPK/aldolase	1. Myalgias responding to treatment
HYPERCALCEMIA / HYPERCALCURIA / NEPHROLITHIASIS	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis - no stone analysis 2. Nephrolithiasis with negative family history for stones
NON-THORACIC LYMPH NODE	1. Positive biopsy	1. New palpable node above waist 2. Lymph node > 2 cm by CT scan	1. New palpable femoral lymph node
RENAL	1. Treatment responsive renal failure 2. Positive kidney biopsy	1. Steroid responsive renal failure in patient with diabetes and/or hyper tension	1. Renal failure in absence of other disease
BONE MARROW	1. Granulomas in bone marrow 2. Unexplained anemia 3. Leukopenia 4. Thrombocytopenia		1. Anemia with low MCV

MRI = magnetic resonance image; CSF = cerebrospinal fluid; EMG = Electromyogram; CT = computed tomography;
PFT = pulmonary function tests; D_LCO = diffusing capacity of the lungs for carbon monoxide; BAL = bronchoalveolar lavage;
EKG = electrocardiogram; IVCDs = interventricular conductor defect ; LFT = liver function test; MCV = mean corpuscular volume

AFFECTED RELATIVE REMINDER LETTER

Dear **Case/Control's Name**:

Thank you for your recent participation in A Case-Control Etiology Study of Sarcoidosis. During the review of your family history, you reported a **name type of relative** who had a history of sarcoidosis. We have not yet received the letter from your **name type of relative** indicating **his** or **her** willingness to participate in this study. It is important that the doctors doing this study confirm all reported cases of sarcoidosis in families.

As we stated before, the participation of your **name of type of relative** is voluntary, but should only take about five minutes and can be done over the phone. Any information we collect from your **name type of relative** will remain confidential and will be used for only research purposes.

We have enclosed another permission letter to give to your **name type of relative**. The doctors doing this study cannot contact your **name type of relative** until **he** or **she** signs this letter and returns it to them.

Thank you for your help and participation in this study.

Sincerely,

ACCESS Principal Investigator

A Case Control Etiologic Study of Sarcoidosis

Chest Roentgenography Interpretation Form
(Form 30)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of Form 30 is to record standardized readings of chest X-ray films for all patients enrolling as cases in ACCESS. The information for the chest roentgenography interpretation will be used to determine the patient's category in the spectrum of sarcoidosis and for the sarcoidosis assessment system. Each case should have a good quality postero-anterior (PA) chest X-ray film available for clinical indications. Use Form Type CR01 for baseline X-rays and CR02 for follow-up X-rays.

3.	Film quality	Good: a film in which the bases of both lungs, the diaphragm, and the apices of the lung are identified. The spinal processes are seen through the heart and parenchymal infiltrates can be distinguished. There is good visualization of the heart and mediastinal structures. There has apparently been good inspiration and the reader can distinguish the parenchyma easily, detecting densities as small as 2 mm. Acceptable: a film in which the bases of both lungs, the diaphragm, and the apices of the lung are identified. The spinal processes are seen through the heart and parenchymal infiltrates can be distinguished. However, resolution is such that one cannot be sure of the hilum distinctly from the heart borders; the patient did not take a full inspiration; or there is motion artifact. Poor: a film in which the bases of both lungs, the diaphragm, and the apices of the lung are identified. The cardiac silhouette is identified but the penetration is such that it is difficult to interpret the parenchymal infiltrates. Subtleties such as small nodules less than 2 mm cannot be identified. Unacceptable: a film in which one cannot see either the bases, the diaphragm, the apices, or other parts of the lung parenchyma.

Do not complete this form for films of unacceptable quality. Obtain another film for interpretation. If another film is available from clinical files, use the other film. If no other film is available, one should be obtained as clinically indicated.

4.	Are there previous films available for comparison?	Earlier films available for comparison to the current films.
4A.	Date of most recent comparison film:	Date comparison chest roentgenography performed.
5.	Are the findings on the current film completely normal?	All bony, hilar, mediastinal and other soft tissues as well as pulmonary parenchyma are well visualized and normal in appearance.

6.	Any <u>interstitial</u> infiltrates?	Interstitial infiltrates are reticulonodular or small nodular (< 5 mm). Infiltrates are often contiguous but there is no evidence of confluence, i.e., mass densities greater than 5 mm.
7.	Any <u>alveolar</u> infiltrates?	Alveolar infiltrates are consolidations with dense homogenous patterns of > 1 cm in one or two lobes.
8.	Any adenopathy (hilar or mediastinal)?	In particular look at the right hilum and the right peritracheal area for widening or thickening.
9.	Hilar retraction?	Is the hilum pulled up towards the apices? The normal configuration of the left hilum higher than the right hilum should be preserved. If the normal configuration is not preserved, hilar retraction may be inferred.
10.	Bullae or blebs (cysts)?	The presence of radiolucencies > 1 cm, usually seen in the upper lobes, often surrounded by more dense parenchyma.
11.	Any cardiomegaly?	Defined by the cardiac silhouette being > 50% of the diameter of the chest on a PA film.
12.	Any pulmonary artery enlargement?	Increase in size of the pulmonary arteries. This may be difficult to assess in the presence of hilar adenopathy, but in a case in which there is no adenopathy and there is enlargement of the hilum, then this enlargement should be attributed to the pulmonary artery.
13.	Pulmonary fibrosis?	Diffuse reticular or reticulonodular infiltrates which may be seen best in the lower lung zones. The reticular pattern may be coarse, multi-cystic or honey combed. The volume of the lungs may appear to be reduced.
14.	Any pleural abnormalities? (Thickening, effusions, plaques)	These include thickening, pleural effusion, pleural plaques, blunting of the angles of either side. Any such findings are abnormal.
15.	Other abnormalities?	Any bony, soft tissue or pulmonary parenchymal images that are not normal. Please specify (e.g., “3 cm mass in right apex”).

16.	Scadding stage	Check one stage only. Determine the Scadding stage on the basis of a general overview of the chest X-ray film and not on any particular finding. If more than one stage seems to fit, classify as the higher of the stages. Stage 0: Normal hilum, mediastinum and parenchyma - no parenchymal infiltrates or adenopathy. Stage I: Hilar adenopathy alone with no evidence of parenchymal disease. Stage II: Parenchymal disease plus hilar adenopathy. Parenchymal disease is interstitial disease and/or alveolar disease. Patients may have more than one type of parenchymal infiltrate. Stage III: Parenchymal infiltrates alone. Parenchymal disease is interstitial disease and/or alveolar disease. Patients may have more than one type of parenchymal infiltrates. Stage IV: Substantial pulmonary fibrosis. This is usually reflected not only in hilar retraction but also in bullous and cystic abnormalities in the upper lobes.
17.	Date of reading	Date film(s) reviewed by ACCESS staff.
18.	Reader	Clinical Center Principal Investigator or designated ACCESS physician (e.g., co-investigator) responsible for this reading.
19.	Research Coordinator:	The research coordinator verifies the thoroughness and accuracy of completion of this form.

A Case Control Etiologic Study of Sarcoidosis

Diagnostic Specimen Report
(Form 31)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of Form 31 is to document the tissue diagnosis for all patients with sarcoidosis enrolling as cases in ACCESS. In addition to the information concerning the interpretation of slides, this form provides information concerning the tissue(s) positive for histopathology and the stains performed to exclude other diagnoses. This form is completed after a patient's slides have been reviewed in the ACCESS Clinical Center. If the presence of noncaseating granuloma(s) consistent with the diagnosis of sarcoidosis is definite, the patient may be enrolled as a case in ACCESS.

2.	Date of examination of specimen	Date ACCESS pathologist reviewed slides.
3.	Results of examination Presence of noncaseating granuloma consistent with diagnosis of sarcoidosis?	A diagnosis of sarcoidosis should be made on the basis of the presence of non-caseating granulomas as outlined in the Procedures Manual. A "definitely-positive" reading indicates the biopsy has the histologic features typical for sarcoid granulomas. There should be no evidence of a foreign body reaction in the biopsy areas. A "definitely negative" reading indicates the histologic picture is not consistent with granulomatous inflammation. A "probable" diagnosis indicates that many but not all of the typical features for sarcoid granulomas are present. A "possible" reading indicates less certainty or that fewer features of sarcoid granulomatous inflammation are present on the pathologic specimen. A classification of either "probable" or "possible" reading should result in sending the slides to the Clinical Coordinating Center for distribution and further review among the Clinical Centers.
4.	If the results was **definitely positive**, was there a single site which provided the results?	The site of biopsy from which a diagnosis of sarcoidosis is established, i.e., a "definitely positive," should be selected.
5.	If there were multiple sites which provided a definitely positive diagnosis, which sites were involved?	If more than one site provided a definite histologic confirmation of a diagnosis of sarcoidosis indicate which ones among those listed.
6.	Was there a transbronchial biopsy?	Indicate whether or not a tissue diagnosis was attempted on the basis of transbronchial biopsy specimens collected at bronchoscopy.
6A.	Number of transbronchial biopsy specimens	Number of lung parenchyma specimens collected on transbronchial biopsy.

7.	Are the stains for histoplasmosis negative?	Stains for histoplasmosis should be negative before a "definitely positive, probable, or possible diagnosis" of sarcoidosis is made. Stains which are positive for histoplasmosis indicate the subject is not to be entered into the study. Occasionally tissue specimens obtained from referring physicians may not have been stained for histoplasmosis. Collection of appropriate specimens to stain for histoplasmosis is required.
8.	Are the stains for other fungal diseases negative?	Stains for fungal diseases other than histoplasmosis should be negative before a "definitely positive, probable, or possible diagnosis" of sarcoidosis is made. Stains which are positive for fungal disease indicate the subject is not to be entered into the study. Occasionally tissue specimens obtained from referring physicians may not have been stained for fungal disease. Collection of appropriate specimens to stain for fungi is requried.
9.	Are the stains for tuberculosis negative?	In accordance with a histopathologic diagnosis of sarcoidosis, stains for tuberculosis must be negative. The specific stains used for determination of acid-fast bacilli (AFB) is left to the discretion of each Clinical Center but should employ the stains routinely used for detection of acid-fast bacilli. Examples of such stains include Ziehl-Nielson stain, modified Kinyoun's stain or Auramine-Rhodamine stains.
10.	Is birefringent material present?	All specimens must be examined under polarized light and presence or absence of birefringent material indicated.
10A.	If Yes, describe	If birefringent material is present describe amount, intensity, location, etc.
11.	Principal Investigator or co-investigator	This form should be signed by either the Principal Investigator or Co-investigator who is responsible for the data reported.
12.	Signature of ACCESS Pathologist	This form should be signed by the ACCESS Pathologist who examines the specimen(s).
13.	Research coordinator	This form should be signed by the research coordinator responsible for verifying the accuracy and completeness of data recording. .

A Case Control Etiologic Study of Sarcoidosis

Bronchoalveolar Lavage Form
(Form 32)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of Form 32 is to document the circumstances of collection of bronchoalveolar lavage (BAL) specimens and processing to obtain supernatant and cells for storage in the Central Repository. Provisions have been made in ACCESS for collection of BAL in the course of clinically indicated procedures for patients who have given consent for the use of their BAL specimens by ACCESS in advance of the clinically indicated bronchoscopy. If the patient gives consent for use of BAL specimens in ACCESS, three pairs of slides (one stained and one unstained in each pair) should be prepared -- one pair for use in the Clinical Center, one pair to be sent to the BAL Core Laboratory and one pair for the Central Repository. BAL specimens will be kept properly labeled and frozen in the Clinical Center until a batch of patients' specimens is sent with a Bronchoalveolar Lavage Transmittal List (Form 60) to the Central Repository as described in the Procedures Manual Volume I (Chapter 6).

2.	Date of bronchoalveolar lavage (BAL)	Date bronchoscopy for BAL was performed.
3.	Area lavaged (fluid from only one area should be sent to central repository)	If fluid is available from more than one area, only fluid from one area should be used. The suggestion is to use the right middle or lingula area first. If neither of these is a choice, then the right upper or left upper lobe would be the next choice. If neither of these is available, then use the "other" area (this would be a lower lobe). Please specify the area which was sampled if "other" is used.
4.	Volume of fluid instilled	This should be at least 100 ml. The standard for the study is 120 ml instilled. Anything $\geq$ 100 ml will be acceptable. If < 100 ml are instilled, this is not an acceptable BAL.
5.	Volume of fluid withdrawn	This is the total amount of fluid pooled on aspiration. This is the amount prior to the aliquoting. At minimum, this should be at least 10 ml fluid. If less than 10 ml are withdrawn from a $\geq$ 100 ml lavage, the fluid should be considered inadequate and is not acceptable as an ACCESS specimen.
6.	Technique for aspiration	Please indicate whether this was "hand held syringe" or "low pressure suction."
7.	First 20 ml included in total aspirated fluid	Although the recommendation is that the first 20 ml be included, BAL collections that do not include the first 20 ml in the total aspirated fluid, will be acceptable as ACCESS specimens for the Central Repository.
8.	Aspirated fluid passed through gauze	The recommendation is that the fluid NOT be passed through gauze. However, fluid that is passed through gauze will be acceptable for ACCESS specimens in the Central Repository.

9.	Specimens sent for	Please indicate the cultures for which the specimens were sent. Recommendations are that the fluid be sent for both mycobacterial and fungal cultures, but this is not required in order for the patient's fluids to be sent to the repository.
10.	Cytocentrifuge slide stain	Staining of the slides is recommended using either Wright-Giemsa or Diff-Quik. If "Other" was used, this should be specified. If staining of a cytocentrifuged slide was not done, please indicate "Not Done."
11.	Method for cell count	Indicate whether this was done by hemocytometer, Coulter counter, or Other. If done by "Other" technique, please specify. If "Not Done," please note.
12.	Method for determining lymphocyte populations	Indicate whether done by flow activated cell sorter (FACS), immunohistochemistry, or Other. If done by "Other" technique, please indicate. If "Not Done," please indicate. Do not report which FACS machine or what monoclonal antibodies were used to determine cell subpopulations.
13.	Cell count of neat fluid	This should be reported as a multiple of 10^4 cell/ml. This should be the total cell count in one ml of fluid.
14.	Differential cell count from stained slide(s)	Indicate the percentage of macrophages, neutrophils, bronchial (epithelial) cells, lymphocytes, eosinophils, and other cells. It is possible that 100% macrophages or neutrophils may be identified. If cells other than those indicated above are seen in the specimen, please note what those cells are.
15.	Lymphocytes subpopulation	
15A.	Mononuclear cells	The percentage of nucleated cells that were stained by the PNT marker should be indicated. This would be the number of cells that are mononuclear cells and would represent the general population of lymphocytes.
15B.	CD4+	The percentage of cells that are CD4+, i.e., the percentage of the mononuclear cells that are selected by the FACS machine.

15C.	CD8+	The percentage of the mononuclear cells that are positive for CD8. For example, a report on a patient who has BAL fluid will include the number of mononuclear cells of the total cells scanned. This will, for example, be 40% mononuclear cells (in the left lower quadrant of a FACS machine analysis system). Of these mononuclear cells, 80% may be CD4+ and 10% CD8+. Then you would record that 40% of the cells were mononuclear cells, 80% were CD4+, and 10% were CD8+. Do not calculate the absolute percentage of lymphocytes: that is, 40% times 80%, which would be 32% of the total number cells are CD4+, and 10% of 40%, or 4% or the cells were CD8+.
16.	Number of cell-free supernatant aliquots (2 ml) frozen for central repository (Four aliquots recommended)	Ideally, this should be four aliquots. Please indicate the number of aliquots frozen.
16A.	Storage temperature (-80°C recommended)	Please indicate the storage temperature as plus or minus in degrees centigrade.
17.	Number of pellets frozen for central laboratory	Please indicate the number of cell pellets. It is recommended that one pellet be stored in a 2 ml sample.
17A.	Storage temperature (-80°C recommended)	Please indicate the storage temperature as plus or minus in degrees centigrade.
18.	Label sheet number	Please record the number from the label sheets provided for these samples. Affix the sheet label on the form page just below the space for recording the number.
19.	Participant has consented to the following use of his/her BAL specimens	Check the appropriate response based on the participant's consent form. The ACCESS Clinical Coordinating Center will notify the Central Repository of specimen numbers which have restricted use.
20.	Pulmonary physician	A physician certified in ACCESS should verify that the data reported are accurate. Ideally the ACCESS certified physician would have performed the bronchoscopy.
21.	Research coordinator	The ACCESS research coordinator should verify that the data have been collected completely and accurately.

A Case Control Etiologic Study of Sarcoidosis

Missed Contact / Visit Form
(Form 33)

PURPOSE AND GENERAL INSTRUCTIONS This form should be completed whenever a case enrolled in the Clinical Course Study cannot be located for a telephone contact or does not come to the Clinical Center for his/her two-year follow-up visit.

In order to document which contact or visit is missing, use the following numbering system.

Missed Contact/Visit	Form Type Number on Form 33
Six-Month Telephone Contact (TC01)	MC01
Twelve-Month Telephone Contact (TC02)	MC02
Eighteen-Month Telephone Contact (TC03)	MC03
Two-Year Follow-up Visit	MC04

Case Control Etiologic Study of Sarcoidosis

Follow-up Questionnaire for Cases Only (Part I)
(Form 35)

PURPOSE The purpose of this questionnaire is to obtain information on the patient's access to medical care, any medical conditions the patient may have, and the patient's employment status. This information is used to produce estimates on the types of insurance people have, the kinds of places people go to receive medical care, from whom they receive medical care, and why they seek care. Some of the questions may be considered sensitive, and care must be taken to ask questions and record responses in a nonjudgmental manner. The exact wording and order of questions should be followed to ensure standardization. Items in BRACKETS and/or CAPITAL LETTERS are instructions to the interviewer and are not read to the participant.

GENERAL INSTRUCTIONS: Several of the questions ask about conditions or activities occurring "since your ACCESS baseline interview." Each time this phrase is used, remind the case of the date of his/her interview. Example: "Since your ACCESS baseline interview on November 15, 1996."

II. ACCESS TO HEALTH CARE SERVICES

3. Currently, what is your main health insurance plan?

Interviewer should read list of responses. The following is a list of definitions:

(1) Private health insurance differs from public plans by who pays for the insurance. Private health insurance refers to any type of health insurance paid for all or in part by a family member out of pocket or all or in part by an employer. Coverage could be by fee-for-service, single- or multiple-provider HMO plans, or combination plans - e.g., plans with a single provider in which the patient can go elsewhere/anywhere for an additional payment. It does not include publicly paid programs listed below. Public plans are those in which the government pays for most or all of the cost of care for some people - e.g., those 65 years or age or older on Medicare.

(2) Medicare refers to the Federal health insurance coverage most common for persons 65 years and over. In certain situations people under 65 may be covered;

(3) Medicaid refers to a medical assistance program that provides health care coverage to low income and disabled persons. The Medicaid program is a joint federal-state program which is organized and administered by the States;

(4) Other public plans refer to other state or federal health insurance programs not listed above and can include:

  (a) Military health care refers to health care available to active duty personnel and their dependents; in addition, the VA provides medical assistance to veterans of the Armed Forces, particularly those with service-connected ailments.

  (b) CHAMPUS (Comprehensive Health and Medical Plans for the Uniformed Services) provides health care in private facilities for dependents of military personnel on active duty or retired for reasons other than disability.

  (c) CHAMPVA (pronounced CHAMP V-A) (Comprehensive Health and Medical Plan of the Veterans Administration) provides health care for the spouse, dependents, or survivors of a veteran who has a total, permanent service-connected disability.

If the respondent answers with “None” or “Don’t Know”, go to Question 6. Otherwise, ask Questions 3A, 3B, 3C, 4, and 5.

4.	Does your health insurance limit your ability to receive care for your sarcoidosis?	"Limit one's ability to receive care" means having to pay additional money for a visit or being restricted in the doctors or places where care can be provided paid for by the insurance. Include those that can go anywhere if they pay additional money out-of-pocket. If the respondent doesn't have health insurance, check "Not Applicable." If the answer to Question 4 is "No" or "Not Applicable," skip Questions 4A, 4B, and 4C and proceed to Question 5. If the respondent answers "Yes" to Question 4, ask Questions 4A - 4C.
4A.	Has it limited your access to a specialist for sarcoidosis care?	If the respondent answers "Yes" to Question 4A, ask him/her to specify and write the verbatim response on the line provided.
4B.	Has it limited your receiving tests that your doctor thought should be done for your sarcoidosis?	"Tests" refers to both types and frequency of medical tests. If the respondent answers "Yes" to Question 4B, ask him/her to specify and write the verbatim response on the line provided.
4C.	Has it limited your receiving any medication that your doctor thought you should receive for sarcoidosis?	"Medications" refers to medications prescribed by a doctor which the patients believes are for his/her sarcoidosis. If the respondent answers "Yes" to Question 4C, ask him/her to specify and write the verbatim response on the line provided.
5.	Has sarcoidosis affected the cost of your insurance?	The question relates to increased insurance premiums charged to the patient because of having this disease.
6.	Has sarcoidosis affected your ability to obtain health insurance?	The intent is to ascertain if the patient has or has been denied all or some health insurance coverage because of this disease. If the respondent answers "Yes", ask Question 6A. Not applicable should be used only if the case did not have health insurance at the time of diagnosis of sarcoidosis and did not apply for health insurance after the date of diagnosis. Health insurance is defined in the instructions for Question 3.
6A.	If yes, How?	Write the verbatim response on the line provided.
7.	Is there one particular clinic, health center, doctor's office, other place that you <u>usually</u> go to if you are sick or need advice about your health?	This question is intended to find out if the respondent has a usual source of health care. "Usual source of health care" refers to a place one would usually go if he/she were sick or in need of advice about his/her health. If respondent answers "Yes", interviewer should read Question 7A. If the answer to Question 7 is "No", interviewer should skip to Question 7B.

7A.	If yes, what type of place is it?	Read response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. The following definitions may be helpful: (1) A "doctor's private office" refers to an individual office in a freestanding or office building or a suite of offices occupied by several doctors. Do not consider a suite of individual, private, or unrelated group of doctors' offices as a clinic. (2) A "Hospital emergency room" is the unit of a hospital where persons may receive medical care, often of an urgent nature, without or before being admitted. Emergency rooms are usually open 24 hours a day. (3) A "Hospital outpatient clinic" is the unit of a hospital where persons may go for medical care without being admitted. Outpatient clinics usually provide routine, non-emergency medical care and are usually open only during specific hours. (4) A "Non-hospital clinical center" refers to a private clinical facility that provides ambulatory care and is freestanding in the community. This includes not-for-profit, non-government owned, "free" health clinics which may operate on a sliding scale. Examples include: urgent care centers; private walk-in care centers; Planned Parenthood centers; hospital-related centers not located within the hospital; and commercial (e.g., health care system, HMO-owned) centers employed by the HMO, commercial company or University. (5) A "Public health clinic" refers to a publicly - i.e., locally, state, or federally - supported facility where one or more physicians provide walk-in or ambulatory medical care. This also includes community health clinics which accept insurance but are federally sponsored clinics in under served areas. Skip Questions 7B and 7C and proceed to Question 8.
7B.	If no, is there one particular place where you <u>would</u> go if you were sick or needed advice about your insurance?	This question is intended to find out where the respondent would prefer to go if he/she did have a usual source of health care. If the answer is "No", skip Question 7C and proceed to Question 8. If the answer to Question 7B is "Yes", ask Question 7C.
7C.	What type of place is it?	Read the response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. This question is intended to find out where the respondent would prefer to go if he/she did have a usual source of health care. See Question 7A for definitions.

8. Is your regular doctor a general practitioner, internist, family doctor or doctor who treats a variety of illnesses and gives preventive care or is he/she a specialist (a doctor who mainly treats just one type of health problem)?	Interviewer should read response list. The following definitions may be helpful: (1) "Regular doctor" refers to the usual doctor the respondent usually visits when in need of medical care or advice for either preventive, curative, or continuing health care. This is the doctor you would go to for a new complaint or who coordinates your care. (2) The central concept is to differentiate whether the respondent's regular doctor is a primary physician or a specialist physician. In addition, some primary care doctors limit their care to people of particular ages - e.g., children for pediatricians or adults for internal medicine doctors (internists). A "general practitioner" or "family physician" refers to a generalist medical doctor who provides comprehensive medical care on a continuing basis to patients of any age or sex regardless of the specific nature of the patient's health problems. (3) A "specialist" refers to a medical doctor whose practice is limited to a particular branch of medicine or surgery such as reproductive or urinary problems, or who is a pediatric or internal medicine physician who treats one organ system or category of disease. A specialist has advanced training and is certified by a specialty board as being qualified to limit his/her practice to that field. Examples of specialists are surgeons, internists specializing in pulmonary (lung) diseases, pediatricians specializing in heart problems, psychiatrists, obstetricians, proctologists, ophthalmologists, and so forth.
9. Since your ACCESS baseline interview, was there any time when you wanted to see a doctor but could not?	This question is intended to find out if the respondent could not get health care when he/she thought it was necessary. The question refers to <u>any</u> reason the respondent could not see a doctor. If the respondent answers "Yes" to Question 9, ask Question 9A. If the respondent answers "No", skip Question 9A and proceed to Question l0. If the respondent says he/she could have seen some doctor but not his/her own doctor, check "No".
9A. If yes, why?	This question is intended to find out why the respondent could not get health care. Read the response list and mark all appropriate answers. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
10. Since your ACCESS baseline interview, have you delayed seeking medical care because of worry about the cost?	This question is intended to find out if the respondent put off or delayed seeking medical care because he/she was worried about the costs involved. It refers to the respondent's wanting to see or be referred to a doctor but not being able to afford to see the desired doctor. If the respondent answers "Yes" to Question l0, ask Question l0A. If the respondent answers "No" to Question l0, skip Question l0A and proceed to Question 11.

10A.	If yes, approximately how many times?	If the respondent answers with a range of numbers (e.g. 10-12 times), ask the respondent for a single number. If the person persists with a range, put down a number at the middle of this range - e.g., 11.
11.	Since your ACCESS baseline interview, have you delayed or had difficulty getting medicine prescribed when you needed it?	This question is intended to find out if the respondent was not able to get medication prescribed by a doctor even when he/she thought it was necessary. It means that the respondent had been prescribed medicine but delayed in getting or did not get the medicine initially, or when he/she ran out of the medication but was supposed to continue to use the medicine. If the respondent answers "Yes", ask Question 11A. If the respondent answers "No" to Question 11, proceed to Question l2.
11A.	If yes, was it because of:	This question is intended to find out why the respondent could not get medication prescribed by a doctor even though he/she thought it was necessary. Read the response list. Mark all appropriate answers. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
12.	Since your ACCESS baseline interview, was there any time when you needed medical care specifically for sarcoidosis but could not get it?	"Needing medical care" means any time either you or the doctor thought you should have a visit but either you or the doctor thought the visit could not be paid for by insurance. If the answer is "Yes," ask Question l2A, if "No", proceed to Question 13.
12A.	If yes, about how many times?	If the respondent gives a range of numbers (e.g., 3 or 4), ask the respondent for a single number.
13.	If your regular doctor at your usual source of health care is a specialist, does he or she also provide care for your sarcoidosis?	If the respondent's usual doctor is not a specialist, mark "Not Applicable". If the patient usually goes to a doctor - e.g., an Ob/Gyn specialist - for their usual care, does that doctor also care for the sarcoidosis symptoms, or does the person go to another specialist for sarcoidosis care?
14.	Since your ACCESS baseline interview, how many times have you made appointments to see a doctor for your sarcoidosis?	If the answer is "Zero (0)", skip Questions 14A and 14B and proceed to Question 15. If the answer to Question 14 is at least one (1), ask Question 14A.
14A.	How many of these appointments did you miss?	A "missed appointment " is an appointment that was scheduled or requested by the doctor but not made or not kept. A scheduled appointment that is canceled but rescheduled and kept would <u>not</u> be missed. If the respondent answers 14A with more than one number (e.g., 2 or 3), ask the respondent for a single number. If the answer to Question 14A is zero (0), skip Question 14B and proceed to Question 15. If the answer to Question 14A is at least one (1), ask Question 14B.

14B.	If you had to miss at least one appointment, what was the main reason?	Read the response list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line.
15.	During the period since your ACCESS baseline interview has your sarcoidosis affected any of your organs?	Script on form should be self-explanatory.
16.	During the period since your ACCESS baseline interview have you needed treatment for your sarcoidosis?	Script on form should be self-explanatory.
III.	**Medications**	**Patients should be instructed to bring all current medications in a plastic bag, with as many old pill bottles as possible.**
17.	I am going to read from a list of medications used for treatment of sarcoidosis. As I read each medication please indicate if you have taken it for your sarcoidosis since your ACCESS baseline interview. We are not asking about any medication you stopped taking prior to your ACCESS baseline interview.	Answer questions in Columns 3, 4, 5, and 6 if usage was Current or Not Current. "Not Current" means the case took the medication sometime since the baseline interview but is not taking it as of the interview date. "Off and On" (Column 4) means sometimes off medication and sometimes on medication, or intermittently on medication over months. "Response to Therapy" (Column 6) is the cases's subjective evaluation of his/her symptoms. "Improve" would be lessening of symptoms. "Same" would be no change in symptoms and "Worse" would be an increase in number or intensity of symptoms. If case did not indicate that he or she took prednisone in Question 17A, do not ask Question 17L, but check N/A.
18.	We would like to know for what problem related to your sarcoidosis you were taking the medications we just discussed?	Script on form should be self-explanatory.
19.	When was the first time you began taking medication for your sarcoidosis?	This is the date case first began taking medication for sarcoidosis, even if it was before enrollment in ACCESS.
20.	I would like you to think about how you took your sarcoidosis medicines in the PAST WEEK.	For Questions 20A, 20B, and 20C, read the words "On how many days did you" before each question. If the person does not provide a definite number of days, say "<u>about</u> how many days or your best estimate." If the respondent gives more than one number (e.g., 3 or 4), ask the respondent for a single number.
20A.	On how many days did you <u>forget</u> to take some or all of it?	"Forget" refers to not taking the medication at all. This does not refer to taking the dose later in the day.
20B.	On how many days did you <u>not take</u> some or all of it?	"Not take some" indicates the patient consciously decided not to take the medication.

20C.	On how many days did you take <u>more</u> of any of it than your doctor told you to?	"Take more" indicates that the patient consciously decided to take more than the prescribed dose.
21.	Would you say that you take your sarcoidosis medicine just the way your doctor told you to take it?	Interviewer should read the response list. If the response to Question 21 is "All of the time", skip Questions 22 and 23 and proceed to Question 24. If the answer to Question 21 is any other response, proceed to Question 22.
22.	Was there any time since your ACCESS baseline interview you did not obtain your sarcoidosis medication because you could not afford it?	This means the patient did not purchase and have the medication as the doctor indicated and/or did not take the medication in the amount and at the times indicated. Include persons who were getting free medication but could not afford to travel to obtain medication.
23.	When you don't take all the medication that was prescribed, what is the most important reason for taking less?	Interviewer should read list. If the answer is not one from the list of responses, check the response "Other" and write the verbatim response on the "Specify" line. If more than one reason is given, ask the respondent to specify the most important or most usual reason.
24.	Has your doctor ever directly asked you about how well you take your sarcoidosis medicine?	Include any inquiries by the doctor as to the frequency or regularity of taking the medications.
25.	How confident are you that you can control your sarcoidosis by taking your medicine each day?	This question refers to the patient's belief that his/her medication can improve his/her health or slow down the course of the disease. Interviewer should read response list.
26.	If you don't take your sarcoidosis medicine, what are the chances that something bad will happen to your health in the next year?	This question investigates the patient's belief that without the medication the sarcoidosis will progress to new places in the body or worsen in places already affected. Interviewer should read response list. Do not accept "Don't Know". Encourage patient to make a choice from the responses listed.
27.	If you don't take your sarcoidosis medicine, what might happen?	If the case says "I don't know," check the "Don't Know" response. If the case provides an answer, the Interviewer should record the respondent's answer verbatim.
28.	How often do people in your daily life help you by reminding you to take your sarcoidosis medicines?	This question investigates whether there is someone who inquires about the patient and his/her medication. Interviewer should read response list.
29.	Most people forget to take their medicine occasionally. How often does this happen to you?	If the person says "Don't Know" or "Not Sure", have them estimate which category is most likely. Interviewer should read response list.

Case Control Etiologic Study of Sarcoidosis

Follow-up Questionnaire for Cases Only (Part II)
(Form 36)

PURPOSE The purpose of this questionnaire is to obtain information on the patient's access to medical care, any medical conditions the patient may have, and the patient's employment status. This information is used to produce estimates on the types of insurance people have, the kinds of places people go to receive medical care, from whom they receive medical care, and why they seek care. Some of the questions may be considered sensitive, and care must be taken to ask questions and record responses in a nonjudgmental manner. The exact wording and order of questions should be followed to ensure standardization. Items in BRACKETS and/or CAPITAL LETTERS are instructions to the interviewer and are not read to the participant.

GENERAL INSTRUCTIONS: Several of the questions ask about conditions or activities occurring "since your ACCESS baseline interview." Each time this phrase is used, remind the case of the date of his/her interview. Example: "Since your ACCESS baseline interview on November 15, 1996."

II. MEDICAL HISTORY

3 - 16	I am going to read you a list of health problems. For each problem, please tell me if you have ever had the problem. If you have had the problem, I will ask you to tell me your age when you first got it and whether you still have it.	For each condition, the response should be coded as "Yes" if a doctor indicated that the condition was present. For instance, sinus trouble should be checked "No" if the case reports a stuffy nose, but should be checked "Yes" if a doctor told the case he/she had sinus problems. Likewise, allergies should be determined from a skin test or some other form of verifying the presence of an allergy. In Part B, the case should indicate the age at which the symptoms were first present regardless of when the problem was diagnosed.
17.	Have you had any other health problems I have not asked you about?	This addresses other health problems not previously specified. Make sure you do not write any health problem that is listed in Questions 3-16. If the patient has no other health problems, go to Question 18.
19.	Have you been in the hospital as a patient since your ACCESS baseline interview.	This includes emergency room visits as well as an in-patient.
19A.	How many times were you in the hospital?	This number should include all emergency room visits and in-patient admissions since the ACCESS baseline interview.
19B.	Give the following information for each time you were in the hospital:	Both the name and address or location of the hospital should be noted, and a signed release for permission to obtain records should be obtained.
20.	During the past six weeks have you experienced any of the following?	Question is self-explanatory.
21.	Have you taken prednisone during the past six weeks?	Question is self-explanatory.
22.	Have you changed your job since your ACCESS baseline interview?	"Changed your job" would include changes in job status such as retiring, becoming unemployed, going on disability, etc. as well as going from one job to another.
23.	Have any of your brothers, sisters, spouse/mate, or other relatives or friends been found to have sarcoidosis since your ACCESS baseline interview?	A "Yes" response should mean a physician has diagnosed sarcoidosis in the affected person(s).

24. Have any of your children been found to have sarcoidosis since your ACCESS baseline interview?

A "Yes" response should mean a physician has diagnosed sarcoidosis in the affected person(s).

25. Have you ever smoked any tobacco products?

"Smoking" is defined as smoking one cigarette (or its equivalent) or more per week. (If the response is "No," skip Questions 26-33 and go to Question 34.

26 to 33.

The purpose of these questions is to determine if there has been any change in the participant's smoking habits (either starting or stopping a given tobacco product) since the ACCESS baseline interview.

28 - 29. Have you stopped/started smoking cigarillos since your ACCESS baseline interview?

Cigarillos are cigar-like products in the size and shape of cigarettes. It does not include the smoking of cigars.

34. Do you spend more than three hours a week in rooms filled with smoke from other smokers?

This question is designed to provide some estimate of passive smoking. It is to be administered to all participants regardless of their own smoking status. It should include rooms at home or at work where persons other than the participant smoke.

IV. INCOME

35. Was the total combined FAMILY income during the past 12 months more or less than $20,000 – that is, yours as well as that of all the members of your household, including Armed Forces members living at home? Include money from jobs, social security, retirement income, unemployment payments, public assistance, and so forth. Also include income from interest, dividends, net income from business, farm or rent, and any other money income received.

Give the participant the appropriate income card (if < 20,000, Card J, if > 20,000, Card I) and read the paragraph before reading the question. Read the statement printed on the questionnaire if the respondent refuses to answer the income items or questions the need for our collecting income data. After reading this, re-ask Questions 35 and 36, if necessary. If the respondent still will not answer, footnote the reason(s) for refusal. Definitions that may be helpful:

36. Of these income groups, which letter from the hand cards best represents the <u>total</u> combined FAMILY income during the past 12 months. Include wages, salaries, and other items we just talked about.

(1) "Family income" refers to the money income before deducting for taxes, retirement, insurance, union dues, etc. This includes the income of the participant plus that of all his/her relatives who are currently household members, including Armed Forces members living at home and children, or temporarily absent but usually resident in the home.

35-36 (Continued):

(2) Income includes:

(a) Wages and salaries including tips, commissions, Armed Forces pay and cash bonuses, as well as subsistence allowances;
(b) Net income from unincorporated businesses, professional practices, or farms, or from rental property. ("Net" means after deductingbusiness expenses, but before deducting personal taxes.);
(c) Social Security, or Supplemental Security Income;
(d) Retirement, disability, and survivor pensions;
(e) Interest and dividends;
(f) Cash public assistance payments (welfare), excluding food stamps;
(g) Veteran's payments;
(h) Unemployment or workmen's compensation;
(i) Alimony and child support;
(j) Money regularly received from friends or relatives not living in the household; and
(k) Other periodic money income.

Be sure the respondent understands that the income questions are for the past 12 months, not for the last calendar year. Ask Question 35 once for a family to obtain the total combined income during the past 12 months for all household members related to the reference person. Be sure to include all family members, as even a child could receive income (savings account interest, AFDC payments, etc.) Do not include the income of unrelated household members or other person not related to the reference person. After you ask the question, give the respondent enough time to prepare an estimate, then mark the appropriate box. When necessary, help the respondent obtain the total by summing the income of several family members or the income from several sources. If the income is reported in terms of a periodic (weekly, monthly, etc.) paycheck, be sure the respondent understands that we are interested in the amount before taxes and other deductions, not the take-home amount. Help compute the yearly total, if necessary. If the respondent is living alone or with no other relatives, include his/her income only. "Zero" income, break-even, or loss reported - When no one in the family had income or when a "loss" or

35-36 (Continued):

"broke even" was reported as the total income for the family, mark the appropriate box in Question 35. Before accepting an answer of "No Income," be sure the respondent understands all of the categories counted as income. If the respondent is not sure of the income, try to get the best estimate possible. In difficult cases, you may have to help the respondent. Find out who worked during the past 12 months, how much they made a week, etc.; find out who operated a business or farm; or who received any pension, dividents, etc. If the response is still "Don't Know," enter "DK" in Question 35 or Question 36, as appropriate.

A Case Control Etiologic Study of Sarcoidosis

Change in Organ Involvement Since
Initial Examination (Form 37)

General Instructions: This form is a comparison of the nature and extent of organ involvement at the baseline physical examination with the organ involvement at the follow-up examination.

When completing this form, the physician should compare the responses recorded on the baseline Physical Examination Form (Form 24, PE01) with the responses recorded on the follow-up Physical Examination Form (Form 24, PE02). The Form 37 should be completed in accordance with this comparison. Clinical resolution or improvement of symptoms should be coded "better." New involvement or worsening of symptoms since the baseline examination should be coded "worse." Involvement includes past (since the baseline examination) and present.

Definition of organ involvement: 1) Positive biopsy of the organ or one of the following conditions. 2) Assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease). 3) Other situations may be specified. 4) Treatment for sarcoidosis such as corticosteroids, chloroquine, or methotrexate.

A Case Control Etiologic Study of Sarcoidosis

Tissue Sample Shipping Form
(Form 40)

PURPOSE AND GENERAL INSTRUCTIONS This form should be completed whenever a pathology report at the Clinical Center indicates probable or possible presence of noncaseating granuloma consistent with diagnosis of sarcoidosis or if requested by the Clinical Coordinating Center for quality control purposes. The form should be data entered and a copy of this form and the pathology slides should be sent to the Clinical Coordinating Center. The form must be entered into the local data management system within one week of sending materials to the Clinical Coordinating Center.

After the slides have been examined by the reviewing pathologist, the Clinical Coordinating Center will return the slides and a new Diagnostic Specimen Report (Form 31) to the Clinical Center. The information on the Form 31 should be entered into the local data management system.

4.	What tissues are included in this shipment?	For each listed tissue please indicate whether a specimen is or is not included in this shipment and, if it is included, the number of slides for that tissue.

A Case Control Etiologic Study of Sarcoidosis

Review of Tape Recorded Interview
(Form 41)

PURPOSE AND GENERAL INSTRUCTIONS The purpose of this form is to collect data on the quality of the ACCESS interview procedures. This form is completed by site or audit visit teams at site or audit visits when they listen to tapes of ACCESS interviews performed by the interviewers at the Clinical Center. Principal Investigators and Research Coordinators are also requested to listen to interview tapes from their own Clinical Center selected by the ACCESS Clinical Coordinating Center from time to time. This form is completed for each tape as the Principal Investigator and Research Coordinator listen to the tapes.

A Case Control Etiologic Study of Sarcoidosis

Bronchoalveolar Lavage Transmittal List
(Form 60)

For Shipments to the Central Repository)

For each case for whom bronchoalveolar lavage is performed four 2 ml. Cryostat tubes containing supernatant, one 2 ml. cryostat tube containing a cell pellet and one pair of slides are to be sent to the Central Repository. The specimens are to be sent in batches at one month intervals. The cryostat tubes are to be sent on dry ice. Specimen number is the number on the label attached to the specimen tube. The slides may be sent in the same package as the cryostat tubes or separately. If they are sent in the same package, the slides should be labeled with the case's ACCESS specimen number label, inserted into standard slide transport packaging (e.g., cardboard slide holders) and secured so that slides will not fall out of the holders. In order to protect the slides from any condensation that might occur because of the cold temperatures in the package, place the slide holders inside a sealed plastic bag. If the slides are sent separately, the packaging should be similar to that described above, except the plastic bag may be omitted and the slide holders should be packed in a padded envelope or box to prevent breakage.

If a biological specimen is known to be infectious it must be shipped using the following **additional** procedures: 1) In addition to the usual primary and secondary sealed containers provided by the Central Repository, the contained sample must be placed in a United Nations approved cushioned box with appropriate labeling. The Central Repository will send each Clinical Center one of these special boxes to use when needed. If you use this box, please call Steven Lindenfelser (301-340-1620) for a replacement. 2) A special "Dangerous Goods" form **must** accompany the sample. Be sure the bottom of the form is filled out correctly, or the sample will be returned to you. Most Infectious Disease departments have both boxes and sample forms. Please check with the Infectious Disease department of your hospital to be sure you have completed the form correctly.

If the slides are sent with the cryostat tubes, tubes and slides may be listed on the same Transmittal List. If the slides are sent separately, a separate Transmittal List should be sent with each shipment, with tubes listed on one list and slides on another. In either case the page numbers should be recorded in the upper right hand corner of each page and copies of all Transmittal Lists sent to the Central Repository should be mailed or sent by FAX (410-435-0689) to the Clinical Coordinating Center within a week of the date of shipping the BAL material to the Central Repository. Do not use this form to accompany slides sent to the BAL Central Laboratory (Dr. Robert Baughman).

A Case Control Etiologic Study of Sarcoidosis

DNA Blood Specimen Shipping Form
(Form 61)

This form is to be sent to the DNA Core Laboratory with five large purple top tubes of blood for each case and each control. Since the blood is to be sent by Federal Express on the day the specimens are collected, a separate Shipping Form should be completed for each case's or control's blood specimens. Specimen number is the number on the label attached to the specimen tubes.

If a biological specimen is known to be infectious it must be shipped using the following **additional** procedures: 1) In addition to the usual primary and secondary sealed containers provided by the Central Repository, the contained sample must be placed in a United Nations approved cushioned box with appropriate labeling. The Central Repository will send each Clinical Center one of these special boxes to use when needed. If you use this box, please call Steven Lindenfelser (301-340-1620) for a replacement. 2) A special "Dangerous Goods" form **must** accompany the sample. Be sure the bottom of the form is filled out correctly, or the sample will be returned to you. Most Infectious Disease departments have both boxes and sample forms. Please check with the Infectious Disease department of your hospital to be sure you have completed the form correctly.

A copy of this form should be mailed or sent by FAX (410-435-0689) to the Clinical Coordinating Center within a week of the date of shipping the blood to the DNA Core Laboratory.

A Case Control Etiologic Study of Sarcoidosis

L-Forms Blood Specimen Shipping Form
(Form 62)

This form is to be sent to Dr. Peter Almenoff with one small purple top tube of blood for each case and each control. Since the specimens are to be sent by Federal Express on the day of collection, a separate Shipping Form should be completed for each case's or control's blood specimens. Specimen number is the number on the label attached to the specimen tube. An additional label should be attached to the form in the space provided.

If a biological specimen is known to be infectious it must be shipped using the following **additional** procedures: 1) In addition to the usual primary and secondary sealed containers provided by the Central Repository, the contained sample must be placed in a United Nations approved cushioned box with appropriate labeling. The Central Repository will send each Clinical Center one of these special boxes to use when needed. If you use this box, please call Steven Lindenfelser (301-340-1620) for a replacement. 2) A special "Dangerous Goods" form **must** accompany the sample. Be sure the bottom of the form is filled out correctly, or the sample will be returned to you. Most Infectious Disease departments have both boxes and sample forms. Please check with the Infectious Disease department of your hospital to be sure you have completed the form correctly.

A copy of this form should be mailed or sent by FAX (410-435-0689) to the Clinical Coordinating Center within a week of the date of shipping the blood to Dr. Almenoff.

A Case Control Etiologic Study of Sarcoidosis

Bronchoalveolar Lavage (BAL) Slide Transmittal List
(Form 65)

(For Shipment to the BAL Core Laboratory)

This form is to be sent to the BAL Core Laboratory (Dr. Robert Baughman) with one pair of slides for each case for whom bronchoalveolar lavage is performed. Since the slides may be sent in batches, one form may accompany slides for several cases. Use as many pages as necessary to record all the slides in a given shipment. Record the page numbers in the upper right hand corner of each page. List the slides for each case separately. Specimen number is the number on the label attached to the slides. Slides should be sent in batches at one month intervals.

If a biological specimen is known to be infectious it must be shipped using the following **additional** procedures: 1) In addition to the usual primary and secondary sealed containers provided by the Central Repository, the contained sample must be placed in a United Nations approved cushioned box with appropriate labeling. The Central Repository will send each Clinical Center one of these special boxes to use when needed. If you use this box, please call Steven Lindenfelser (301-340-1620) for a replacement. 2) A special "Dangerous Goods" form **must** accompany the sample. Be sure the bottom of the form is filled out correctly, or the sample will be returned to you. Most Infectious Disease departments have both boxes and sample forms. Please check with the Infectious Disease department of your hospital to be sure you have completed the form correctly.

A copy of this form should be mailed or sent by FAX (410-435-0689) to the Clinical Coordinating Center within a week of the date of shipping the slides to the BAL Core Laboratory. Do not use this form to accompany BAL slides sent to the Central Repository.

A Case Control Etiologic Study of Sarcoidosis

Kveim Biopsy Slide Transmittal List
(Form 66)

(For Shipment to Dr. Alvin Teirstein)

This form is to be sent to Dr. Alvin Teirstein with the slides for each case for whom a Kveim biopsy is performed. Since the slides may be sent in batches, one form may accompany slides for several cases. Use as many pages as necessary to record all the slides in a given shipment. Record the page numbers in the upper right hand corner of each page. List the slides for each case separately. Specimen number is the number on the label attached to the slides. Slides should be sent in batches at one month intervals.

If a biological specimen is known to be infectious it must be shipped using the following **additional** procedures: 1) In addition to the usual primary and secondary sealed containers provided by the Central Repository, the contained sample must be placed in a United Nations approved cushioned box with appropriate labeling. The Central Repository will send each Clinical Center one of these special boxes to use when needed. If you use this box, please call Steven Lindenfelser (301-340-1620) for a replacement. 2) A special “Dangerous Goods” form **must** accompany the sample. Be sure the bottom of the form is filled out correctly, or the sample will be returned to you. Most Infectious Disease departments have both boxes and sample forms. Please check with the Infectious Disease department of your hospital to be sure you have completed the form correctly.

A copy of this form should be mailed or sent by FAX (410-435-0689) to the Clinical Coordinating Center within a week of the date of shipping the slides to Dr. Alvin Teirstein.

A Case Control Etiologic Study of Sarcoidosis

Request to Extend Time Window
(Form 70)

PURPOSE AND GENERAL INSTRUCTIONS Certain required information for cases may be acceptable even though the time period between the date of collection and enrollment is greater than specified in the Protocol. These requests for Protocol exceptions are to be submitted using the Request to Extend Time Window (Form 70). A description of the request and an explanation concerning the rationale for this request should be written in Item 3. If additional space is needed for explanation, please attach extra sheets to the form.

Please send the form and attachments to the Clinical Coordinating Center. These requests will be forwarded to the Study Chairman or Vice Chairman depending on who is available and their recommendations with regard to the acceptability of information outside of study time windows will be conveyed to the Principal Investigator requesting the exception.

Requests for exceptions should be infrequent. Ideally, all baseline data should be based on observations no more than six months prior to enrollment.

A Case Control Etiologic Study of Sarcoidosis

APPENDIX A

Data Entry Guidelines

The following guidelines for completing forms in ACCESS are suggested to ensure standardized transfer of data entered on the forms to the computer database.

1. Please use an "X" or a check mark (**T**) within parentheses as responses on forms. Do not draw a line through columns of parentheses or circle responses.
2. For items which require a numeric response, the exact number of spaces is indicated. Answers to integer items which require less than the number of spaces provided must be right justified.
3. Do not add decimal points or other punctuation to numeric responses.
4. To correct form item responses, please cross out the incorrect responses; circle, initial and date the correct response.
5. If a comment is required as a response, please print the response legible. Abbreviations should not be used unless absolutely necessary.
6. If you wish to delete a response, please make dark, legible strike marks through the data to be deleted from the form.

A Case Control Etiologic Study of Sarcoidosis

APPENDIX B

THREE-LETTER MONTH ABBREVIATIONS

January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

A Case Control Etiologic Study of Sarcoidosis

APPENDIX C

TWO-LETTER STATE ABBREVIATIONS

Alabama	AL	Kentucky	KY	Ohio	OH
Alaska	AK	Louisiana	LA	Oklahoma	OK
Arizona	AZ	Maine	ME	Oregon	OR
Arkansas	AR	Maryland	MD	Pennsylvania	PA
California	CA	Massachusetts	MA	Puerto Rico	PR
Colorado	CO	Michigan	MI	Rhode Island	RI
Connecticut	CT	Minnesota	MN	South Carolina	SC
Delaware	DE	Mississippi	MS	South Dakota	SD
District of Columbia	DC	Missouri	MO	Tennessee	TN
Florida	FL	Montana	MT	Texas	TX
Georgia	GA	Nebraska	NB	Utah	UT
Guam	GU	Nevada	NV	Vermont	VT
Hawaii	HI	New Hampshire	NH	Virginia	VA
Idaho	ID	New Jersey	NJ	Virgin Islands	VI
Illinois	IL	New Mexico	NM	Washington	WA
Indiana	IN	New York	NY	West Virginia	WV
Iowa	IA	North Carolina	NC	Wisconsin	WI
Kansas	KS	North Dakota	ND	Wyoming	WY

A Case Control Etiologic Study of Sarcoidosis

APPENDIX D

THREE-DIGIT COUNTRY CODES

Listed Alphabetically

Afghanistan	163	Brazil	055
Albania	355	British Virgin Islands	113
Algeria	213	Brunei	673
American Samoa	684	Bulgaria	359
Andorra	033	Burkina Faso	226
Angola	244	Burma (Myanmar)	166
Anguilla	123	Burundi	257
Antigua & Barbuda	145	Cambodia (Kampuchea)	168
Argentina	054	Cameroon	237
Armenia	167	Canada	011
Aruba	297	Cape Verde	238
Australia	061	Cayman Islands	169
Austria	043	Central African Republic	236
Azerbaijan	165	Chad	235
Bahamas	809	Chile	056
Bahrain	973	China	086
Bangladesh	880	Colombia	057
Barbados	190	Comoros	269
Belarus	111	Congo, Republic of	242
Belgium	032	Cook Islands	682
Belize	501	Costa Rica	506
Benin	229	Croatia	385
Bermuda	112	Cuba	114
Bhutan	975	Cyprus	357
Bolivia	591	Czech Republic	042
Bosnia & Herzegovina	387	Denmark	045
Botswanna	267	Djibouti	253

A CASE CONTROL ETIOLOGIC STUDY OF SARCOIDOSIS

ACCESS

PROCEDURES MANUAL

VOLUME III

September 1996

Prepared by:

Clinical Trials & Surveys Corp.
The Village of Cross Keys
350 West Quadrangle
Baltimore, Maryland 21210

ACCESS PROCEDURES MANUAL

Volume III

DATA MANAGEMENT PROCEDURES FOR CLINICAL CENTERS

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 1

DATA PROCESSING OVERVIEW

1.1 INTRODUCTION

The ACCESS Distributed Data Management System has been designed to facilitate the entry, quality assurance, and management of case and control data. The system also provides a means for local backup and for the transfer of data to the Clinical Coordinating Center. Local office functions in conjunction with ACCESS are also available through an office suite software.

The system is implemented using a powerful and flexible relational database management system on a Pentium-class microcomputer.

1.2 FUNCTIONS PROVIDED

The ACCESS Distributed Data Management System provides the following basic functions:

1. Data entry and correction of ACCESS Forms with built-in error checking through screens that resemble the forms;
2. Display of keyed ACCESS forms;
3. Local edit of keyed ACCESS Forms resulting in locally printed queries;
4. Entry of Screening Log data;
5. Automated backup of database and microcomputer files onto tape;
6. Generation of appointment schedules and visits expected in a calendar month for cases;
7. Online inventory display of participant (case or control) materials and their status;
8. Data management form processing certification system;
9. Delinquent forms processing;

10. Patient Visit Scheduling; and

11. Remote access capability from the Clinical Coordinating Center to the Clinical Center to retrieve data, upgrade software, and to perform diagnostics.

1.3 DESCRIPTION OF HARDWARE AND SOFTWARE

The hardware and software have been chosen for their robustness, longevity, and integrity. The system includes a graphical user interface (GUI) operating system, a relational database management system, utilities for backup and other maintenance functions, office software and modem hardware and software. These components should facilitate the efficient collection and processing of ACCESS data.

1.3.1 Hardware

ACCESS Distributed Data Management Hardware

Gateway Pentium 100 MHZ Pentium microcomputer with:

32 MB memory,

1.6 GB hard drive,

3.5 “ diskette drive,

8-speed CD-ROM drive,

28,800 bps fax/modem,

1.3 GB tape drive, and

local graphics accelerator with 2MB DRAM.

Vivitron 17-inch super-VGA monitor.

Hewlett Packard LaserJet 5L printer (4 pages/minute).

1.3.2 ACCESS Software

ACCESS Distributed Data Management software includes:

Microsoft Windows 95 and its subsidiary software,

ORACLE Relational Database Management System including Forms and Reports,

Colorado Tape Backup, and

ReachOut for remote access to the Clinical Center from the Clinical Coordinating Center.

1.4 OVERVIEW OF PROCESSING

Figure 1-1 shows the general flow of data management activities at the ACCESS Clinical Centers. Staff certified in data management activities will be permitted to perform ACCESS database functions. For every database function, certified staff must provide a password for access to the database and provide a certification number.

Once logged on staff may choose from several functions. Data entry, correction and display of forms will be the most used functions. Certified staff will choose a form to enter or a form for a specific participant to correct or display. Data entry and correction systems provide automated checking for participant identity, form appropriateness for the participant, illegal codes, and range checks. In addition, remarks are entered in free-form text.

The edit is automatically run after completing data entry or correction. Any resulting queries will be printed locally. All forms newly entered or corrected are edited. Queries should be resolved and corrections made using the correction screen.

All data passing edit will automatically be transmitted when Clinical Coordinating Center staff call Clinical Center machines on a scheduled basis. A special password is required for remote access to protect ACCESS data from intrusion over communications lines.

ACCESS Clinical Center staff can also display a list of materials and their current status via the Participant Inventory Display. Staff may request a complete appointment schedule for any case. The appointment schedule describes when a case should be scheduled for telephone contact or follow-up visit. The list of expected visits includes those cases whose visit window for

telephone contact or follow-up visit opens in a particular month.

The database and other files needed for operation of ACCESS Data Management or the microcomputer will be routinely backed up using the software provided.

1.5 OTHER SOFTWARE PROVIDED

Microsoft Office Professional including:

Microsoft Word (word processing),

Microsoft Excel (spreadsheet),

Microsoft PowerPoint (presentation software),

Microsoft Access (database),

Microsoft Schedule + (appointments), and

Microsoft Bookshelf (dictionary, thesaurus, quotations, encyclopedia, atlas, chronology).

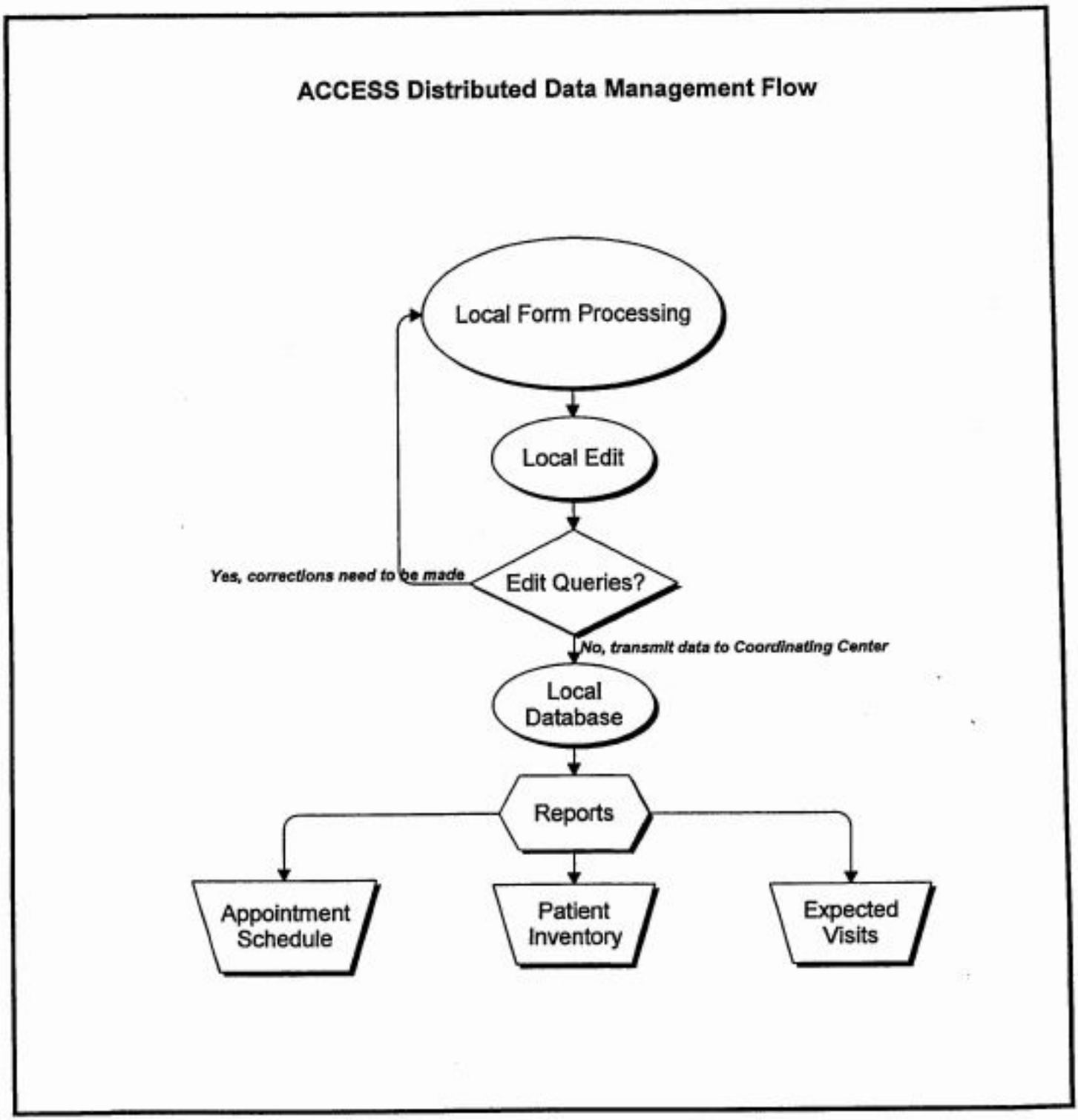
FaxWorks for sending/receiving faxes

Although Microsoft Office Professional and FaxWorks are being provided as a courtesy for local Clinical Center office functions related to ACCESS, they are not utilized in the Distributed Data Management System developed for ACCESS. A CD-ROM with online Help for Microsoft Office and Bookshelf will be provided to each center.

1.6 MICROCOMPUTER PROFICIENCY

It is assumed that certified data management staff have used a microcomputer, a mouse, and a Windows-based system. Additional training on microcomputer use, Windows, and Microsoft Office is available in every city in the United States through community colleges, computer stores, and computer training companies. Basic classes are typically one day in length. In addition, large book stores carry introductory books on microcomputers and Windows 95.

Figure 1-1


ACCESS Distributed Data Management Flow
Local Form Processing
Local Edit
Edit Queries?
Yes, corrections need to be made
No, transmit data to Coordinating Center
Local Database
Reports
Appointment Schedule
Patient Inventory
Expected Visits

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 2

COMPUTER OPERATIONS

2.1 TURNING THE MICROCOMPUTER ON AND OFF

The microcomputer, monitor, and printer are plugged into the provided surge protector. To turn the system on or off, toggle the switch. When the switch is lit, the system is on as long as all components are left in an on position.

Figure 2-1 shows the approximate schematic of the microcomputer and monitor. The ACCESS microcomputers have the 3 ½ " diskette in the bottom bay and the tape drive and CD-ROM in reverse order from the figure. The power button is on the lower right of the microcomputer panel. When the system is on and powered the indicator light will be on. The monitor power button is on the right front of the monitor. The power indicator light will be lit when the monitor is on and powered.

Figure 2-2 shows the Hewlett Packard printer. The printer is on when plugged into the surge protector and the surge protector is on. The paper supports should be in an upright position at all times. The printer uses standard 8 ½ " by 11" photocopy paper.

2.2 LOGGING IN

When the system is turned on, a log in screen appears as in Figure 2-3. This is the Windows 95 log in screen which allows the system to be customized for each user. The username and password are given to each Clinical Center in a sealed envelope.

Specific directions are:

Type in the username.

Press <TAB>.

Type in the password.

Press <ENTER> or click [OK].

The mouse has a left and right button. Unless specifically stated otherwise, "click" means

press the left button.

2.3 THE ACCESS DESKTOP AND FUNCTIONS

When the user logs in, the ACCESS desktop is displayed as shown in Figure 2-4. The desktop is a computer simulation of a desk. Each of the icons on the desktop are like folders on your desk. Each icon starts a program or takes you to another folder. The ACCESS icons match the functions described in Chapter 1.

To start an ACCESS function, double-click on the function on the desktop. Each of the functions is described in Chapters 3 through 8. Alternatively, click on the [START] icon in the lower left corner as shown in Figure 2-5. Click on ACCESS. Click on the desired function.

The ACCESS system is designed to return the user to the desktop after completion of a function to select another function or to shutdown and power down the system.

2.4 SHUTTING DOWN THE SYSTEM

Normally, the system is left on during the day. If data are not scheduled to be transmitted to the Clinical Coordinating Center, the system may be shut down. Figure 2-6 shows the **System Shutdown Dialog Box**. To shut down the system:

Click on [START] menu in lower left corner.

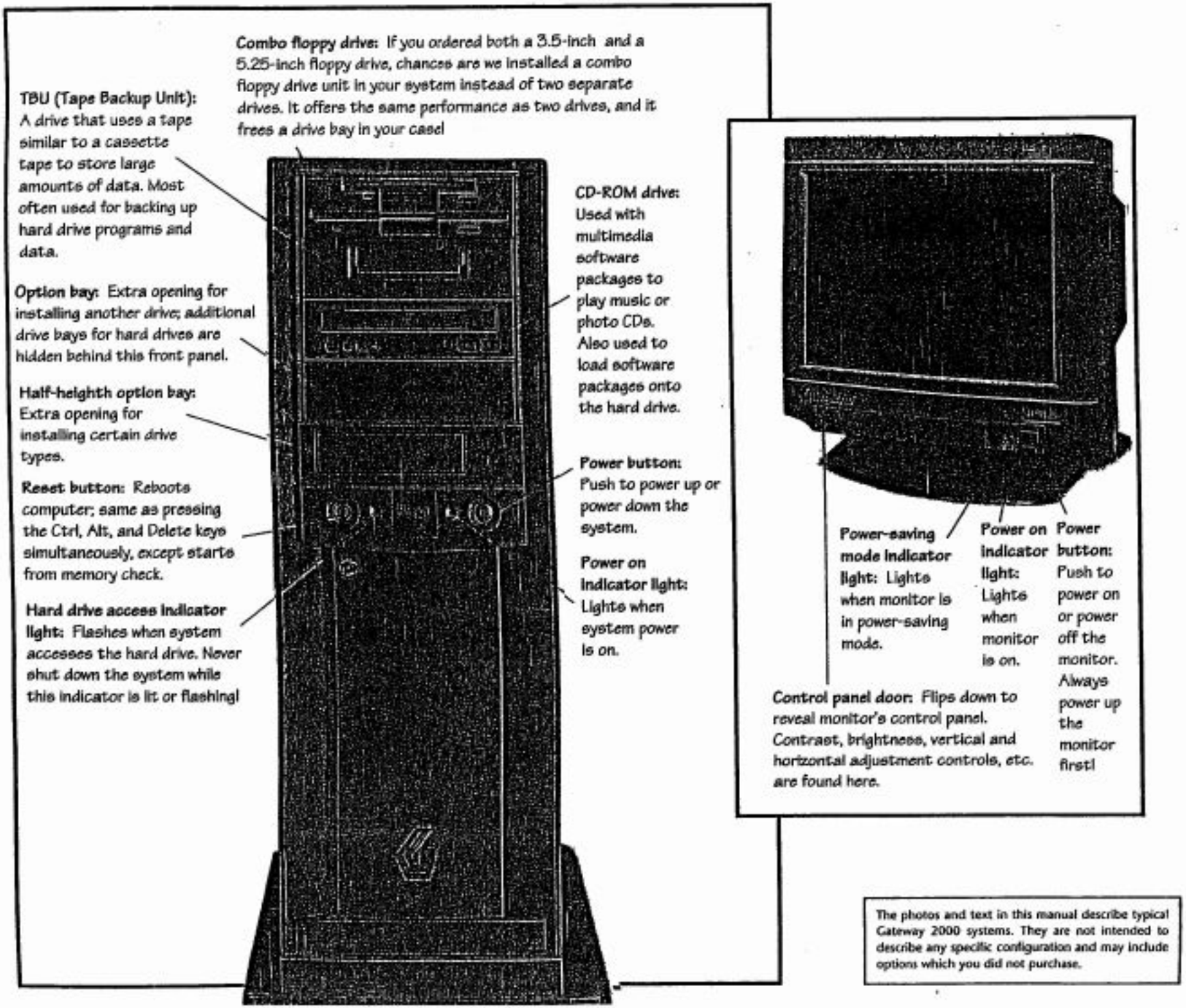
Click on [SHUTDOWN].

Choose “Shut down the computer” by clicking on that choice.

When the system is powered down, the microcomputer will automatically turn off. The monitor must be manually turned off.

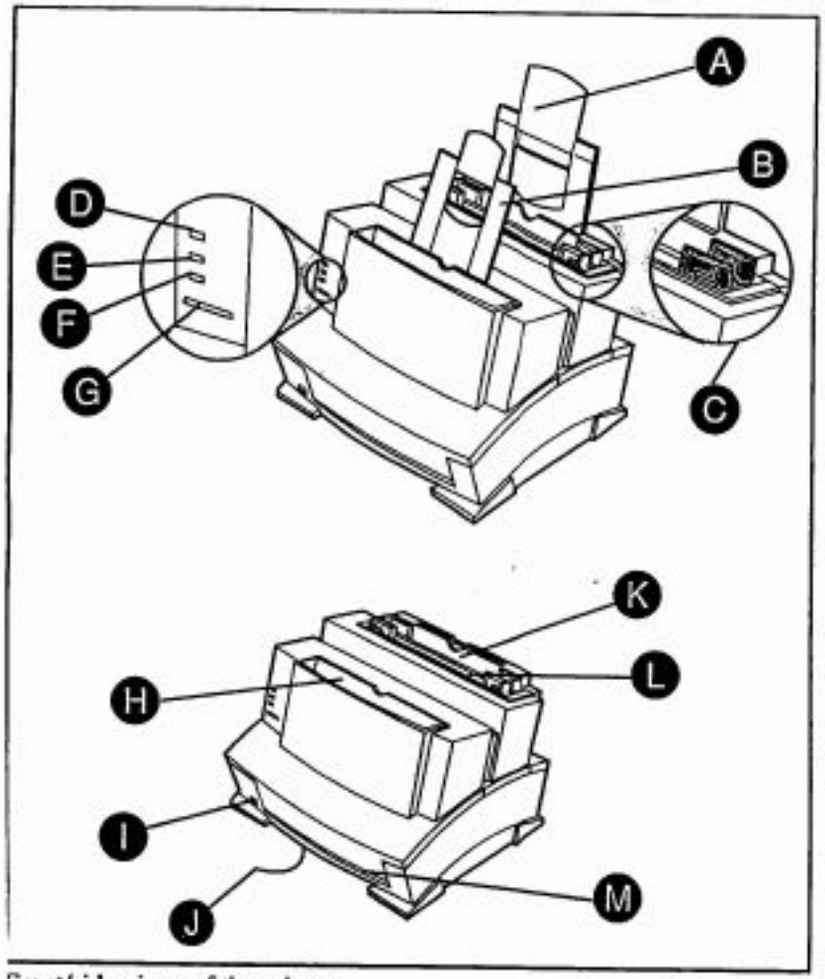
2.5 STARTING AND STOPPING THE DATABASE

To use any ACCESS function, the database must be available. After the Windows 95 log on, choose **Start Database** from the desktop. Before shutting down the system at night, choose **Stop Database**. It is very important to stop the database before shutting down the system since this operation makes sure all work in ACCESS has been copied to the database files.



The photos and text in this manual describe typical Gateway 2000 systems. They are not intended to describe any specific configuration and may include options which you did not purchase.

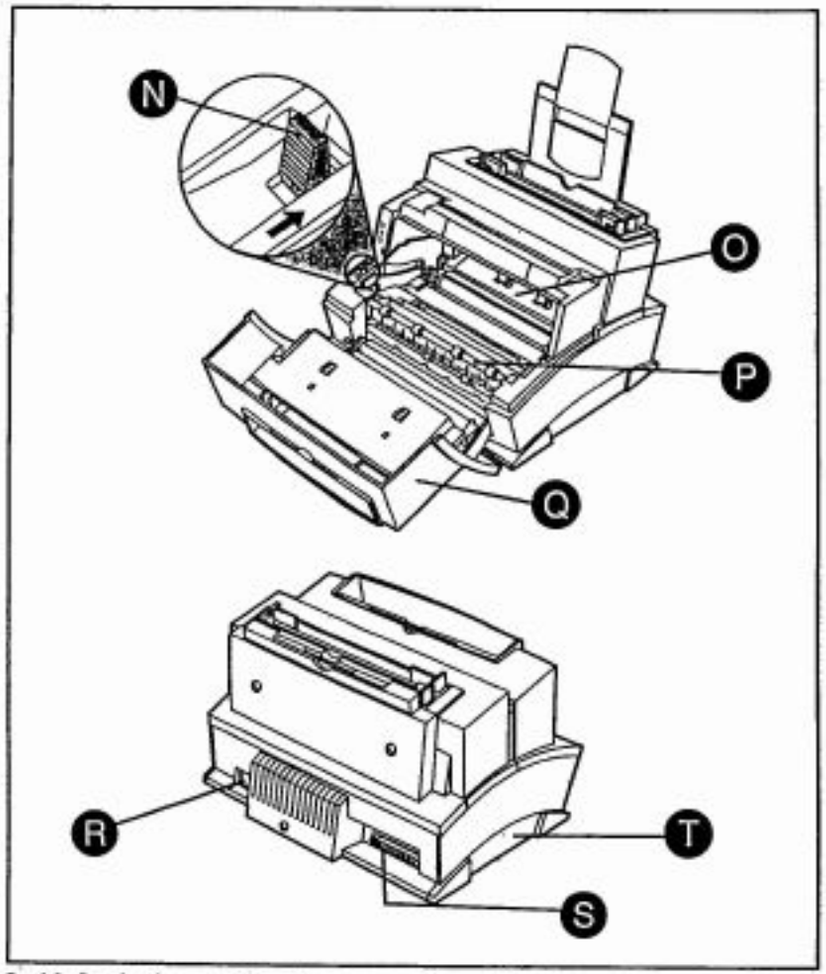
Step 1. Printer Parts and Locations (1 of 2)



Front/side views of the printer

A. Paper Input Support
B. Paper Output Support
C. Paper Guides
D. Error (top) Light
E. Data (middle) Light
F. Ready (bottom) Light
G. Front Panel Button
H. Paper Output Bin
I. Paper Path Lever
J. Serial and Model Number (bottom of the printer)
K. Paper Input Bin
L. Single Sheet Input Slot
M. Front Output Slot

Step 1. Printer Parts and Locations (2 of 2)



Inside/back views of the printer

N. Paper Release Lever
O. Toner Cartridge Compartment
P. Transfer Roller
Q. Printer Door
R. Power Cable Connector
S. Parallel Cable Connector
T. Memory Expansion Cover

This printer has no On/Off switch. The printer automatically switches to SleepMode (see "Attaching the Power Cord" later in this chapter).

Figure 2-3

Windows 95 Log in Screen

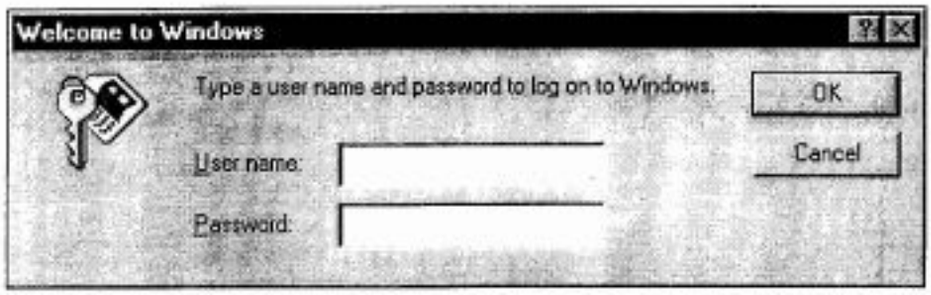


Figure 2-4

ACCESS Desktop

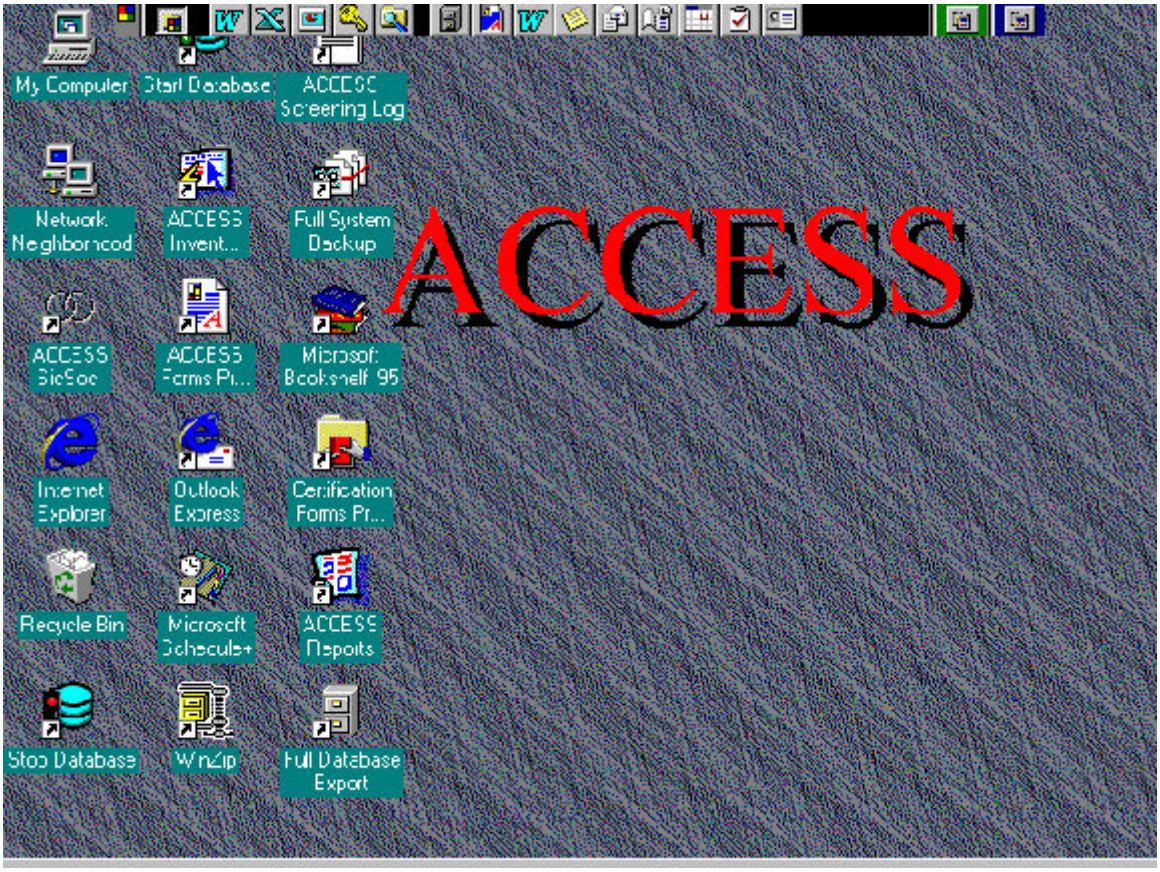


Figure 2-5

ACCESS Start Menu

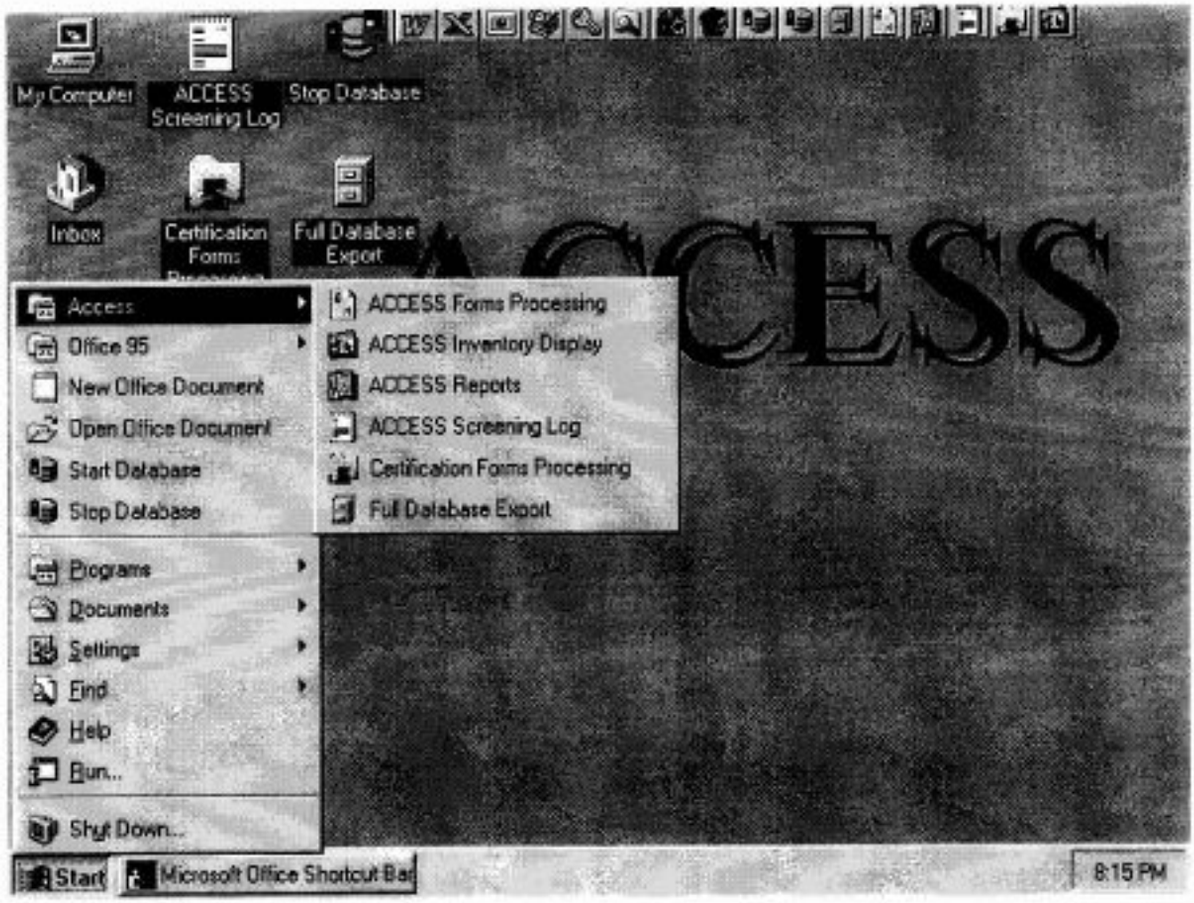
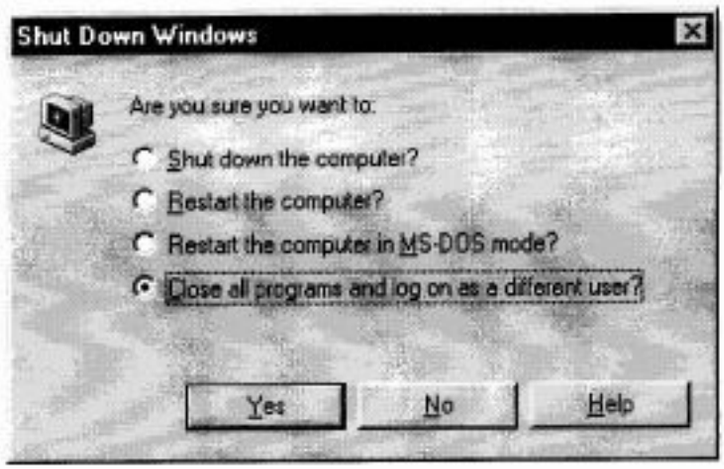


Figure 2-6

Windows 95 Shutdown



A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 3

FORMS PROCESSING

3.1 OVERVIEW

A primary function of the Distributed Data Management System for ACCESS is to facilitate the entry of ACCESS forms into the local database. The system is designed to be used with a mouse, a keyboard or both in combination. The main steps in performing data entry, corrections or display are:

Choose Forms Processing from the Desktop.

Log in to the database security screen.

Log in the Authorization screen.

Choose a form.

Choose a function.

Enter Case or Control Identifying Information.

Enter or correct data.

Review the form.

Save the form.

At the end of each session of data entry (original keying or corrections to previously keyed data), the data management system will automatically initiate an edit of the new or changed data from that session.

3.2 DATABASE SECURITY SCREEN

Figure 3-1 shows the database security screen. The database security screen is displayed whenever a database function is chosen such as Forms Processing, Reports, Screening Log, or

Data Transmission. This screen is used to insure that only ACCESS staff members, who are certified for data management functions, have access to the database systems. The user name and password are supplied in a sealed envelope for each Clinical Center. Clinical Coordinating Center staff have a copy of Security user names and passwords. It is very important to keep this information restricted to staff certified for data management functions.

Specific steps for database log in are:

Enter user name.

Press <TAB>.

Enter password. The password will be displayed as asterisks (*).

Press <ENTER> or click [OK].

3.3 AUTHORIZATION SCREEN

After successfully gaining access to the system, the **Authorization** Screen will be displayed (Figure 3-2). This screen allows a certified staff member to log into the ACCESS applications. Instructions for completing the screen are:

Click on *Certification Number*.

Enter user Certification Number.

(User name will be displayed).

Click [OK] or press <ENTER>.

If an invalid certification number is entered, a **Message Box** will appear (Figure 3-3). Click [OK] and enter a valid certification number. To exit, choose Exit on the *Action Menu* (see Section 3.4).

3.4 CHOOSING A FUNCTION, FORM, AND PARTICIPANT

After successfully gaining access to ACCESS forms processing functions, the **Form Process Selection** screen will be displayed (Figure 3-4). This screen allows selection of the

function to be chosen (data entry, correction or display), the ACCESS form to be processed by that function, and the identity of the case or control. The screen also shows the basic components of all ACCESS forms processing screens including the menu bar, message bar, and data entry area.

3.4.1 Menu and Message Bar

The **Menu Bar** is at the top of the screen (Figure 3-5). The individual menu items are *Action, Field*, Window*, and Help.* The commands for each item and their description is given below.

Action:

Clear All:	Clears all values in data entry area.
Print:	Prints a copy of this screen.
Exit:	Exits this screen, launches the edit of all newly entered and/or corrected forms, and takes user back to the ACCESS desktop.

Field:

Previous:	Moves the cursor to the previous item in the data entry area.
Next:	Moves the cursor to the next item in the data entry area.
Clear:	Clears the current item in the data entry area.
Duplicate:	Copies the last value entered into the current field.

Window:

Entries resize the window and are not useful for ACCESS functions.

Help:

Help:	Provides a message about the current screen.
List:	Lists allowable values for a list if one exists.
Display Error:	Displays the current error in the **Message Bar**.

To use any **Menu Bar**,

Click on individual menu item (*Action, Field,* etc.).

Click on the command within the menu item.

The **Message Bar** is at the bottom of the screen. This bar displays helpful messages such as a description of the current item, the number of forms in a list, and error messages during data entry.

3.4.2 Choosing a Form and Function

A list of forms is displayed in the **Select a Form** box (Figure 3-4). Note that there is a scroll bar to the right of the box. To search the list click on the up or down arrow. The scroll bar at the bottom of the box allows movement left or right to display a form with a longer name than the box can hold. Choose the desired form and Click [OK] or press <ENTER>. Alternatively, click [OK] and enter the form number in the box that appears and then press <ENTER>.

When the form has been selected, the number and name will be displayed at the top of the data entry area and the **Select a Form** box will close.

To choose a function, click on the [DOWN-ARROW] labeled *Function.* Choose *data entry, correction, or display*.

3.4.3 Identifying Information Screen

The identification information screen is used to specify the case or control for whom form data are to be entered or corrected. The items to be entered are Identification Number, Initials, Form Type (unless displayed), and Form Date. Either the mouse can be used to move among the items or press <ENTER> to move forward and <SHIFT-TAB> to move backward. When the items have been entered and checked, Click [OK] or press <ENTER>. It is very important to enter this information correctly. Check the participant identity before moving to the items on that form.

Items on this form are checked against other data in the database for that participant. If this is the first form entered for the case (Form 02) or control (Form 05) , the participant identity is established in the database. If this is another form, the participant identity is checked against previous data. If a Form 02 or Form 05 is entered in error and saved (Section 3.5), follow the procedures in Chapter 9. For other forms, the program lists any errors found in the **Message Bar** or in an **Alert Box**. Checks include identification number vs initials, visit date appropriateness, form expected for case or control, and valid form type. If an error message is displayed, click on the item in error, correct and click on [OK]. Figure 3-6 shows a complete Identifying Information screen.

3.4.4 Windows 95 Title Bar

Windows 95 displays a title bar for any application. In Figure 3-4, this is the bar at the top that is labeled ACCESS on the left with three raised rectangles on the right identified by an underscore (_), box (**9**), and X (X). These raised rectangles are called “buttons.” These buttons are not used for ACCESS functions. In particular, the X button will close the application and work will not be saved.

3.5 DATA ENTRY FORM SCREENS

The data entry form screens are designed to look like the ACCESS forms (Figure 3-7). For the most part, each screen is a page of the form. The certified Clinical Center staff member will enter response codes as they appear on the form, review the data entry and then save the form to the database. The staff member has the option of not saving the form. The data to be entered are the codes in parentheses next to the form items or a write-in response. The cursor will automatically move from item to item for 1 digit fields. Staff members may use the mouse or press <ENTER> for those items where the cursor does not automatically move from item to item. These

screens have a **Menu Bar**, **Message Bar**, and **Display Bar**. The message bar at the bottom of the screen is described in Section 3.4.1.

3.5.1 Display Bar

The **Display Bar** shows the form number, revision, participant identification number, form type, participant initials, and form date of the current form being processed at the top of the screen as an aid to the keyer. Information on the **Display Bar** cannot be changed.

3.5.2 Menu Bar

The **Menu Bar** (Figure 3-8) shows all the menu entries related to data entry, correction, and display of ACCESS forms. Depending on the function chosen, some menu items may be greyed out. Greyed out menu items are not available for the chosen function. The *Action* and *Field* menu items are described in Section 3.4.1. However, choosing Exit from the data entry screen will result in returning to the **Form Process Selection** screen and the form is not saved. The *Record* and *Query* menu items are described in Section 3.7.

3.5.3 Cursor Movement and Auto-Entry

The cursor is always positioned in the item that is about to be entered. For example. in Figure 3-7, the cursor is in the data entry area for item 3. Entry of the field will move the cursor to the next field and so on. One character fields always move automatically from one field to another. However, if a field is more than one character, the keyer must either press <ENTER> or move the cursor to the next field using the mouse. The *Field* menu item at the top of the screen can also be used to move to the Next Field. To move back an item, use the mouse, Previous Field on the *Field* menu item, or press [SHIFT-TAB].

3.5.4 Comment Field

Some items on ACCESS forms ask for specification of a write-in response. These are called Comment fields. If there is a write-in response, enter a 1 in the area for comments and a new comment screen will appear. For example, in Figure 3-7, item 6 requests a designation for race. If the race is other and there is a write-in response on the form, enter a 1 next to the Specify label. Figure 3-9 shows the **COMMENT** screen. Simply enter the text as shown on the paper form. The text will automatically wrap from line to line for long comments. When the comment has been entered, click [OK]. A **Message Box** will be displayed (Figure 3-10) showing that the comment has been registered. The data entry screen will then be displayed again.

The **Comment** screen displays the participant identifying information at the top, and a description of the item for which a comment is being entered. If there is not a comment, simply skip the Specify field (leave it blank) by pressing [ENTER]. The **Comment** screen will not appear. The two fields are always matched. A “1" in the Specify area is matched with a comment from the comment screen.

3.5.5 Checks During Data Entry

During data entry, all items are checked for valid codes. For example, if the preprinted codes for responses are 1 to 5, then only 1, 2, 3, 4, 5 or null is permitted. Items are checked for the correct format. For example, if a particular lab value is of the form xx.x then entering 8.23 will cause an error. Any errors encountered are displayed at the bottom of the screen in the **Message Bar**. Null is a special character to the database. It means nothing is entered and is different from actually entering blanks by pressing the <SPACE> bar. To enter a null, press <Enter> or skip the field using the mouse.

3.5.6 Saving the Form

Once all items have been entered, the form must be saved in the database. The steps are:

Click on *Action* in **Menu Bar**.

Choose Save by clicking on it.

A message will be displayed to review the entry.

To scroll through each page of the form, to ensure that all entries are correct, use the mouse to go to the last field on the current page and press <ENTER> to go to the next page.

Click on *Action* in **Menu Bar**.

Choose Save by clicking on it.

The form is now saved to the database.

Figure 3-11 shows the display when a form is saved to the database. When the form is saved, the **Form Process Selection** screen will be displayed so that the keyer can choose another case or control for the current form or another form, or another function or exit from form processing. If the keyer ends the data entry session by choosing Exit from the **Form Process Selection** screen, the edit for newly entered or corrected forms will be launched automatically and edit messages printed locally.

3.5.7 Exiting Without Saving

If the certified staff member decides not to save the form, then choose Exit from the *Action* item of the **Menu Bar**. The **Form Process Selection** screen will be displayed.

3.5.8 Statistics Displayed

At the bottom of the data entry area, the **Statistics Bar** is displayed whenever a new form is saved to the database, whenever a correction is made, or when a form is displayed for information. The information includes the certification number of the keyer, the date the form was keyed, the date the form was corrected, the form's status, the date the form was edited, and the

last date that the form was transmitted to the Clinical Coordinating Center for inclusion in the master database. The form status includes keyed, corrected, passed edit, and failed edit.

3.6 Edits

Edits are queries to the Clinical Center about data that are out of range or inconsistent with other data on the form. The edit program is launched automatically after a data entry session has been completed. All newly keyed forms or corrected forms are edited. Correction procedures are described in Chapter 3, Section 7. Edit procedures are described in Chapter 8. All forms that have been keyed, corrected or edited are transmitted to the Clinical Coordinating Center. Transmission procedures are described in Chapter 7.

3.7 MAKING CORRECTIONS

In response to edit messages (Chapter 8), certified Clinical Center staff will make corrections to the paper forms and to the electronic forms in the database. The basic steps are to choose the Correction function from the **Form Process Selection** screen. Select the form as in Section 3.4.2 and the identifying information as in Section 3.4.3. Choose Correction from the *Function* list. If the identifying information is correct, the data entry form screen will be displayed. To correct an item, use the mouse or press <ENTER> until the item to be corrected is highlighted. Clear the previously entered data from the item by using Clear Field in the *Field* item of the **Menu Bar,** or by using the mouse to delete it or by using the <DELETE> or <BACKSPACE> key on the keyboard. Enter the correct value. All corrections are automatically logged in the database including the date corrected, the item corrected, and the certification number of the staff member making the correction.

The same checks that occur during data entry also occur during correction. Comments may be added or deleted as described in Section 3.5.4. Section 3.5.6 describes how to save the form. Section 3.5.7 describes how to exit the Correction function without saving.

Some continuous values such as laboratory values may exceed the normal edit ranges (but not the human ranges) and are subsequently verified as correct by reviewing the participant's records. In these cases, the edit message will specify that the item is "Out of Normal Range". To verify that the item has been verified as correct, double-click on the item. A **Dialog Box** will be displayed (Figure 3-12). Click [OK] to verify the value. For items out of normal range, this verification and subsequent save of the form will suppress the edit query for this item.

The values for some items may not be retrievable. In this case, enter the "not available" code. Codes are given in Table 3-1, page 3-35. It is a series of 9"s followed by an 8 in the last place.

To enter a not available code, click on the item that you want to set to the not available code. Choose Clear Field from the *Field* item of the **Menu Bar**. Enter the appropriate not available code. Press <ENTER> twice.

3.8 DISPLAYING A FORM

A staff member may want to review a form or group of forms in the database. Choosing the *Display* Function from the **Form Process Selection** will allow display of a form or group of forms. The groups may be sorted in ascending or descending order.

3.8.1 Menu Bar

Figure 3-8 shows the **Menu Bar**. When display is chosen, the *Record* and *Query* menu items are available for use. A description of these menu items is given below.

Record:

Previous: Display previous form of this group.

Next: Displays next form of this group.

Clear: Clears the current query.

Query:

Enter: Enter the characteristics of the form or forms for display.

Execute: The query will be executed and the form or forms displayed one by one.

Last Criteria: Use the last query criteria for this query.

Cancel: Cancels execution of a query.

3.8.2 Entering a Query

A query is the selection of a form or group of forms for display. No data may be changed when using the *Display* function. The steps to enter a query are:

Choose a form and function as described in Section 3.4. Do not enter participant identification information (Figure 3-13).

Click [OK].

The **Query** Screen is displayed (Figure 3-14).

There are 3 choices:

1. Click on *Query* in the **Menu Bar** and choose Execute (Figure 3-15).

All participants who have the form selected will be displayed one by one in ID Number order.

To go to the next form, use the <DOWN-ARROW>.

To go to the next page of this form, press <ENTER> to navigate through the items on the form.

2. Click on *Query* in the **Menu Bar** and choose Enter.

Double-click on any item on the **Query** Screen.

A **Dialog Box** will be displayed (Figure 3-16). Choose Ascending or Descending sort order.

Navigate through the forms retrieved as above.

3. To look at a form for a particular participant, click on the ID field and enter the ID number.

Click on *Query* in the **Menu Bar** and choose Execute.

Navigate within the form as described above.

3.9 Data Management Certification

All ACCESS Clinical Center staff who perform data management duties must be certified to do so. Procedures are outlined in Volume I, Section 10.3. Staff are required to key three forms for each of two participants to satisfy the data entry requirement. These completed forms (Forms 10,12, and 22) will be sent to each Clinical Center for use in certification. Clinical Coordinating Center staff have set aside two training certification numbers which are of the form XXX-98 and XXX-99; XXX is the Clinical Center number. Four participant Identification numbers and four participant initials have been set aside so that two Clinical Center staff may complete certification requirements at the same time. These identifications are participant number XXX-9996, initials VVV; XXX-9997, initials WWW; XXX-9998, initials YYY; and XXX-9999, initials ZZZ, XXX is the Clinical Center number.

To satisfy certification data entry requirements, choose ACCESS Certification Forms Processing from the ACCESS desktop. The **Authorization** Screen will be displayed. Follow the procedures for entry in Section 3.3. A special certification screen will be displayed (Figure 3-17). Enter the Clinical Center staff name requesting certification, the certification number (XXX-98 or XXX-99), and the participant identification number to be used for certification (one of XXX-9996 through XXX-9999). Click [OK]. If an incorrect certification number is entered or an incorrect participant Identification number is entered a **Message Box** will be displayed (Figures 3-18 and 3-19). If there are no errors, a **Message Box** will be displayed asking if the training certification number and training participant number should be saved (Figure 3-20). Click [Yes]. A **Message**

Box will be displayed indicating the information has been saved (Figure 3-21). Acknowledge the message by clicking [OK]. The **Form Process Selection** screen will be displayed (Figure 3-22). However, only Forms 10, 12, and 22 may be selected. Select the form to be entered and choose *Data Entry* as the function as described in Section 3.4 , and key and save the form as described in Section 3.5. Key one set of Forms (Form 10, 12, and 22) for a participant ID number. Repeat the entire process using the same certification number and a different participant ID number for the second set of Forms (Forms 10, 12, and 22). After the six forms are transmitted to the Clinical Coordinating Center and reviewed for accuracy, a permanent Data Management certification number will be assigned to the Clinical Center staff member who keyed these forms.

Figure 3-1

Database Security Screen

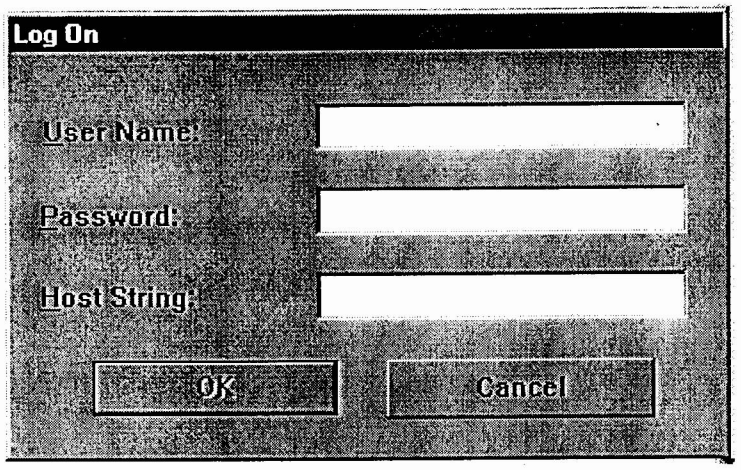


Figure 3-2

Authorization Screen

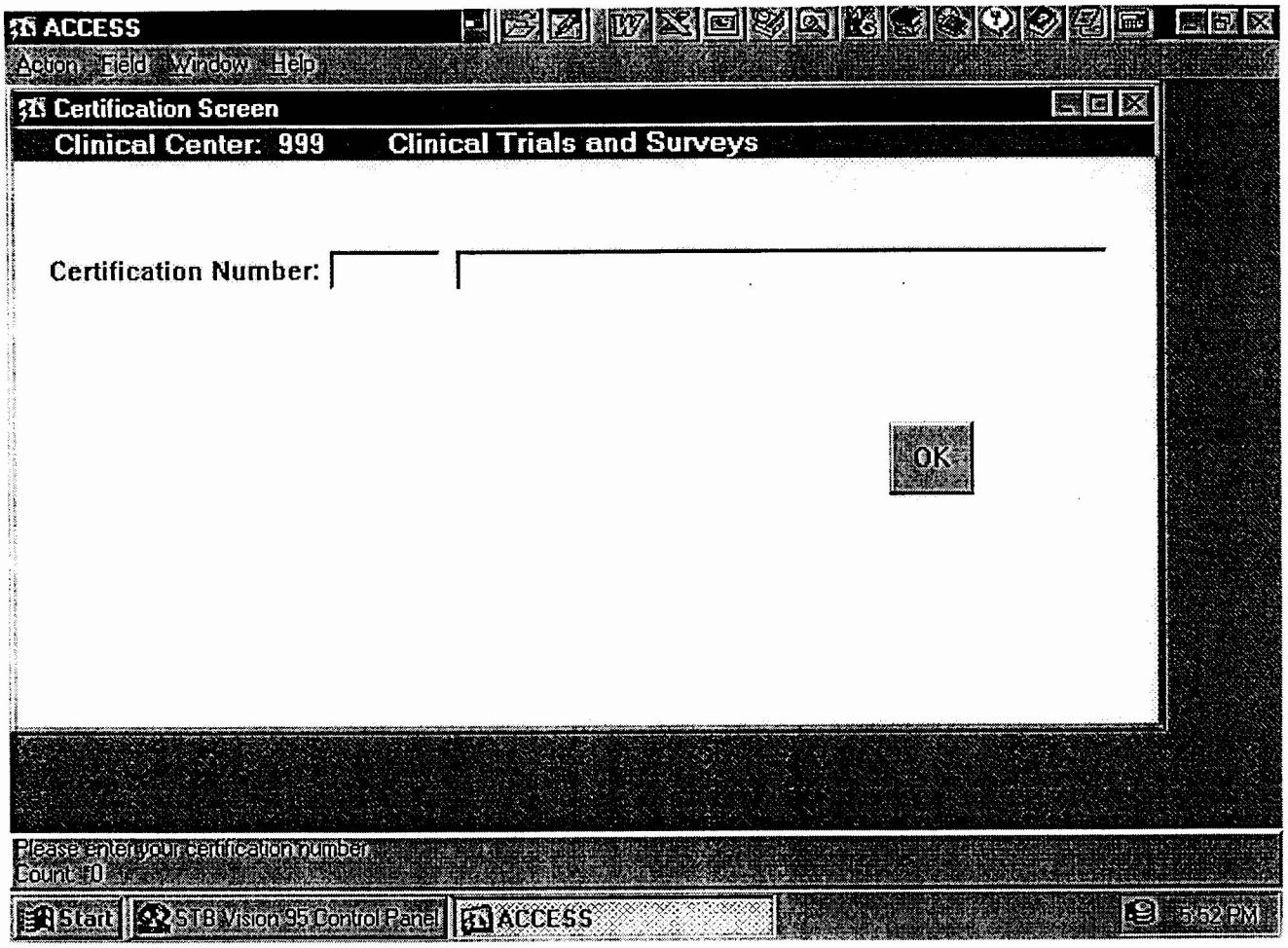


Figure 3-3

Invalid Certification Message Box

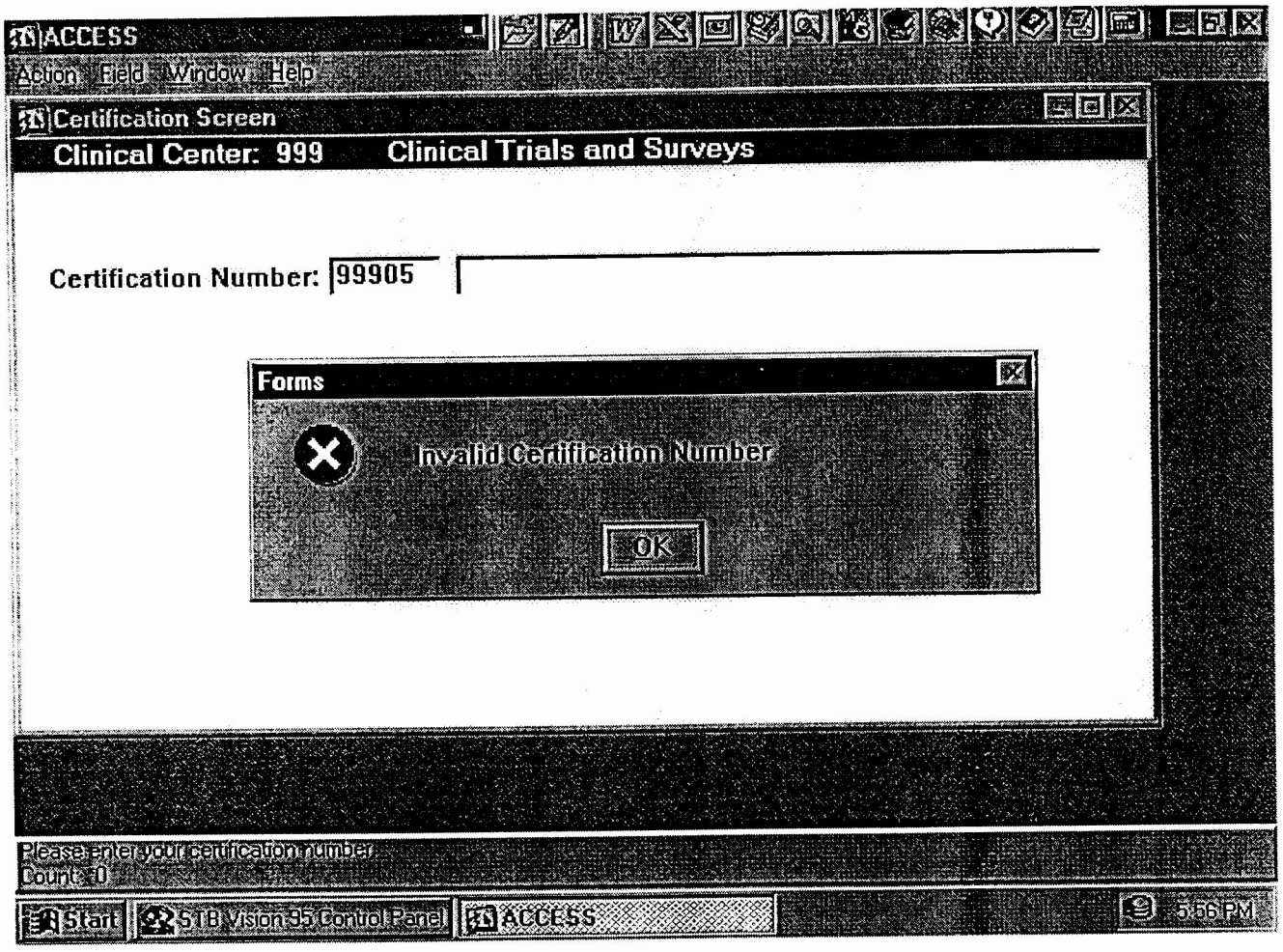


Figure 3-4

Form Process Selection Screen

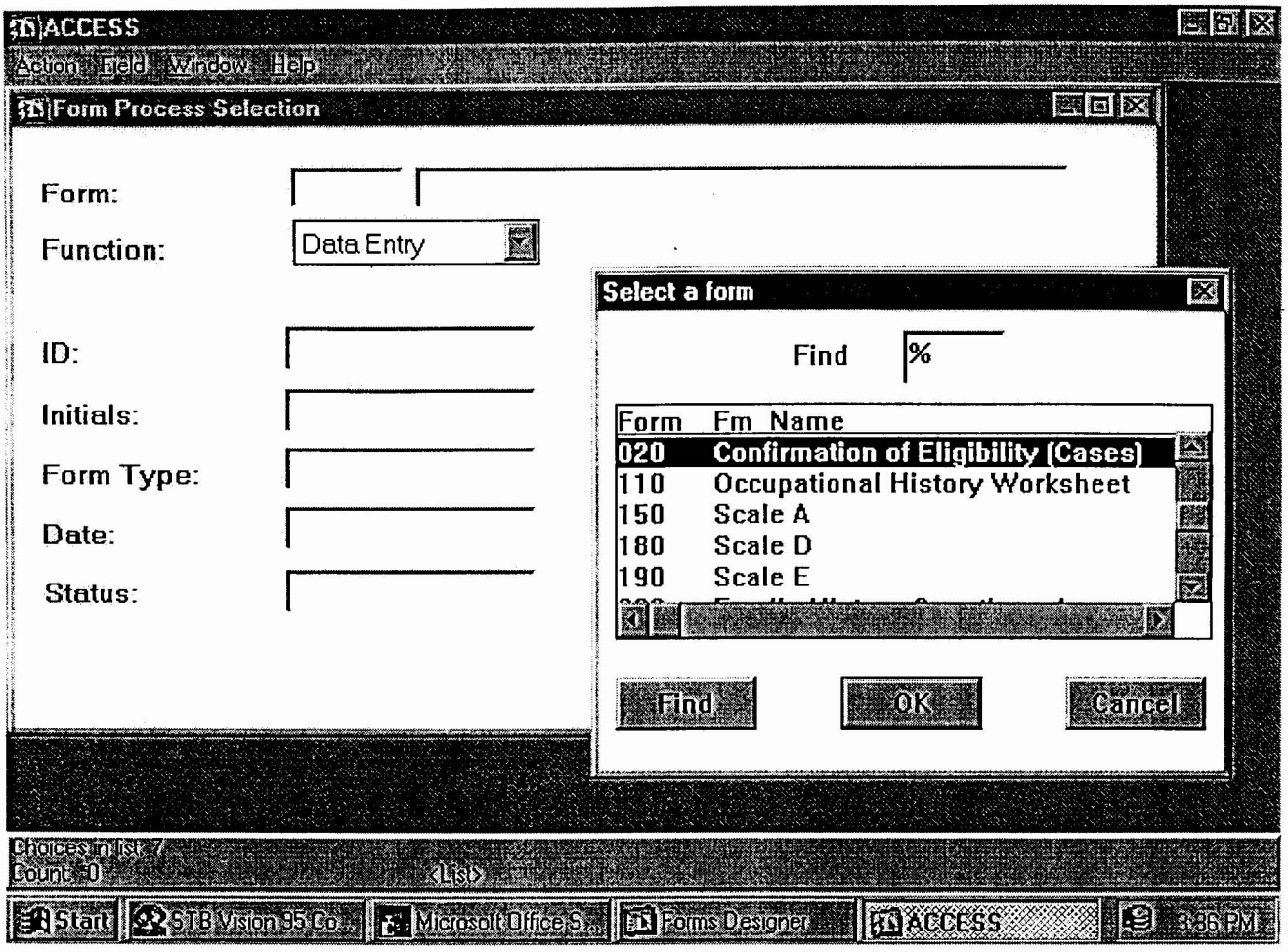


Figure 3-5

Main Menu Bar

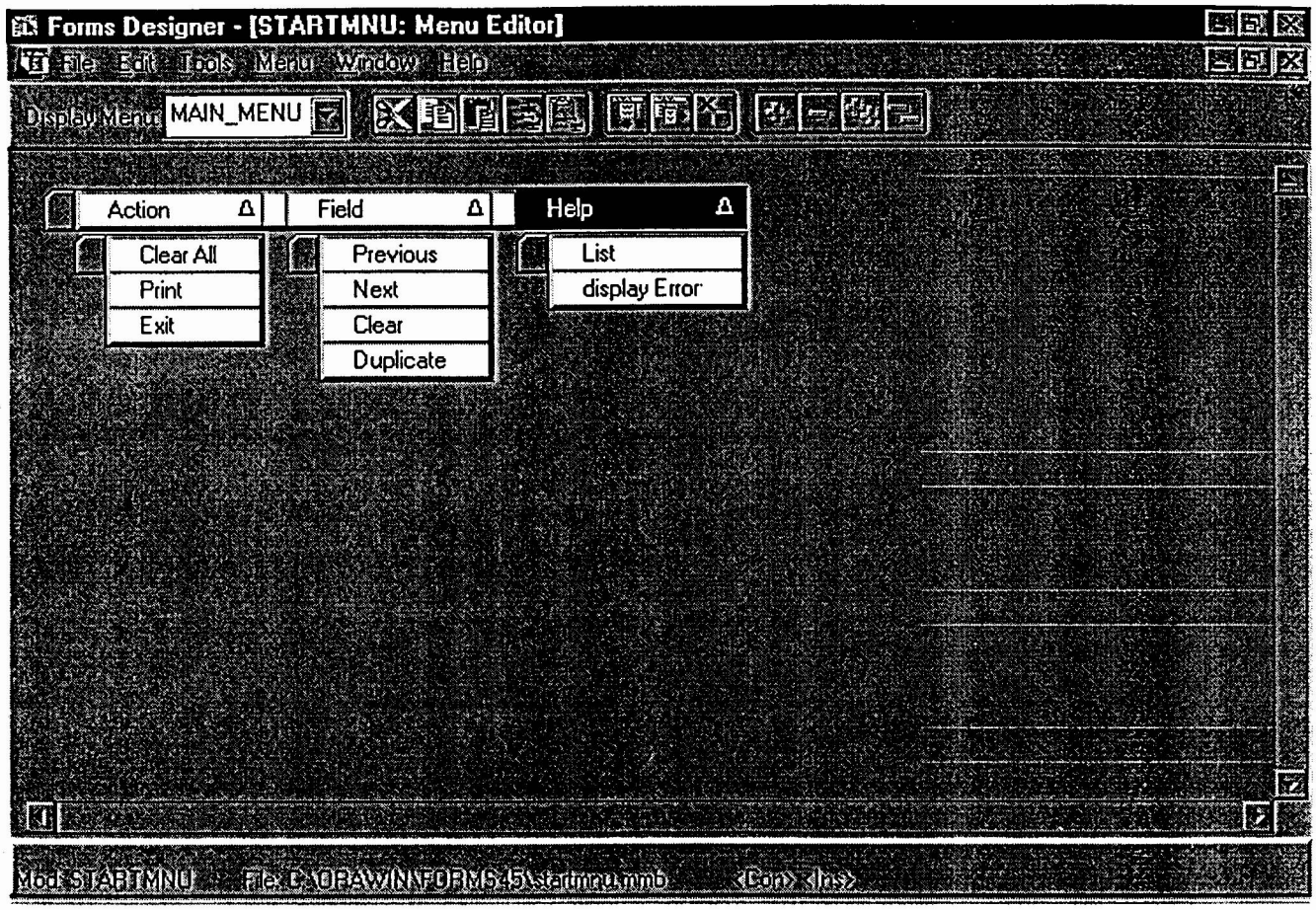


Figure 3-6

Sample Form Process Selection Screen

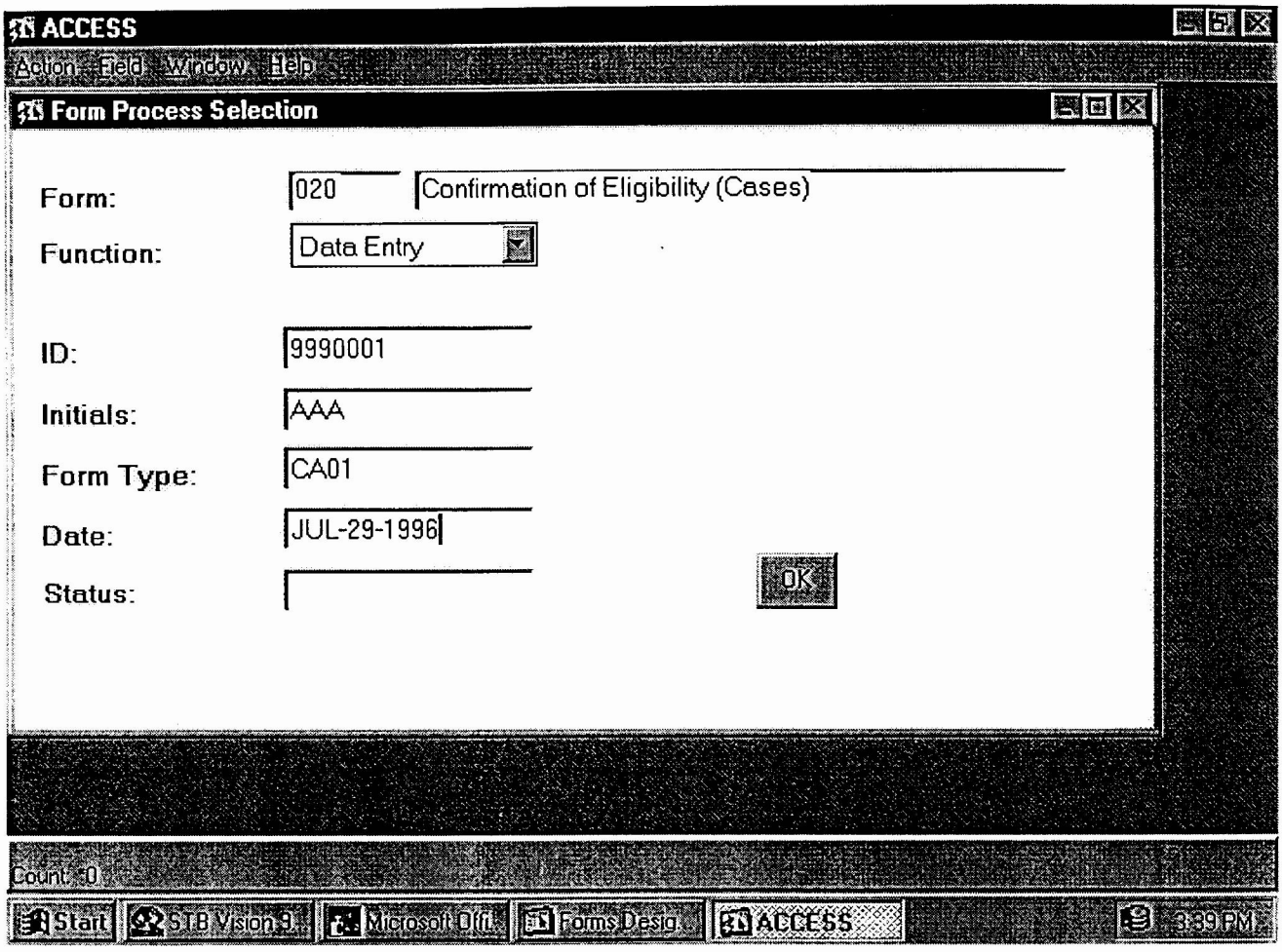


Figure 3-7

Sample Data Entry Screen

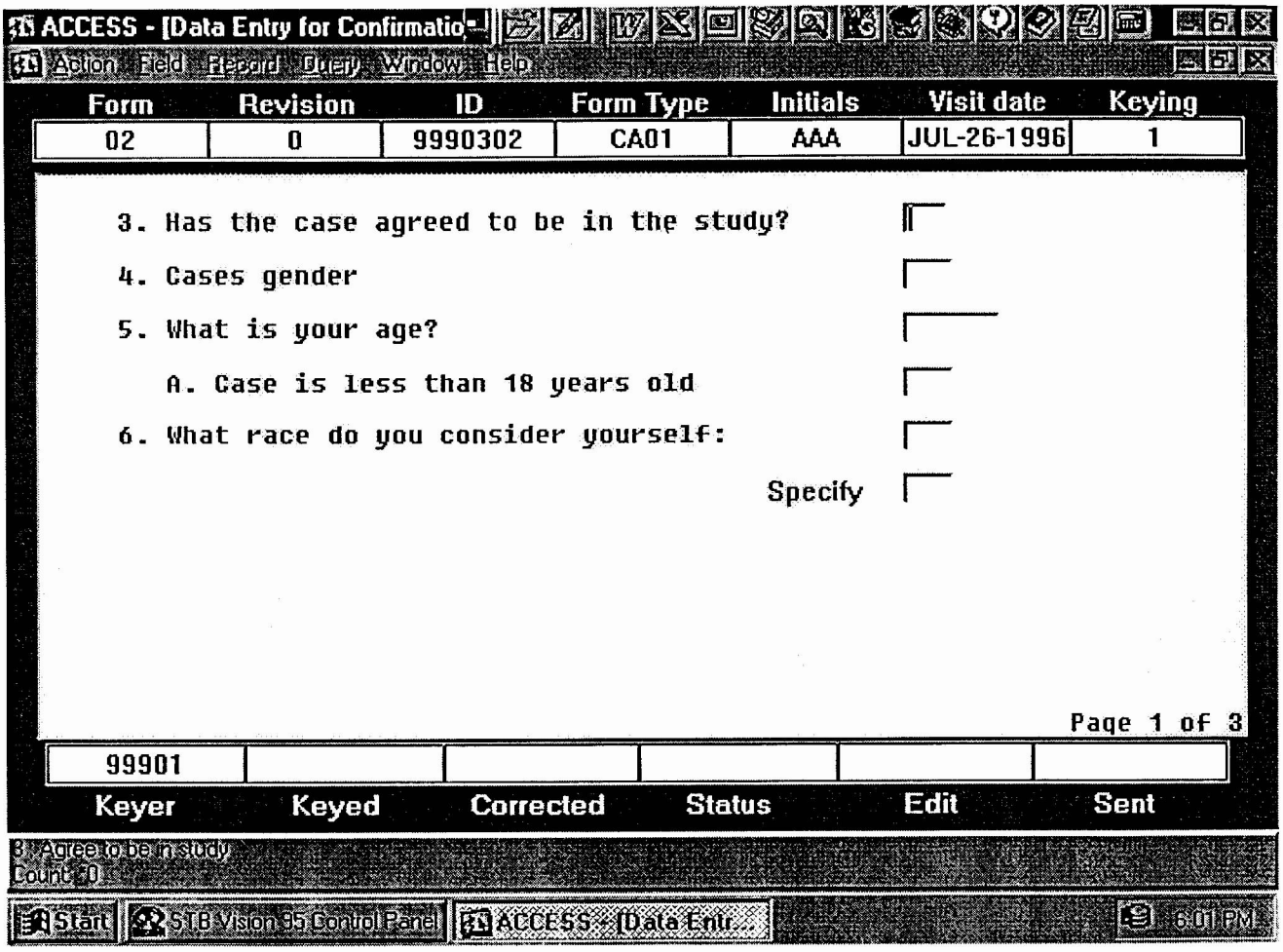


Figure 3-8

Data Entry, Correction and Display Menu Bar

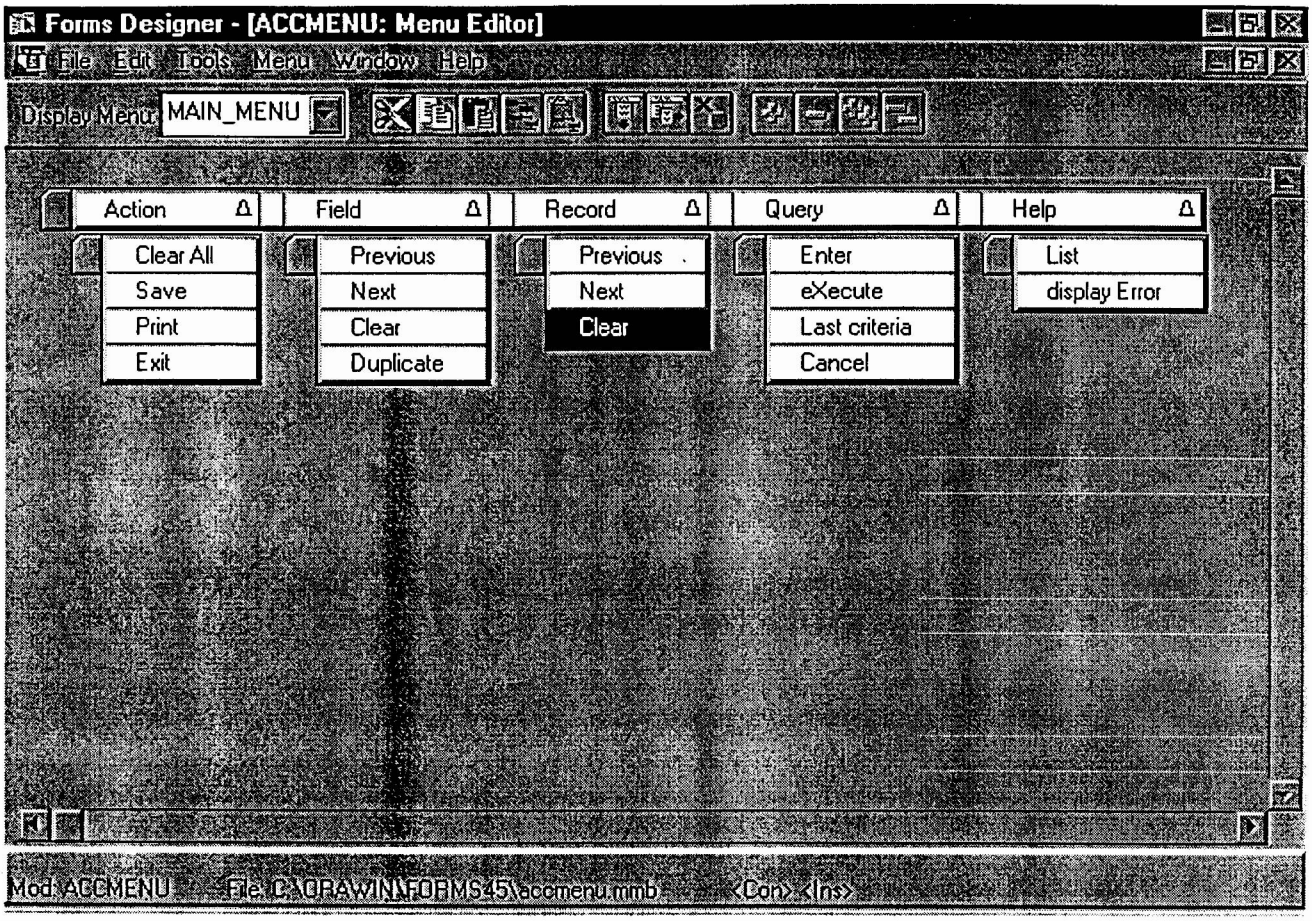


Figure 3-9

Comment Screen

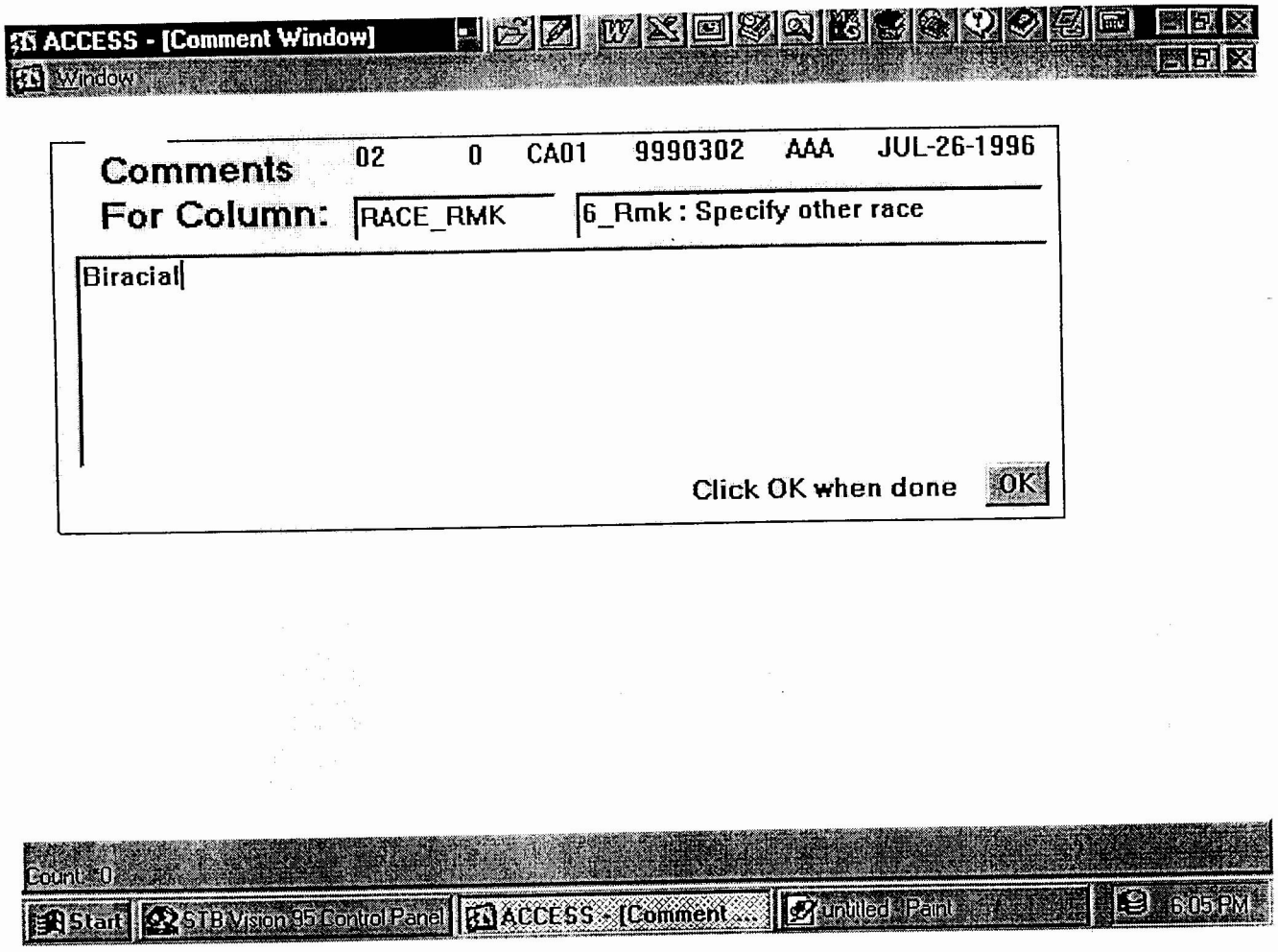


Figure 3-10

Comment Screen Message Box

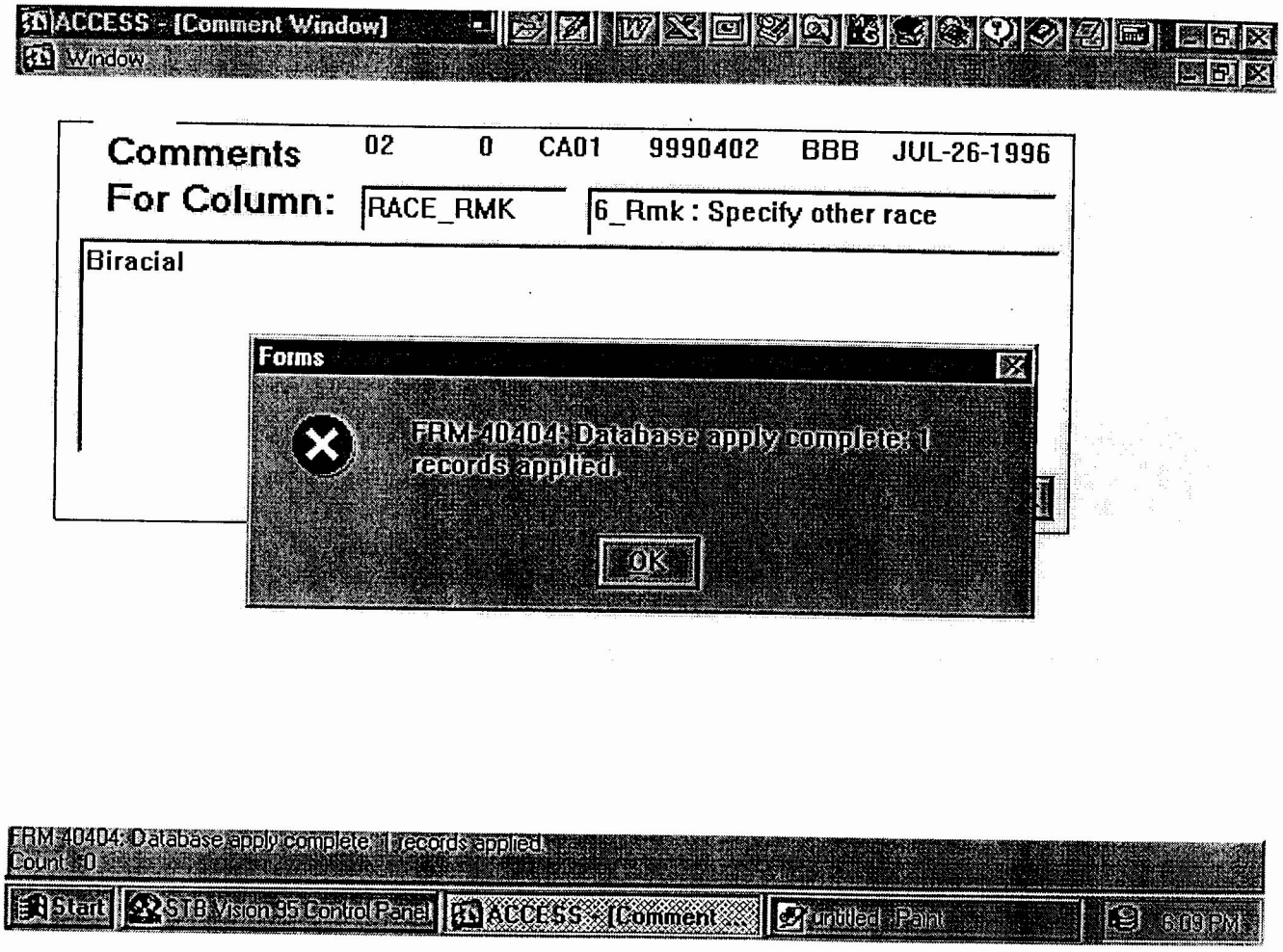


Figure 3-11

Form Save Message Box

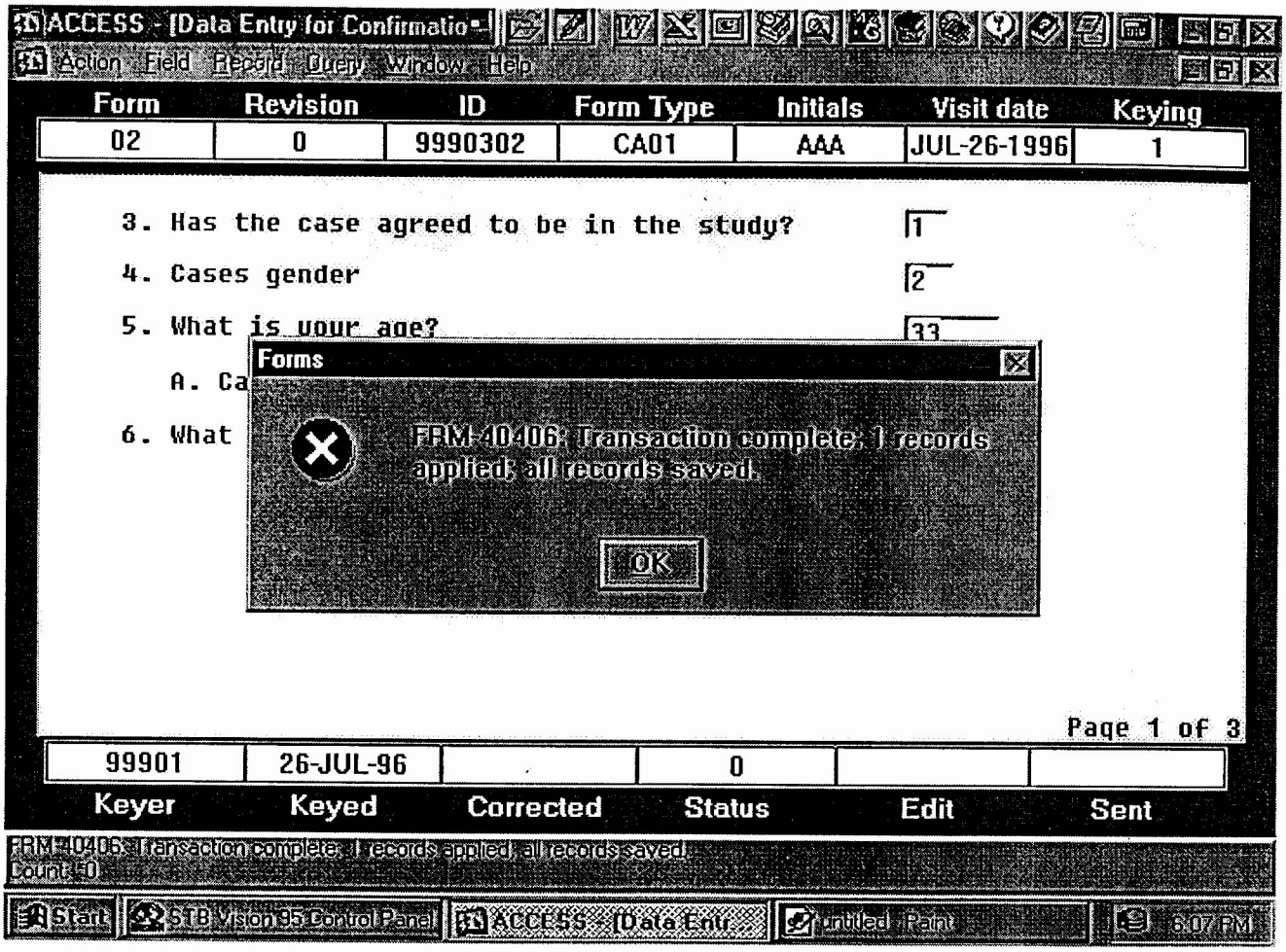


Figure 3-12

Continuous Value Verification Dialog Box

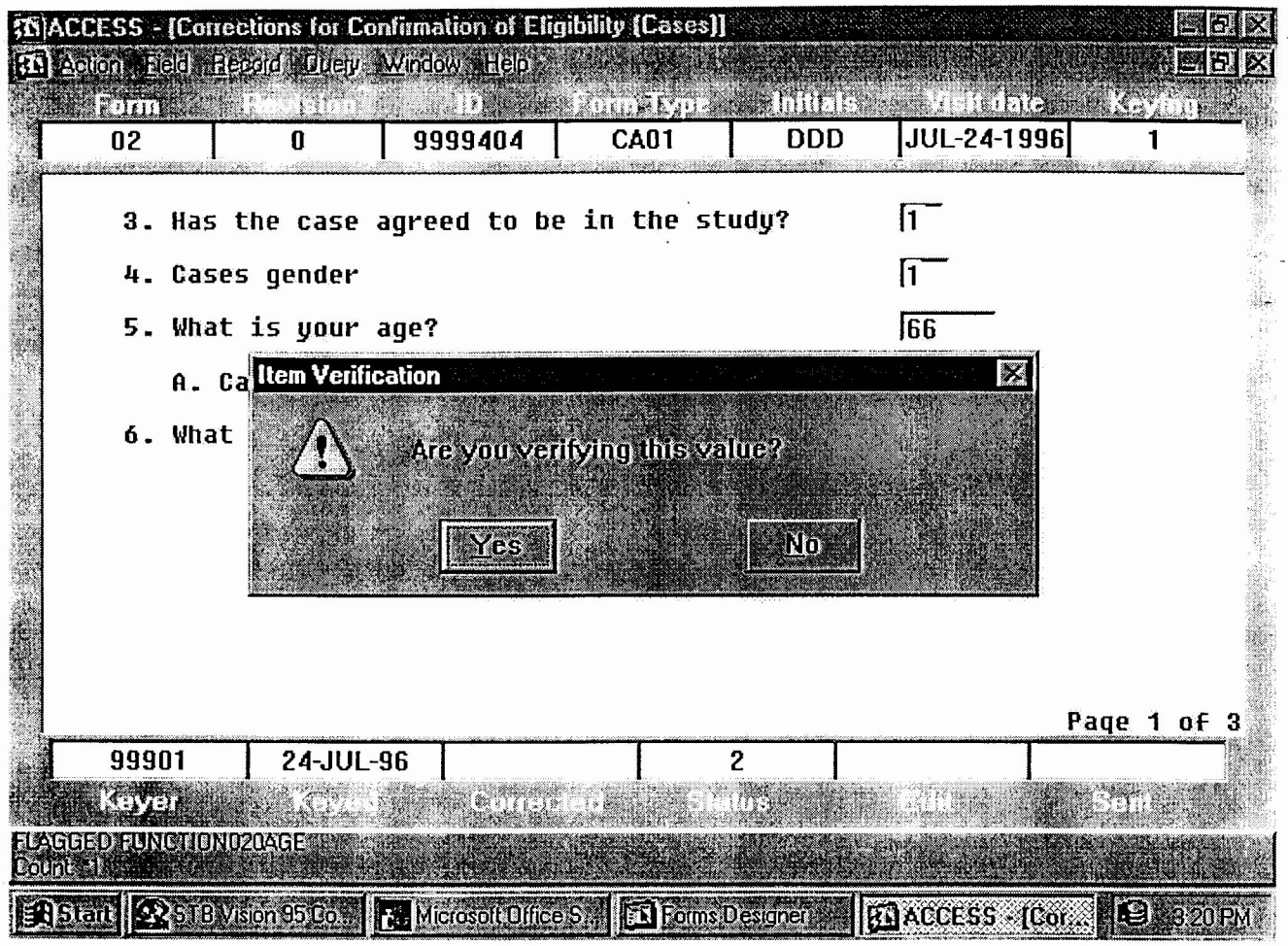


Figure 3-13

Query Form Process Selection Screen

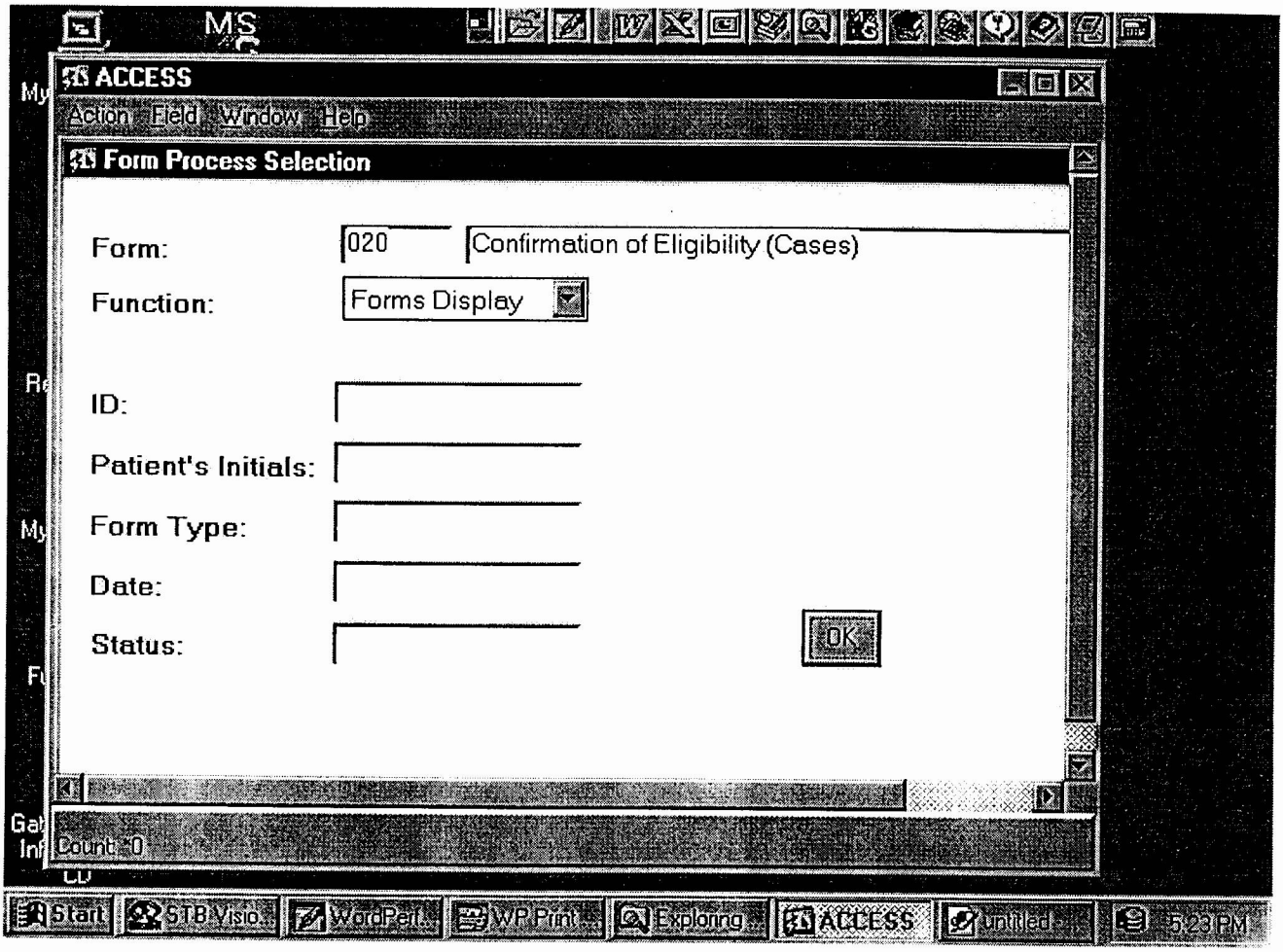


Figure 3-14

Query Screen Entry

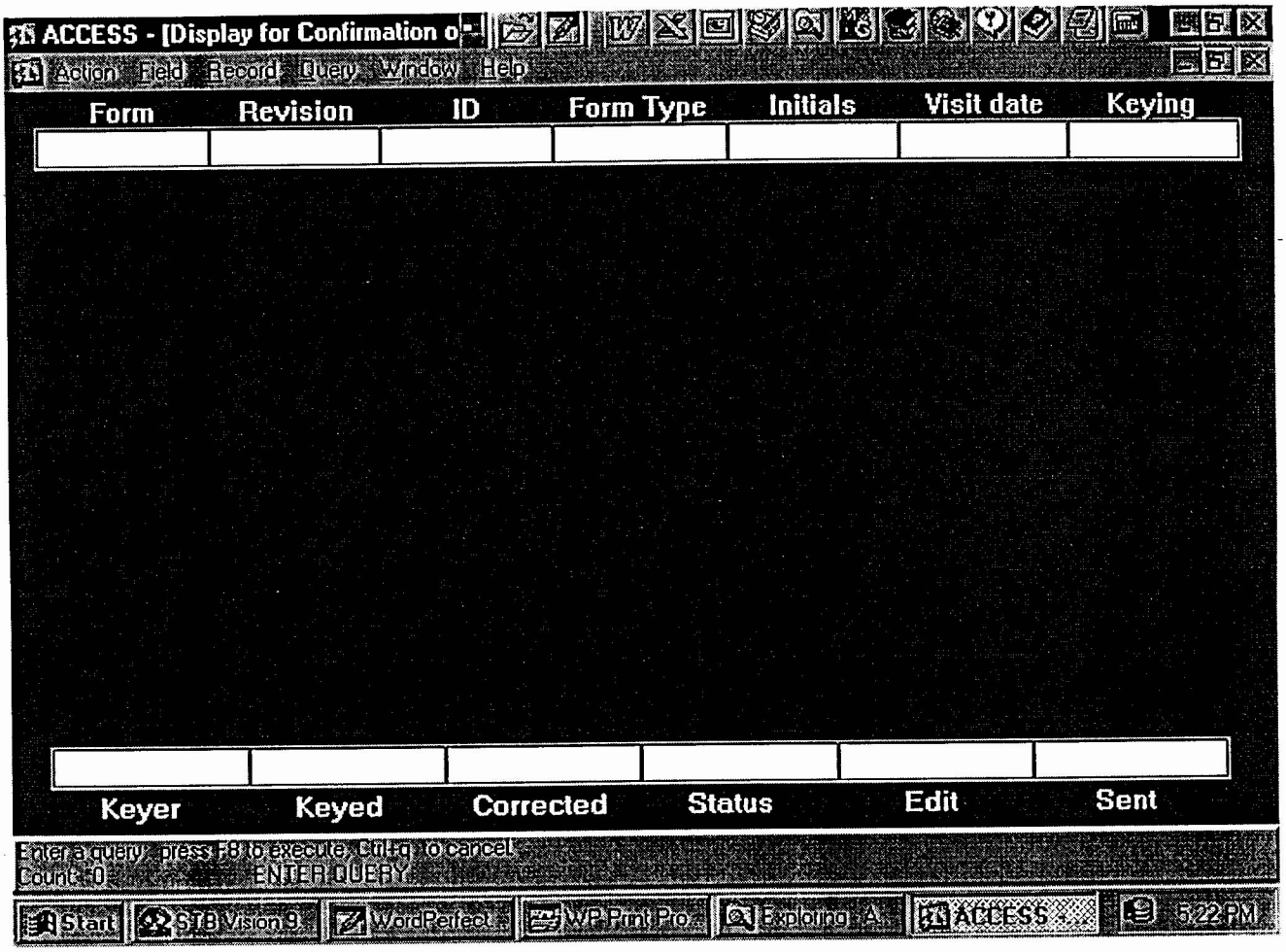


Figure 3-15

Query Screen Execution

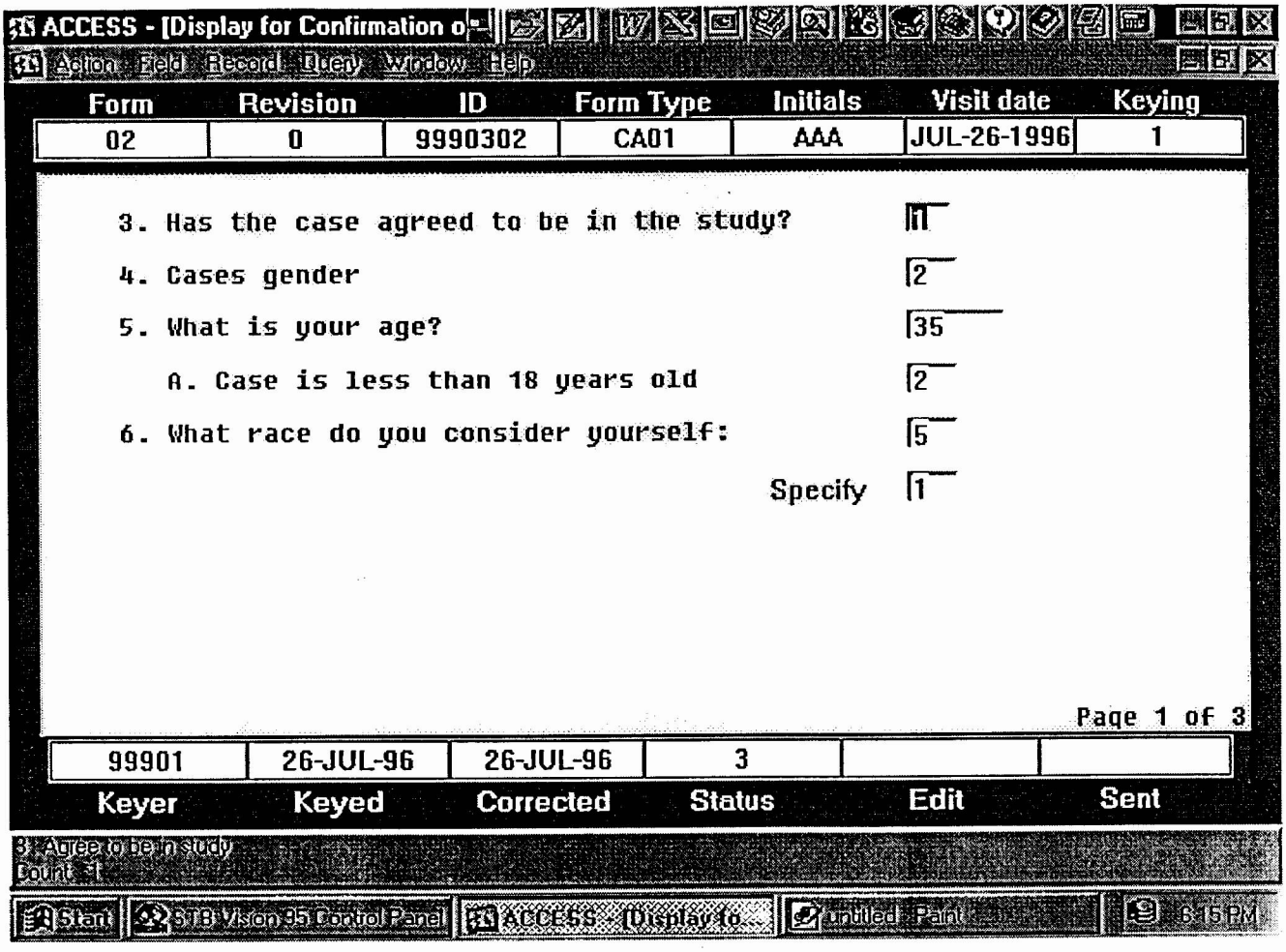


Figure 3-16

Query Screen Sort Order

Figure 3-17

Data Management Certification Screen

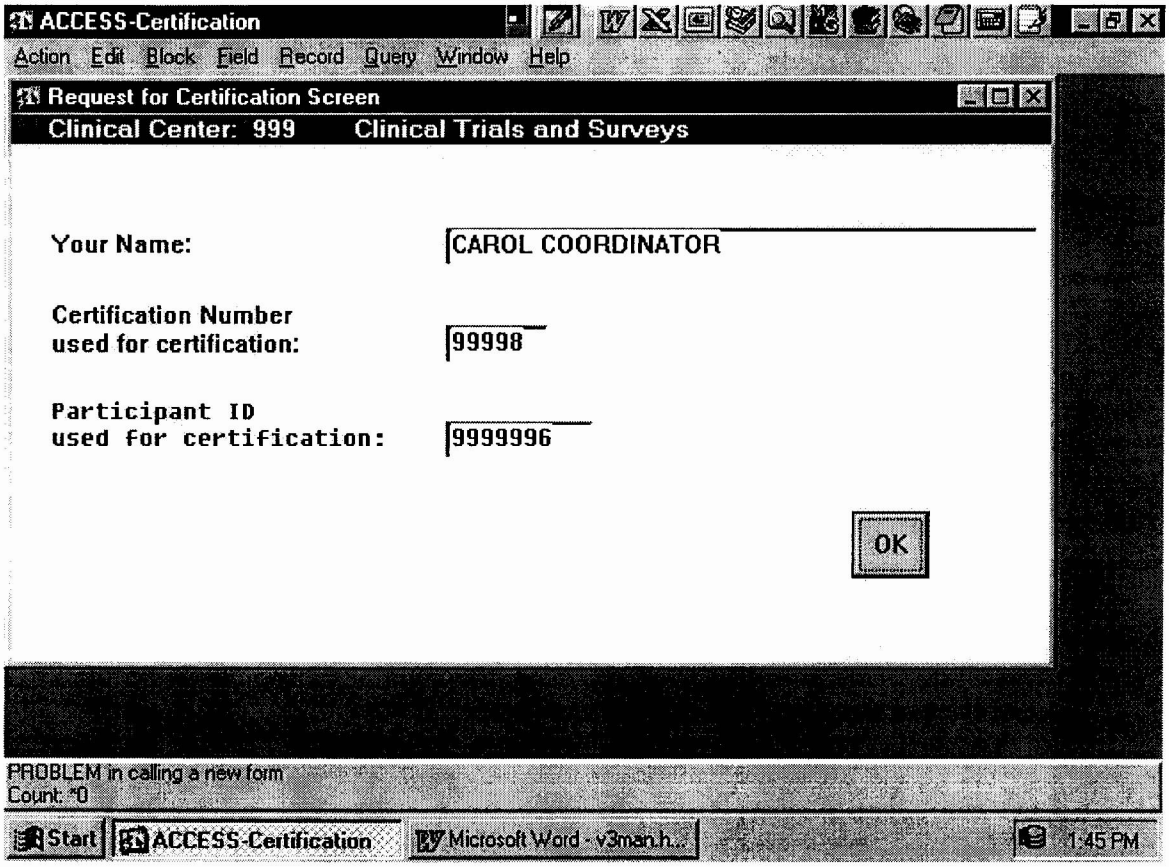


Figure 3-18

Invalid Certification Number Message Box

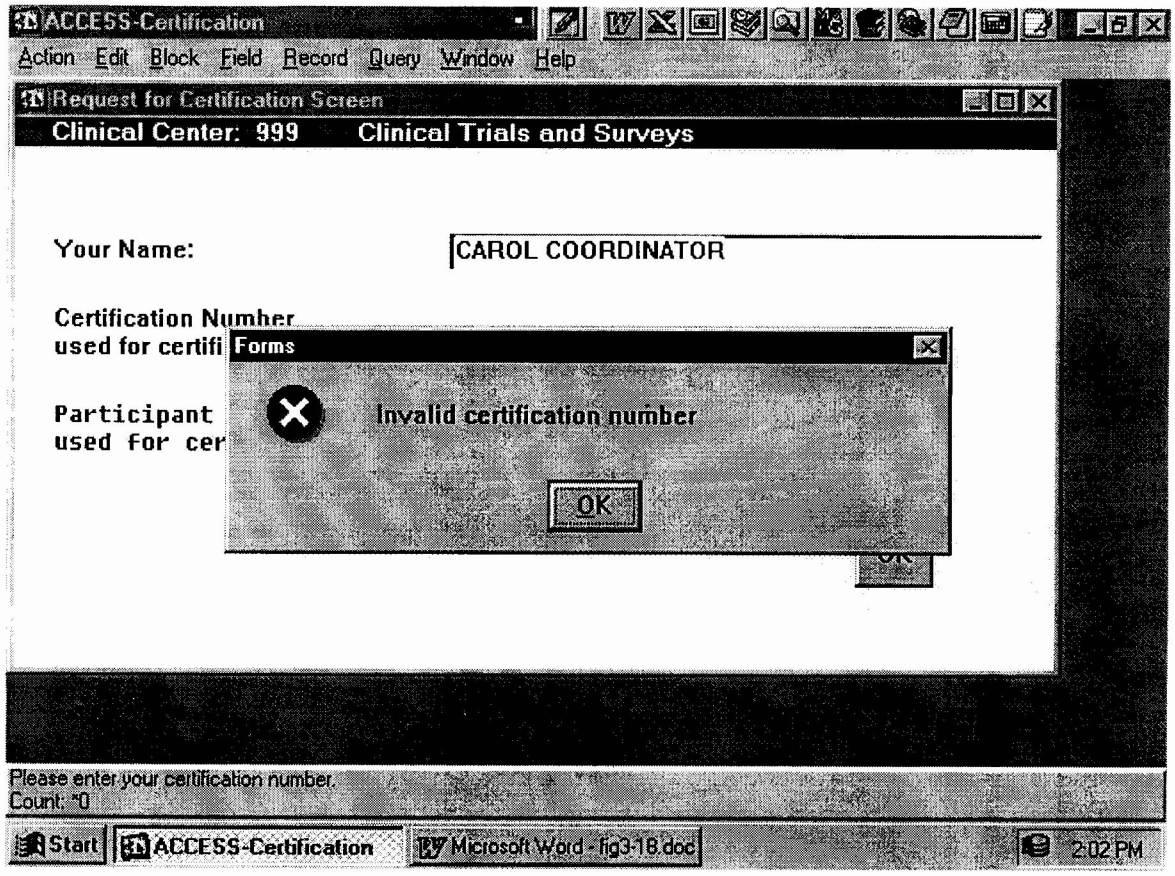


Figure 3-19

Invalid Participant for Certification Message Box

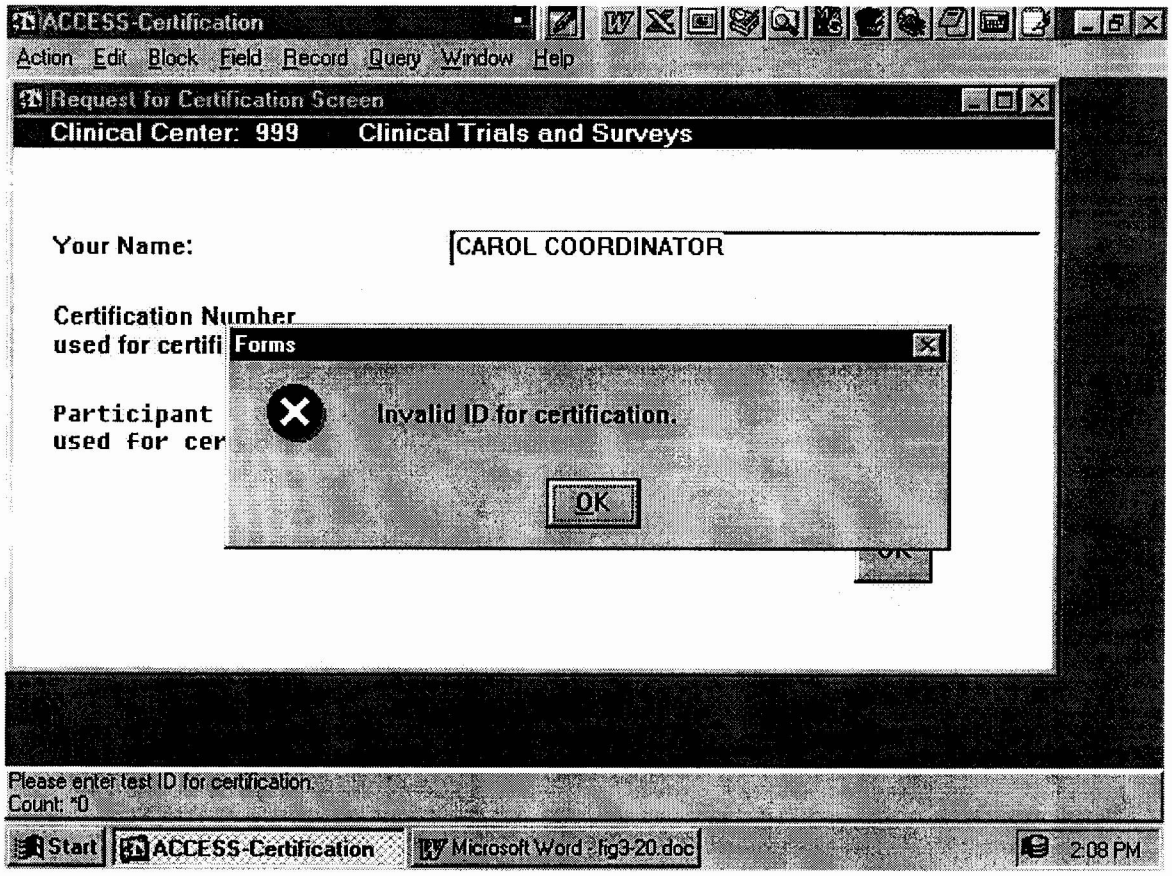


Figure 3-20

Saving Certification Name and Temporary Number

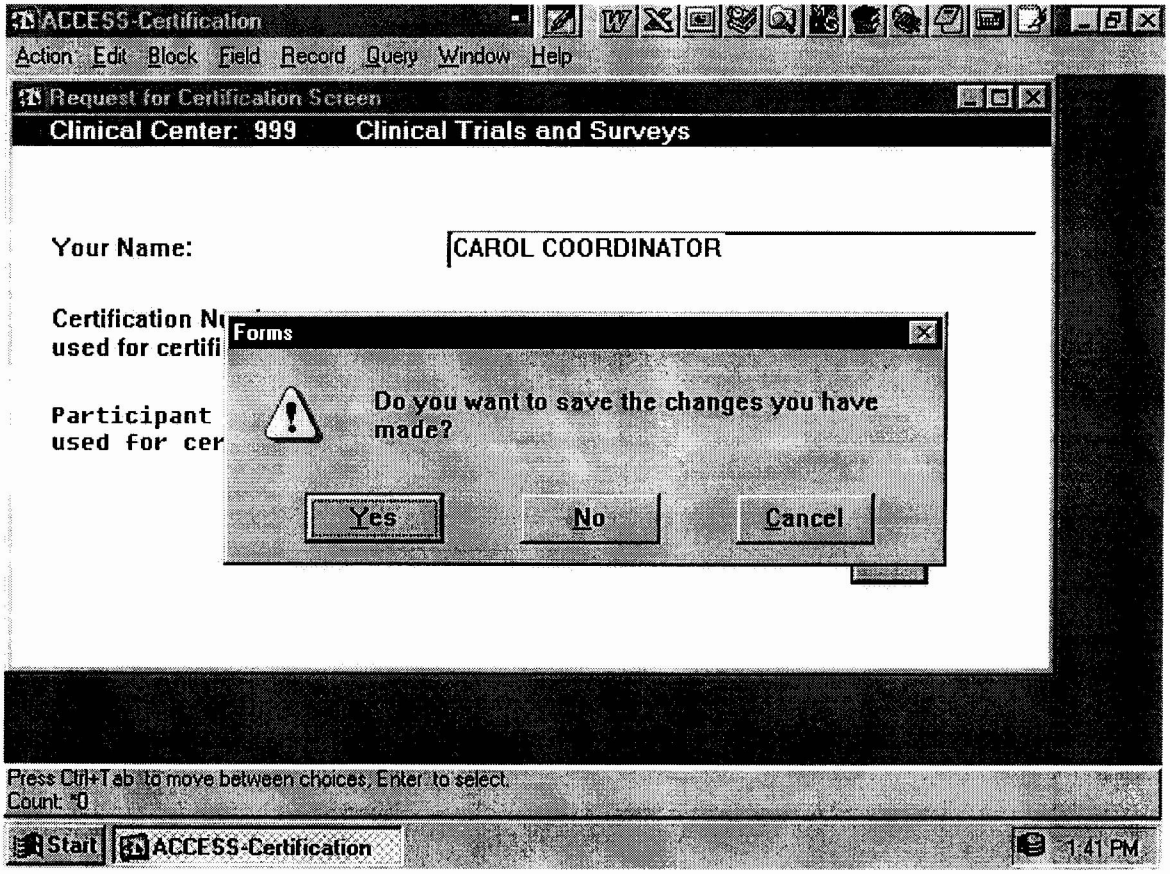


Figure 3-21

Save Participant ID Number for Certification Message Box

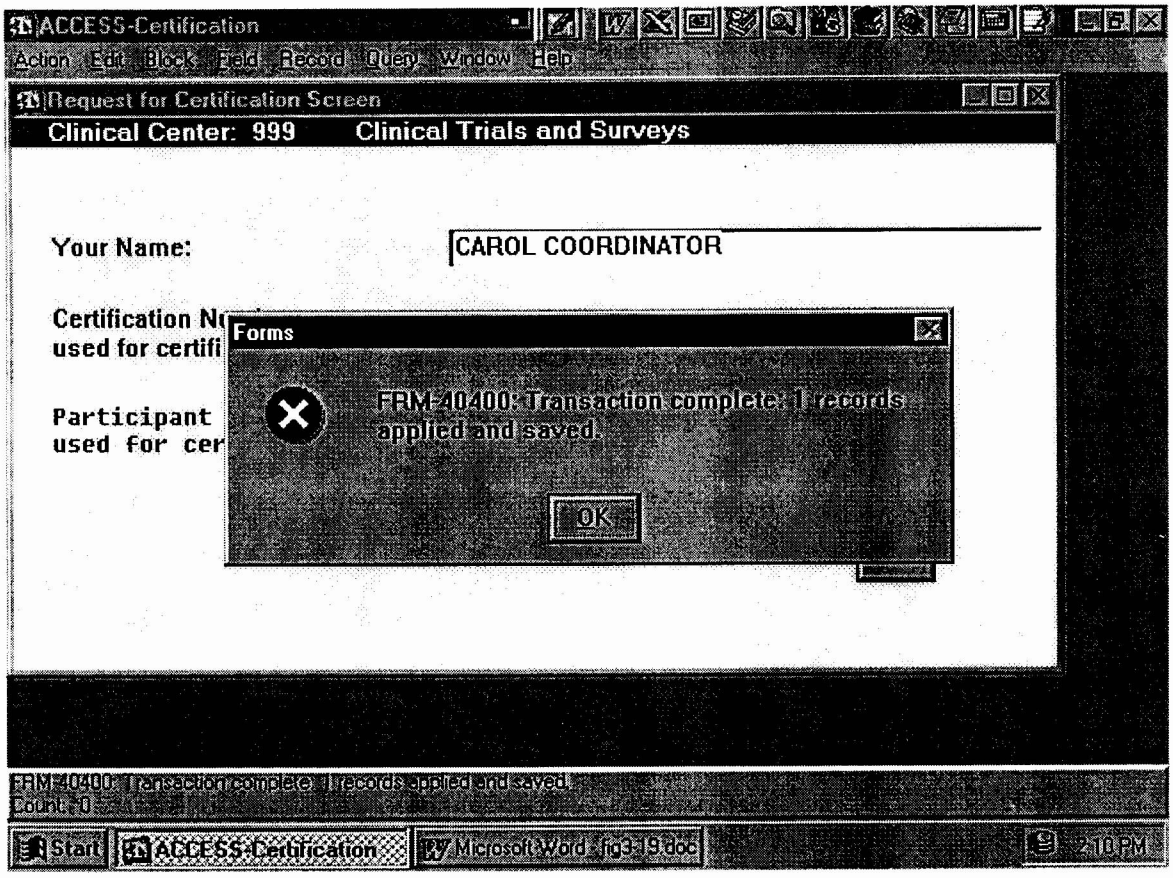


Figure 3-22

Certification Form Selection Screen

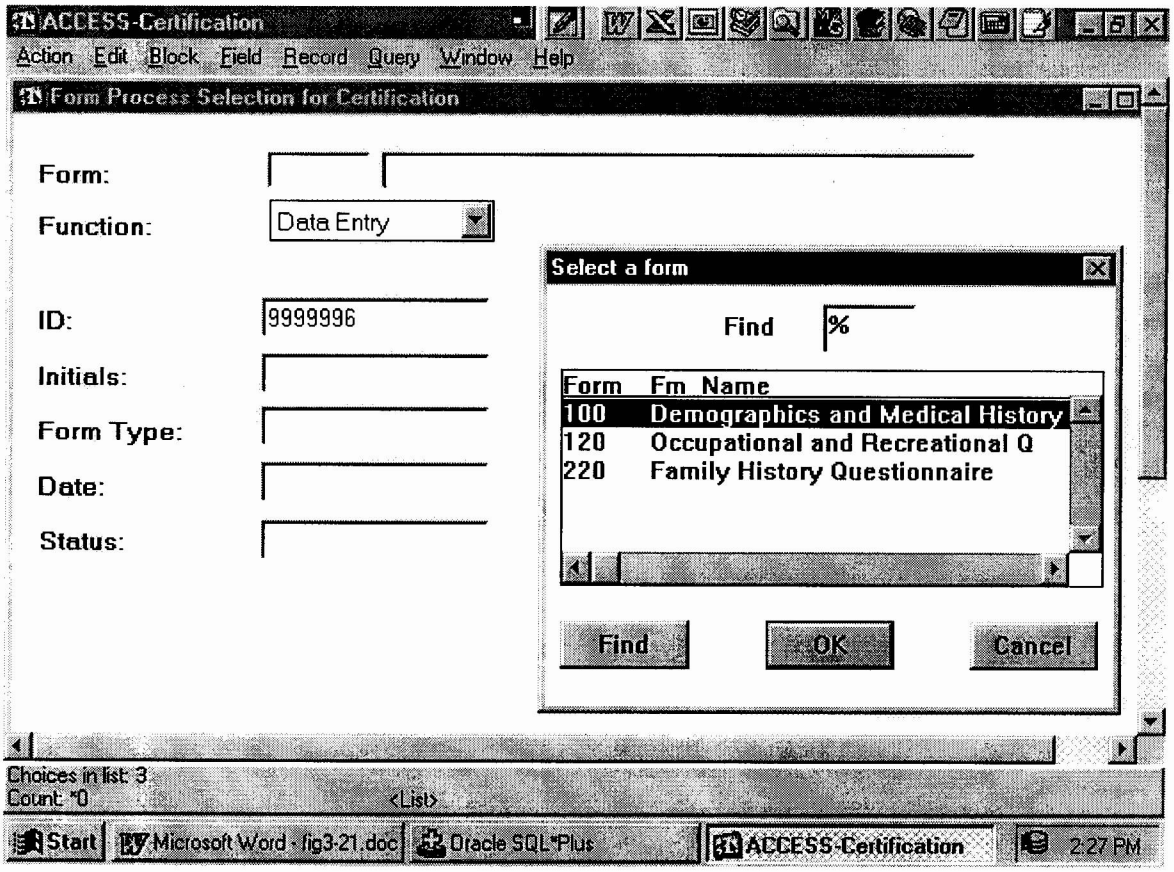


Figure 3-23

Not Available Codes

A series of 9's followed by an 8 in the last place

Examples:

x (1 digit)	9
xx (2 digits)	98
x.x	9.8
xx.xx	99.98
xxx.x	999.8

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 4

SCREENING LOGS

4.1 OVERVIEW

Screening Logs are completed for potential cases and controls. Some cases and controls will be enrolled and some will not be eligible or will refuse to participate during the screening process. The Case and Control Screening Logs data entry screens are identical. The general steps for processing Case or Control Screening Logs are:

Choose ACCESS Screening Log from the ACCESS desktop.

Log into the database security screen.

Log into the Authorization Screen.

Choose the Case or Control Screening Log Form.

Enter the data.

Review the entry.

Save the entry.

Logging into the database **Security** screen is discussed in Section 3.2. Logging into the Authorization screen is discussed in Section 3.3. Choosing a form is discussed in Section 3.4.2. Reviewing the entry and saving the entry is discussed in Section 3.5.6.

4.1.1 Entering Reasons for Ineligibility or Refusal

Each line of the form is a case or control depending on which screen was chosen. The RDD Control Screening Log is shown in Figure 4-1. There may be more than one reason that the case or control is ineligible. Upon entering the column labeled Reasons for Ineligibility or Refusal

another form is displayed (Figure 4-3). Enter the letters for the reasons or select as many reasons as apply and click [OK] when done. The reasons codes will be displayed on the screen.

4.1.2 Entering Race

A value can be entered directly for race or a **List Box** (Figure 4-2) can be displayed by selecting *Help* and then List from the **Menu Bar**. Make a selection and click [OK]. The number of the code will be displayed on the screen.

4.1.3 Entering Health Care Coverage

A value can be entered directly for Health Care Coverage or a **List Box** can be displayed (Figure 4-4) by selecting *Help* and then List from the **Menu Bar**. Make a selection and click [OK]. The number of the reason code will be displayed on the screen.

4.1.4 Saving the Case or Control Entry

When entry of “cases or controls” is completed, click on *Action* in the **Menu Bar**. Choose Save by clicking on it. An **Alert Box** will request verification before saving changes. Either choose “Yes” by clicking on it or press <ENTER> to save the changes. The entries will be saved and the screen will close.

Figure 4-1

RDD Control Screening Log

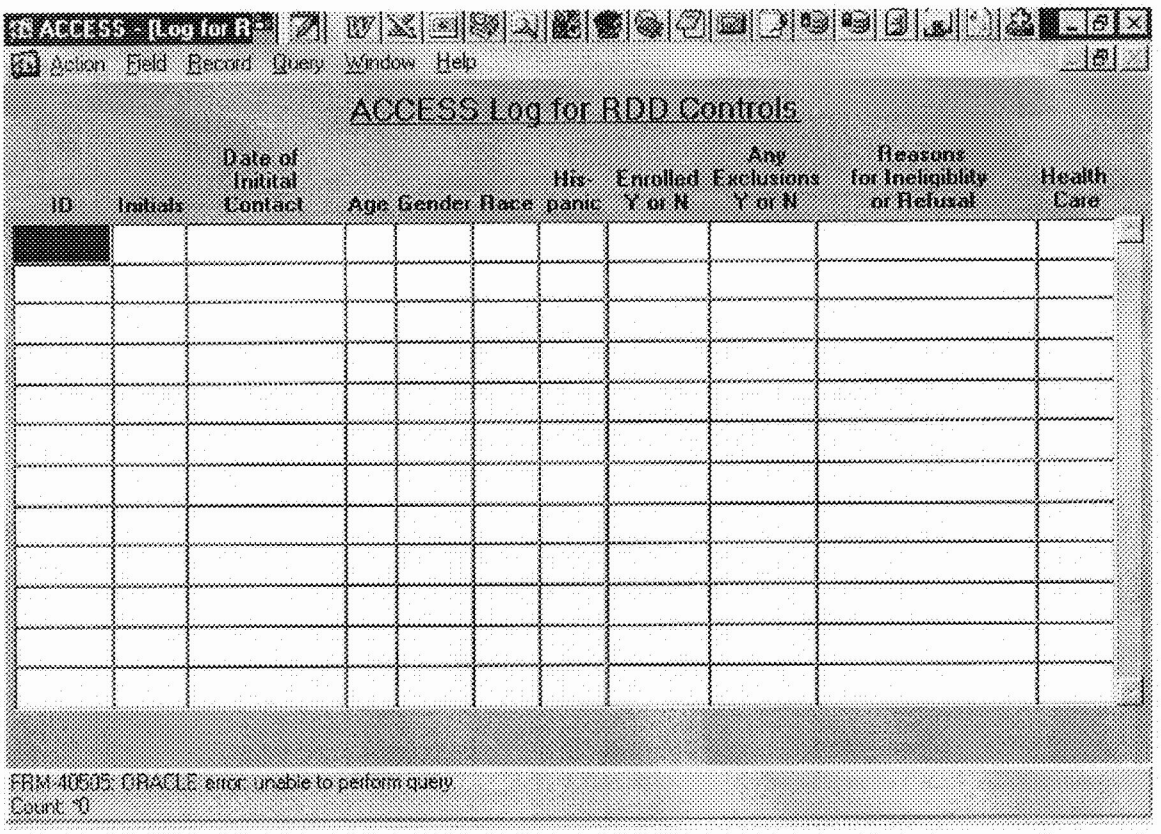


Figure 4-2

RDD Control Screening Log Race Categories

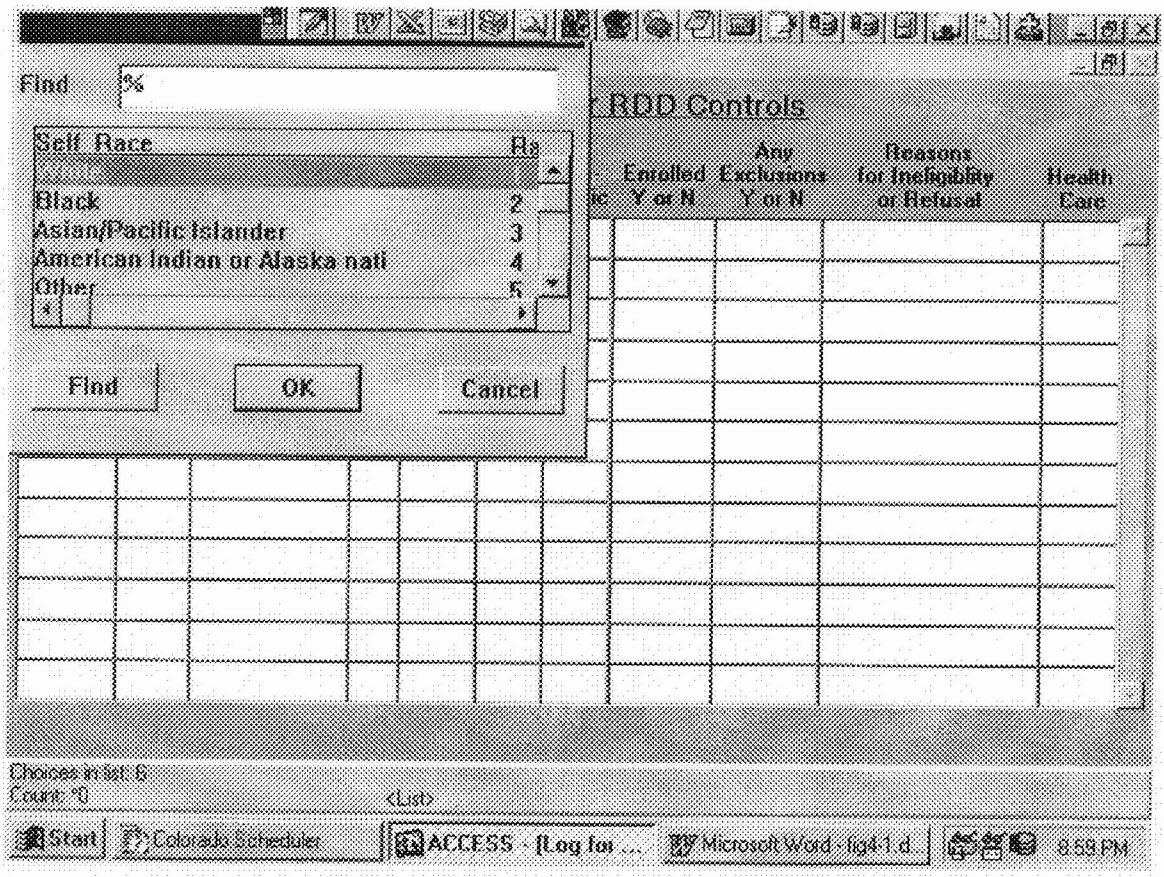


Figure 4-3

RDD Control Screening Log Reasons for Ineligibility or Refusal

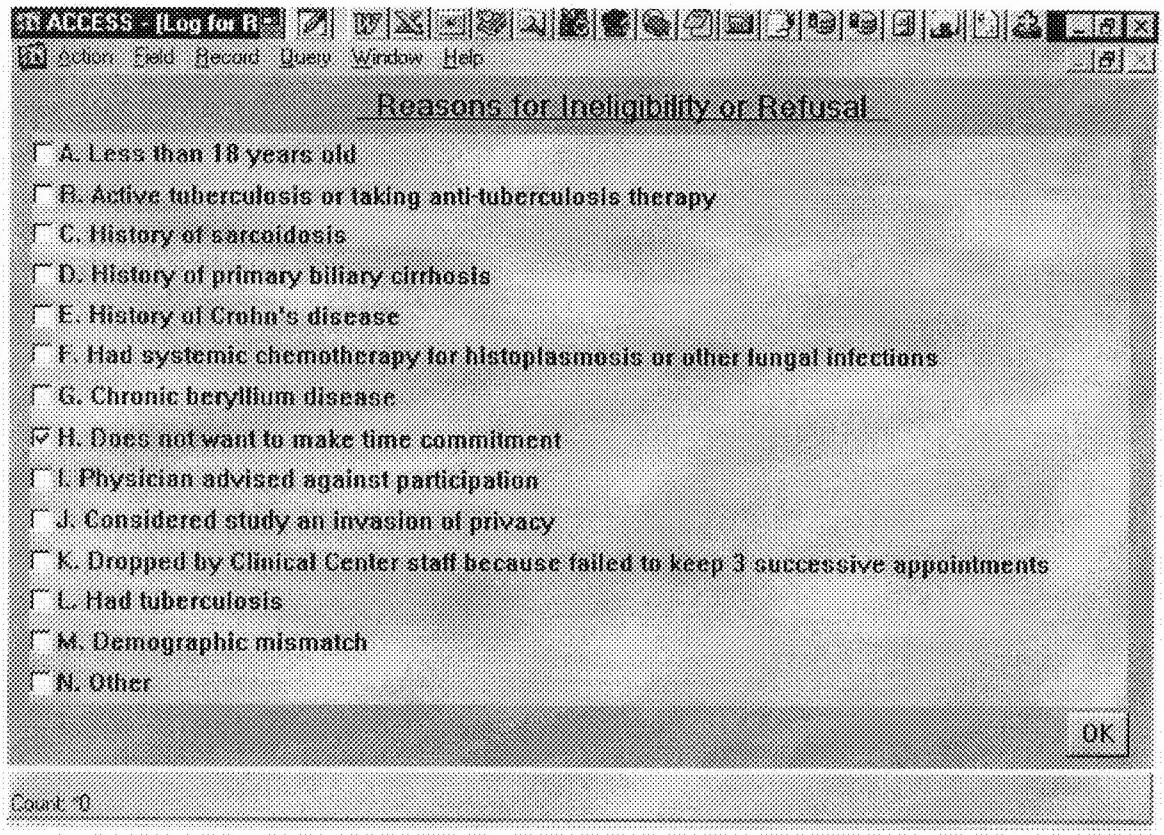
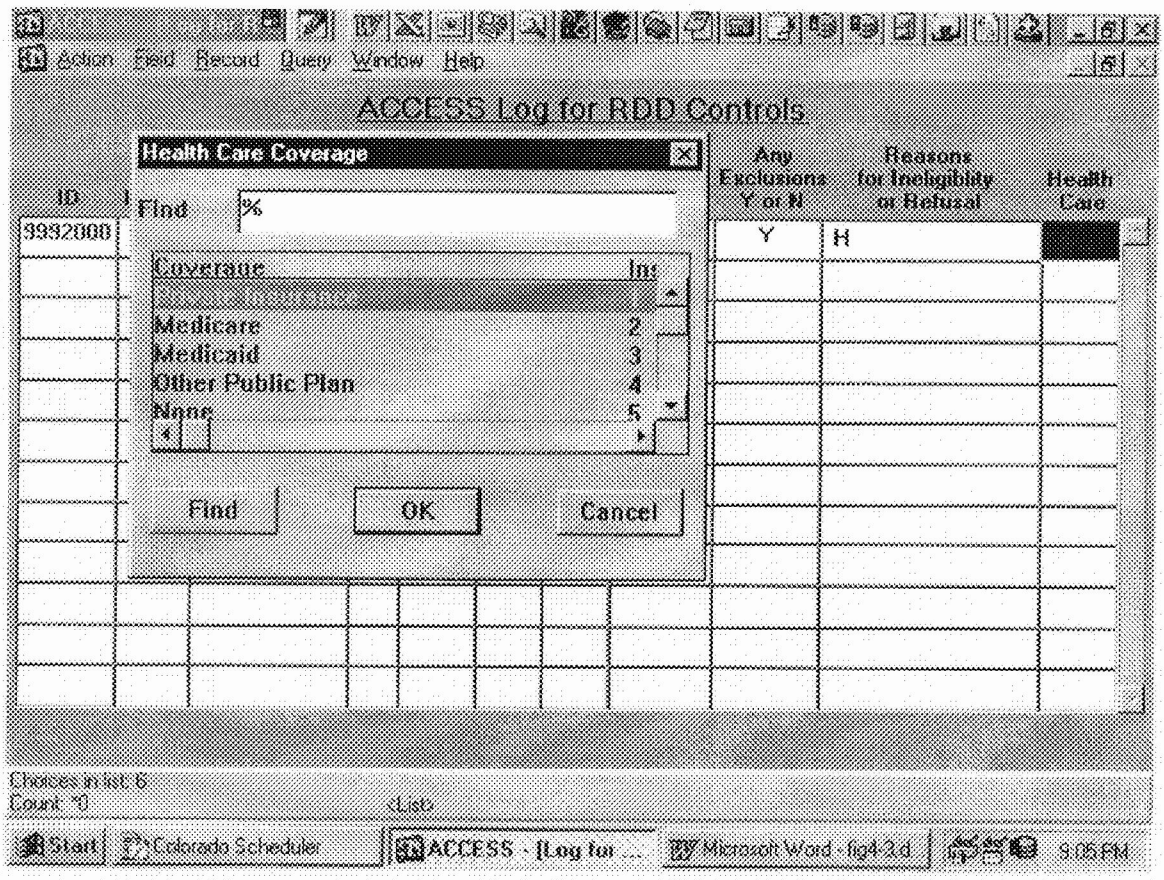


Figure 4-4

RDD Control Screening Log Health Coverage Screen



A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 5

BACKUP OF DATABASE AND COMPUTER FILES

5.1 OVERVIEW

The database and system must be backed up on a regular schedule to protect the database and system files from failure due to hardware or software problems. If a failure occurs and a recent backup does not exist, then either work completed since the last backup will have been lost and need to be re-entered or Clinical Coordinating Center staff will have to repair the system from files at the Clinical Coordinating Center. Both solutions will result in significant down time at the Clinical Center.

5.1.1 Choosing Database Backup from the Desktop

To back up the database onto the hard drive in a format that will preserve its structure in case of a catastrophic failure choose **Full Database Backup** from the desktop. A black screen will appear listing the data structures to be backed up. When the operation has completed, the desktop will be redisplayed.

5.1.2 Choosing Full System Backup from the Desktop

To back up the database and system, insert the next tape in the tape rotation and choose **Full System Backup** from the desktop. Figure 5-1 through Figure 5-3 show the screens that are displayed during the system backup. When the backup is complete a screen acknowledging completion of the operation is displayed. Click [OK]. See Figure 5-4. Then a screen displaying the number of files and bytes on the backup will be displayed (Figure 5-5). Click [OK]. When the

desktop is again displayed, the backup is completed and the tape may be removed from the tape drive.

5.1.3 Tape Rotation

Each Clinical Center should have at least two tapes on hand. The type of tapes to purchase are 680 Mbyte 3M MC 3000 XL mini-cartridges in Taumat format. They should be labeled Week A and Week B. Each week the particular week tape should be placed in the tape drive for that week's backup. Backups should be performed on Thursday nights.

Figure 5-1

Backup Setup Screen

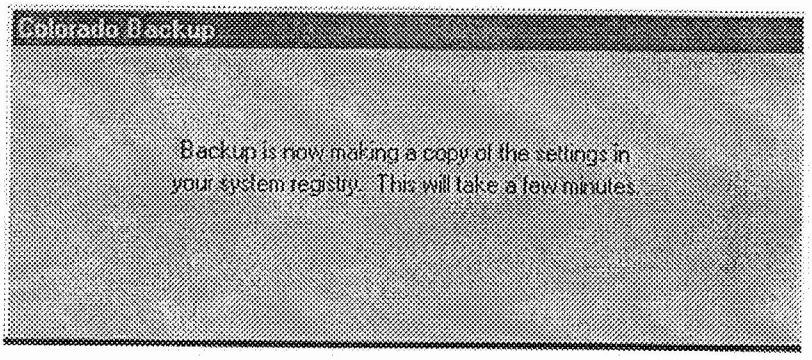


Figure 5-2

Backup File Selection Message Box

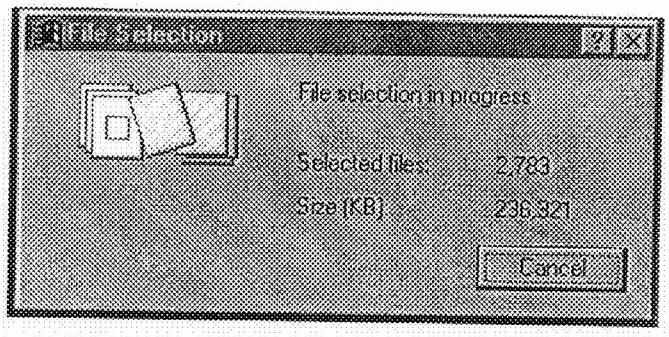


Figure 5-3

Backup File Processing Message Box

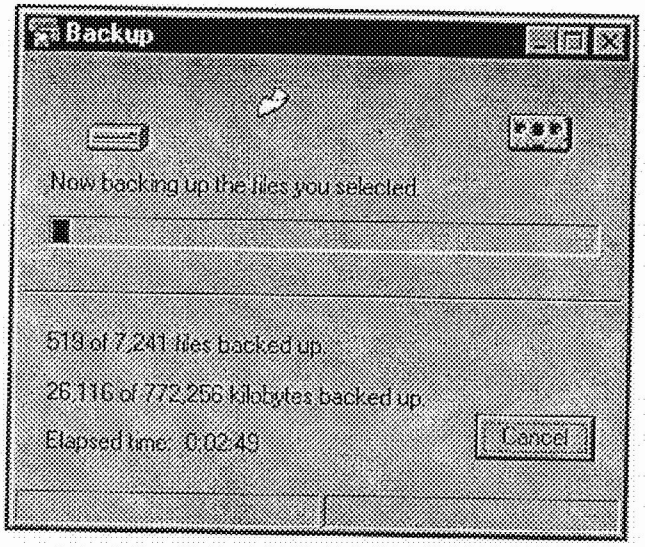


Figure 5-4

Completion of Operation Message Box

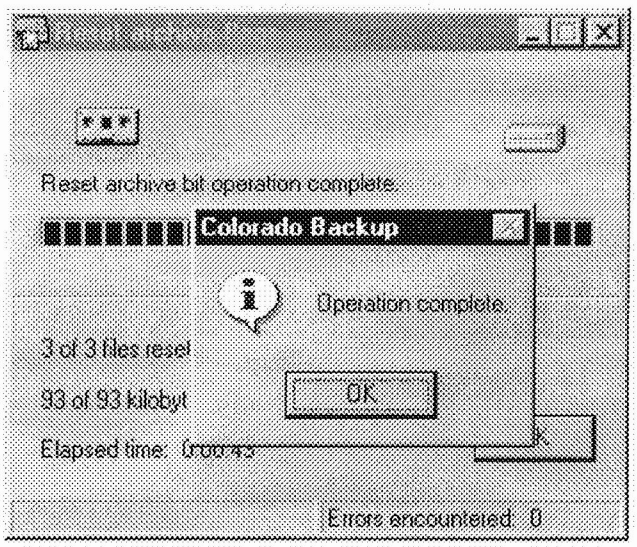
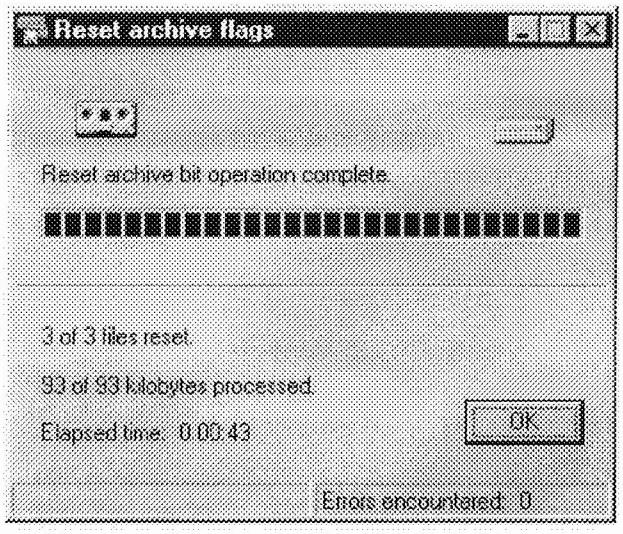


Figure 5-5

Back-up Completion Message Box



A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 6

ADHERENCE AIDS

6.1 OVERVIEW

To aid in protocol compliance, managing participant data, and managing participant appointments, a number of adherence aids are available. Additional aids are added to the ACCESS Distributed Data Management System as needed. The current aids are Case Appointment Schedules, Expected Visits for a Specified Month, Delinquent Forms and Materials, Inventory of Forms and Materials Display, and Calendars. All aids are available from the **ACCESS Reports** icon on the desktop. To exit from any ACCESS Report, click on *Action* in the **Menu Bar** and select Exit.

6.1.1 Appointment Schedule

The appointment schedule shows the full follow-up expected for a case. Figure 6-1 shows a sample appointment schedule. Identifying Information is at the top of the report. The detailed lines of the report describe the Form Type or Visit, and the expected, earliest, and latest date for form completion. The steps in generating an appointment schedule are:

Click on **ACCESS Reports** from the desktop.

Click on **Appointment Schedule** from the list of reports.

Enter the Case identification number or choose from the **List Box** (Figure 6-3).

Click on **Run Report**.

Click on **Reports Server**.

Click on *Action* menu item.

Choose Quit.

Click on *Action*.

Choose Exit.

6.1.2 Expected Visits for a Specified Month

Cases whose visit window begins in a selected month are locally printed to assist in scheduling Cases for visits to the Clinical Center or for completion of the Telephone Contact Form. The steps in generating an expected visits list are:

Click on **ACCESS Reports** from the desktop.

Click on **Expected Visits** from the list of reports.

Enter the Month and Year or choose from the **List Box**.

Follow directions as in Section 6.1.1.

All Cases whose visit window opens in that month will be printed. Figure 6-2 shows a sample list of Expected Visits.

6.1.3 Delinquent Forms or Materials

Forms that have not been completed by the end of the visit window are considered delinquent. These forms should be entered into the data entry system as soon as possible. The steps in generating a Delinquent Forms list are:

Click on **ACCESS Reports** from the desktop.

Click on **Delinquent Forms** from the list of reports.

Follow directions as in Section 6.1.1.

A report will be printed locally.

6.1.4 Inventory of Case or Control Forms

Each case or control is expected to have a number of examinations and interviews associated with screening and baseline. In addition, Telephone Contact and Follow-up examinations and interviews are expected for the group of cases in the Clinical Course study. An

online report of all forms for a particular case or control is available for viewing and printing. The steps in generating an Inventory of Forms are:

Click on **ACCESS Reports** from the desktop.

Click on **Inventory Display** from the list of reports.

Select the case or control participant identification number.

Figure 6-4 shows the screen that will be displayed when **Inventory Display** is chosen from the list of reports. To choose a case or control,

Click on *Query.*

Select Enter.

Enter the query criteria such as participant identification number in the ID field. (If no criteria are entered, all records are retrieved.)

Click on *Query.*

Select Execute.

Figure 6-5 shows an inventory display for a sample case. The display shows each form on a separate line. The form number, revision number, form type, visit date, keyer, date keyed, date corrected, edit status, date edited and date transmitted are displayed for every form for that participant. Scroll bars are to the left of the screen in case the number of forms exceeds the number of display lines. Clicking on the [UP-ARROW] or [DOWN-ARROW] will scroll the display up or down. To print the report select *Action* from the **Menu Bar** and select Print.

6.1.5 Calendars

Clinical Centers must schedule Cases and Controls for visits to the Clinical Center to fulfill screening, baseline, and follow-up protocol requirements. Microsoft Schedule+ allows for weekly and monthly appointment scheduling. Clinical Center staff do not have to use this software package to schedule appointments. Since names are used, these schedules are not part of the

ACCESS database and the files will not be transmitted to the Clinical Coordinating Center. Refer to Figure 6-6. The general steps in creating calendar schedules are:

Click on **Microsoft Schedule+** on the desktop.

Choose Weekly from the left hand tab.

Choose an appointment day and time. To choose another week, click on the *Calendar* button from the **MENU BAR**. It is the item that is to the right of the *Today* button in Figure 6.6.

Enter the Name of the Case or Control.

To add additional information for that Case or Control, right-click on the name and choose Edit. Figure 6-7 shows the **Description Box** where you can enter the type of visit or any other notes.

Click [OK].

To print the weekly calendar choose *File* from the **Menu Bar** and Print. Choose Weekly from the print menu. Choose Monthly for an overview of a particular month. Figures 6-8 and 6-9 show sample weekly and monthly calendars.

Although Microsoft Schedule+ is offered as a method for scheduling appointments, it is not necessary to utilize this program. However, sufficient online help is available to use the program. There are books available devoted to the use of Microsoft Schedule+.

Addendum to section 6.1.3, page 2, Volume III, ACCESS Procedures Manual

Figure 6-10 shows the message displayed when **Delinquent Forms** is chosen. Click [OK]. Figure 6-11 shows a sample page of output from the Delinquent Forms Report. The report is in ID order. Figure 6-12 shows a sample page entitled **Extraneous Forms Listing** that is also produced when the Delinquent Forms Report is executed. It lists those Forms 21 (Relationship Questionnaire B) and 23 (Family History Supplement) that are not necessary based on data entered form the case or control on Forms 20 (Relationship Questionnaire A), and 22 (Family History Questionnaire) respectively. Review the list and if they are extraneous forms, request that they be deleted by completing a Form D-1 as described in Chapter 9.

6.1.6 Calculation of Reference Dates for Control

Reference dates for controls are calculated based on the Interview date from Form 10 and Diagnosis date from Form 02, Item 9 for the case. Both forms must be keyed and in the database in order to calculate the reference dates for the matched control. The steps in generating the reference period for a control are:

Click on **ACCESS Reports** from the desktop.
Click on **Calculate Reference Dates.** (Figure 6-13)
Click [OK].
Select ID from list of Case ID's on right (Figure 6-14)
Click [OK].
    If the date of diagnosis (Form 02) or date of interview (Form 10) is not in the database for the case, an error message is shown (Figure 6-15). In this instance, click [OK] and enter the missing data as described in Chapter 3.
Enter the control ID number and expected data of the control interview (Figure 6-16).
The Reference Dates are listed on the screen. (Figure 6-17)
Click on [Save].
Repeat for as many cases as desired (Select another ID number (Figure 6-14)).
Click on [Print]. (Figure 6-18)
Figure 6-19 shows a sample report for one case.

Figure 6-1

ACCESS Sample Case Appointment Schedule

Sep. 17, 1996

Case ID: 9990020
Initials: SJL
Enroll Date: 28-AUG-96

Visit	Expected Date	Actual Date	Earliest Date	Latest Date
TC01	Feb. 26, 1997	____-__-____	Jan. 28, 1997	Mar. 28, 1997
TC02	Aug. 28, 1997	____-__-____	Jul. 28, 1997	Sep. 28, 1997
TC03	Feb. 26, 1998	____-__-____	Jan. 28, 1998	Mar. 28, 1998
CF01	Nov. 28, 1998	____-__-____	Aug. 28, 1998	Feb. 28, 1999

Figure 6-2

ACCESS Sample Expected Visits for February 1997

ID Number	Visit	Earliest Date	Latest Date
9990011	TC01	JAN-28-1997	MAR-28-1997
9990020	TC01	JAN-28-1997	MAR-28-1997

Figure 6-3

Sample Case Appointment Schedule Screen

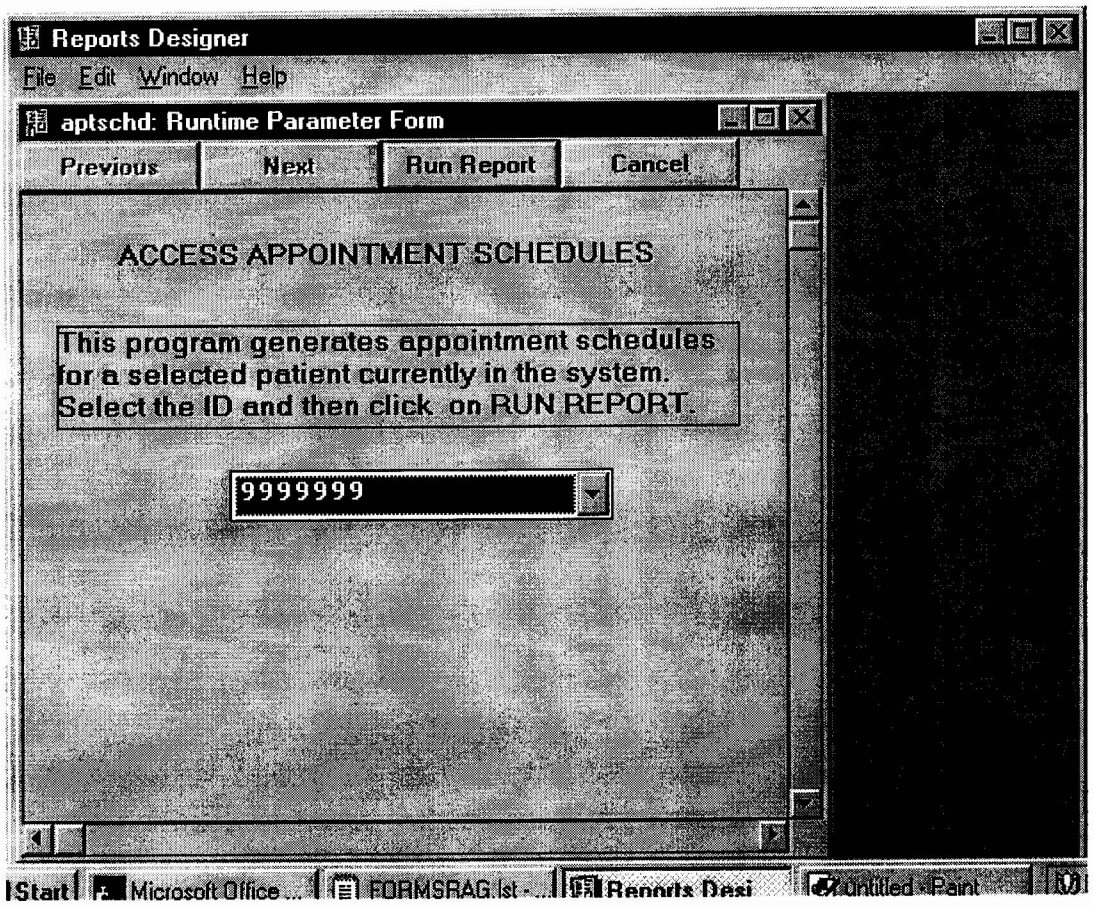


Figure 6-4

Inventory Display Query Screen

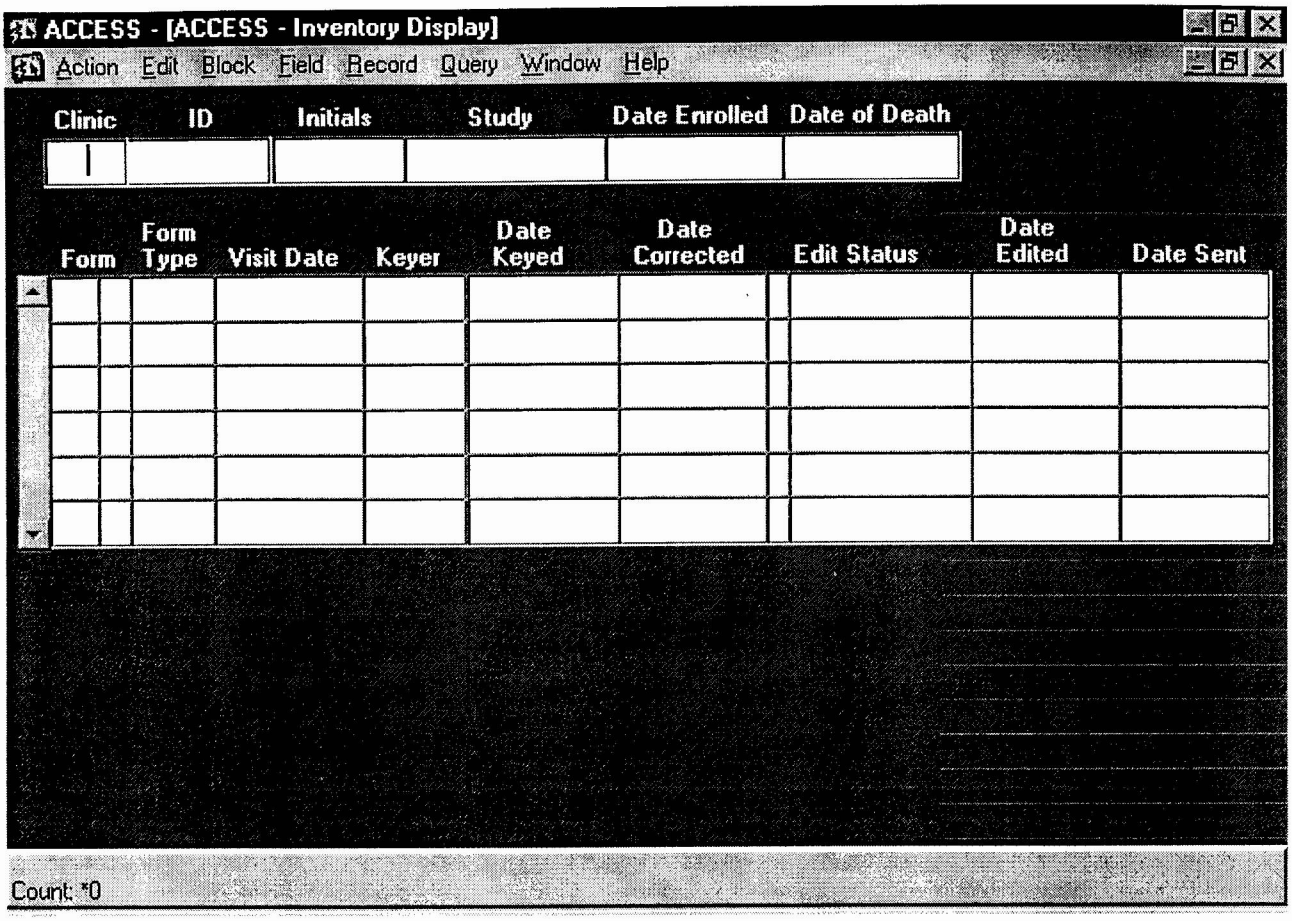


Figure 6-5

Sample Inventory Display

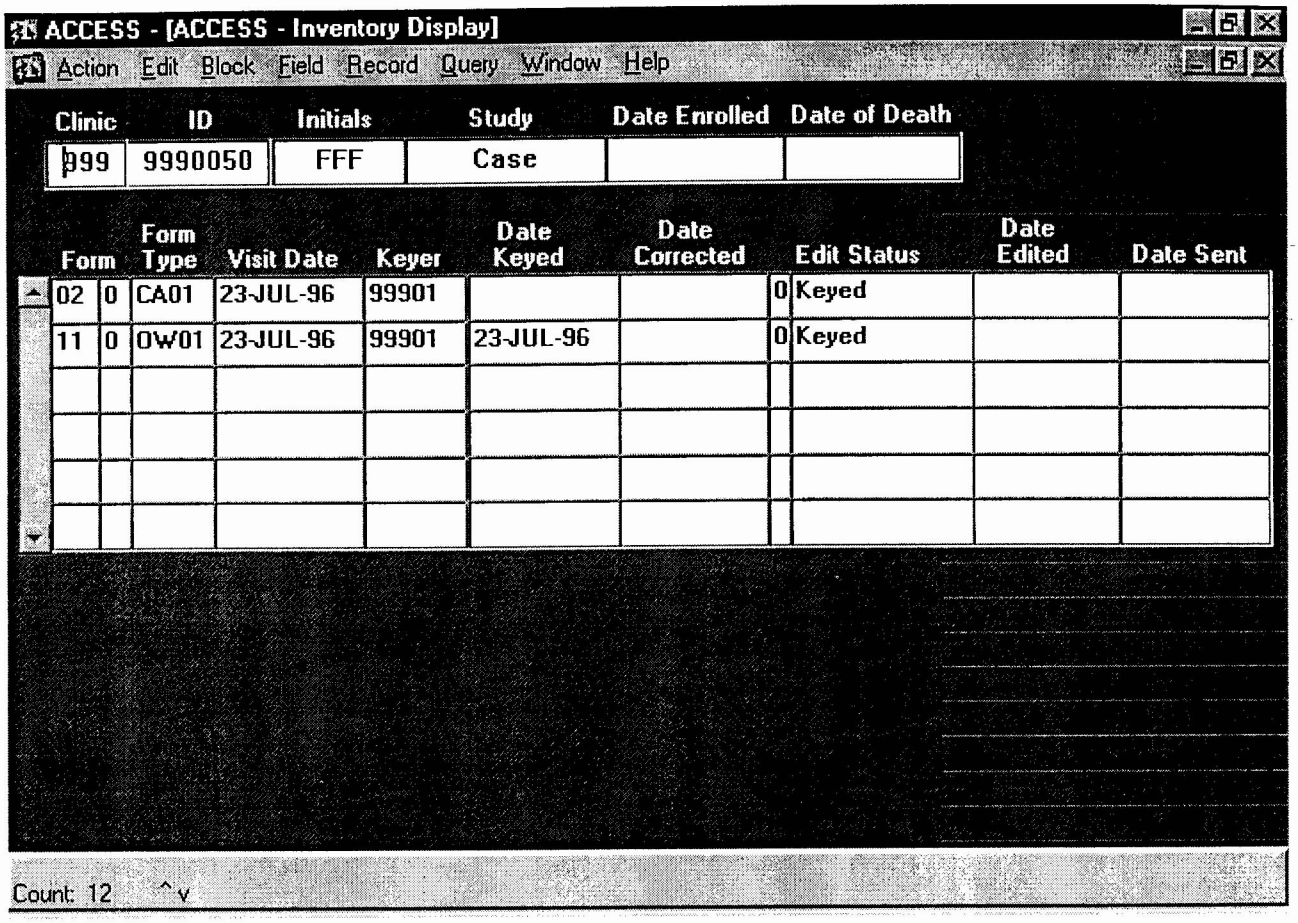


Figure 6-6

Weekly Appointment Name Screen

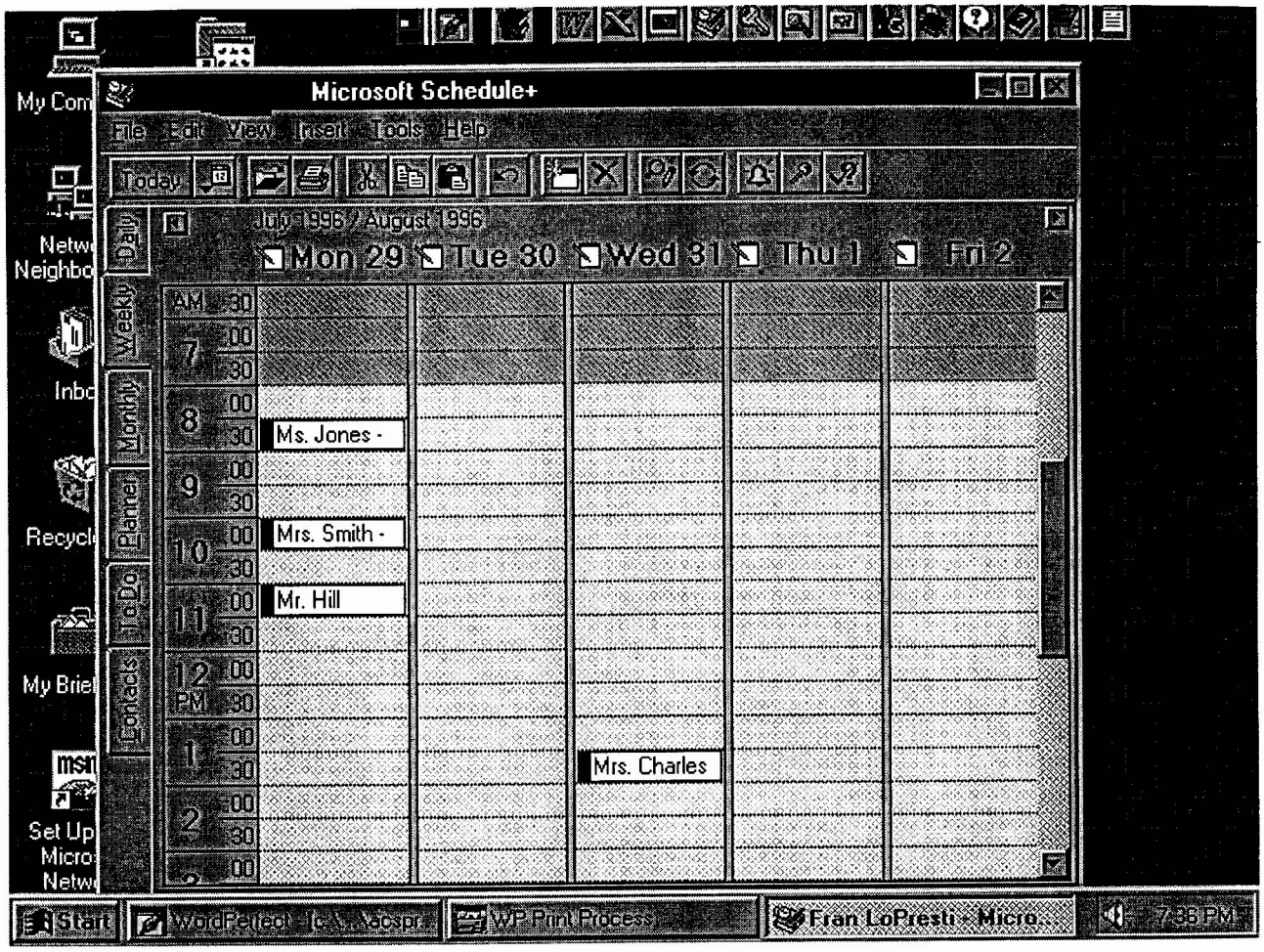


Figure 6-7

Weekly Appointment Note Screen

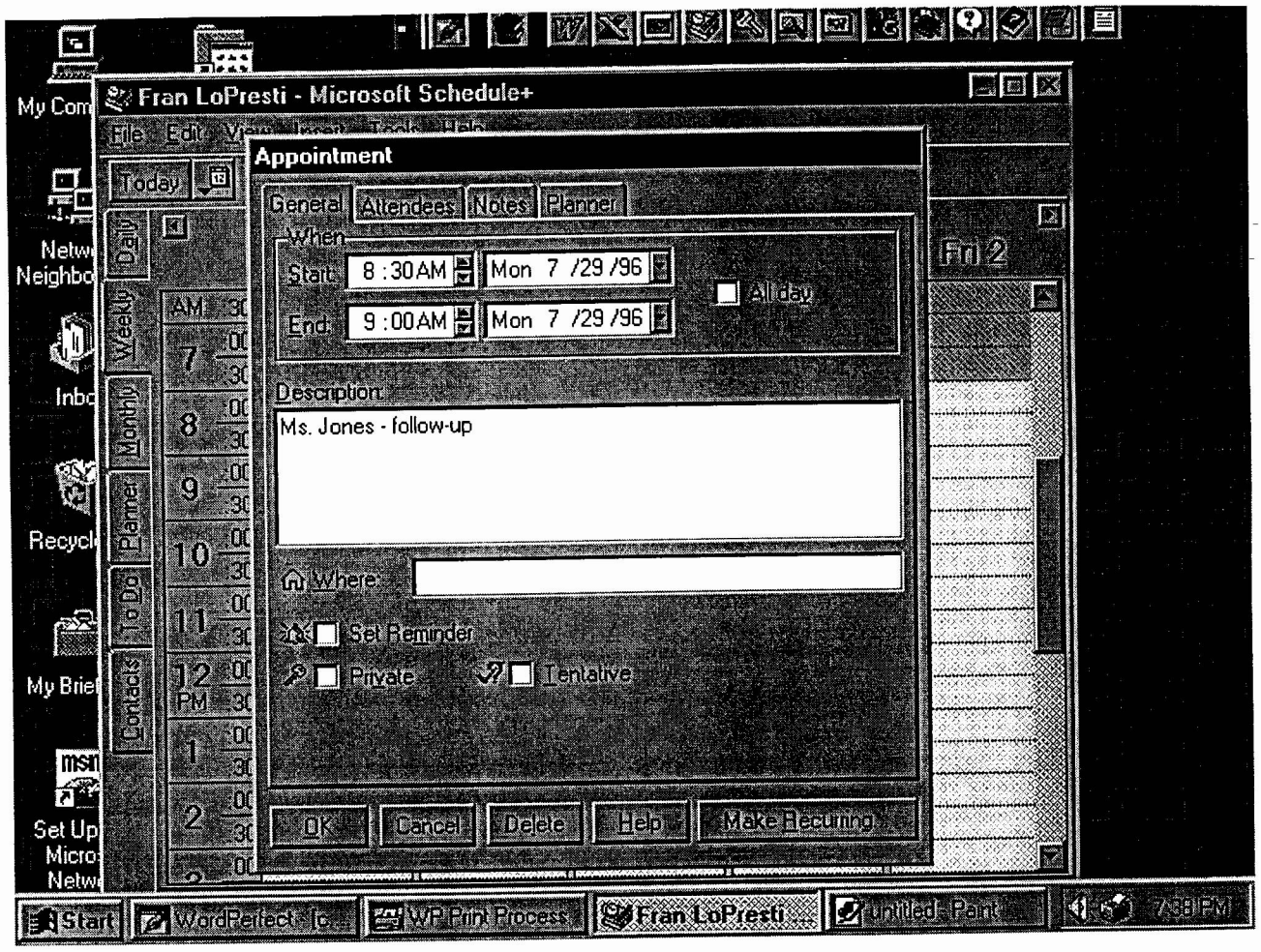


Figure 6-8

Sample Weekly Appointment Calendar

Fran LoPresti

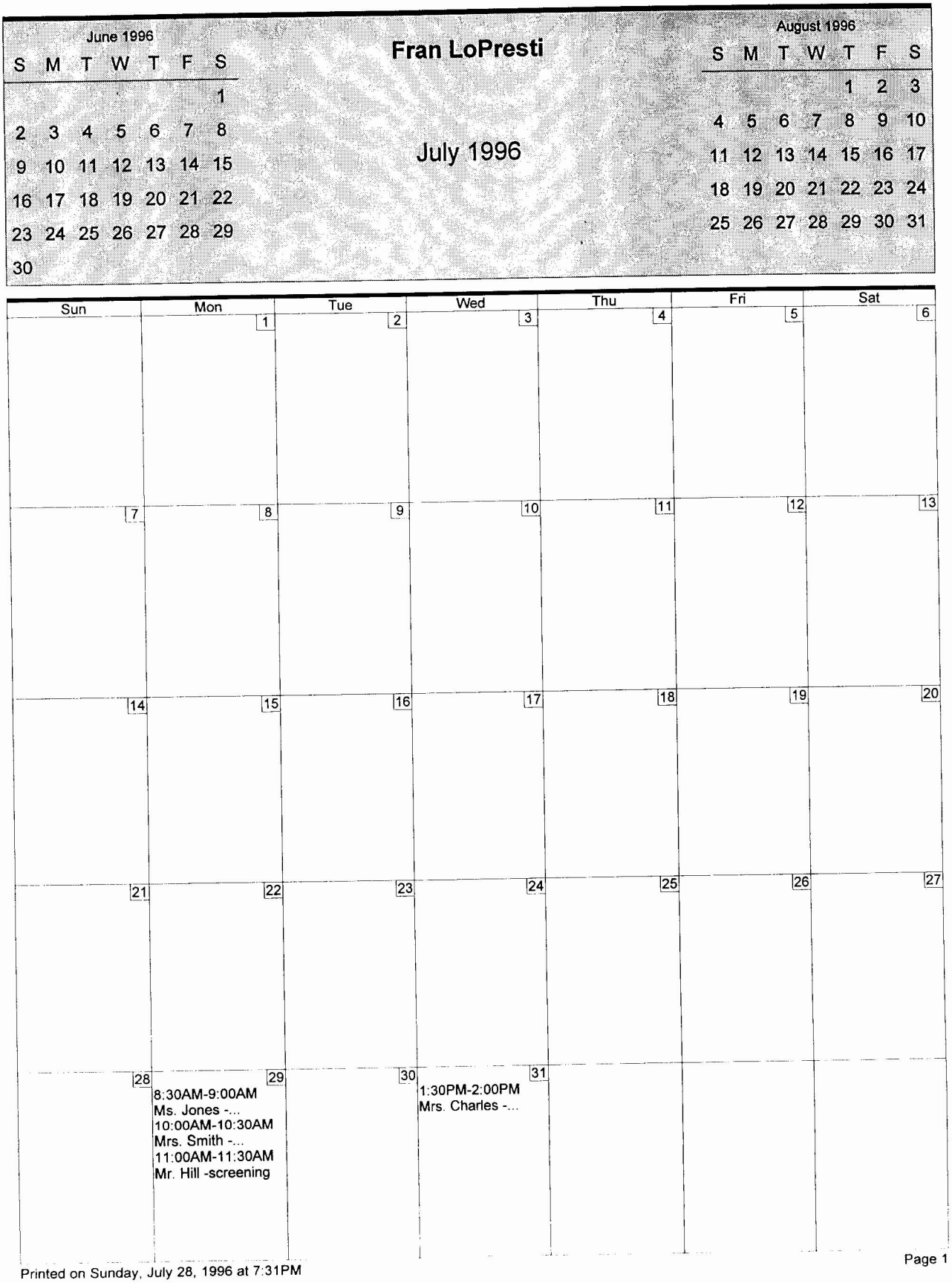
Monday, July 29, 1996

	Monday	Tuesday	Wednesday	Thursday	Friday
8:00					
:30	Ms. Jones - follow-up				
9:00					
:30					
10:00	Mrs. Smith - baseline				
:30					
11:00	Mr. Hill -screening				
:30					
12:00					
:30					
1:00					
:30			Mrs. Charles - baseline interview		
2:00					
:30					
3:00					
:30					
4:00					
:30					
Other:					

Printed on Sunday, July 28, 1996 at 7:31PM

Figure 6-9

Sample Monthly Appointment Calendar



June 1996

S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

Fran LoPresti

July 1996

August 1996

S	M	T	W	T	F	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29 8:30AM-9:00AM Ms. Jones -... 10:00AM-10:30AM Mrs. Smith -... 11:00AM-11:30AM Mr. Hill -screening	30	31 1:30PM-2:00PM Mrs. Charles -...			

Printed on Sunday, July 28, 1996 at 7:31PM

Page 1

Figure 6-10

Delinquent Forms Messages Screen

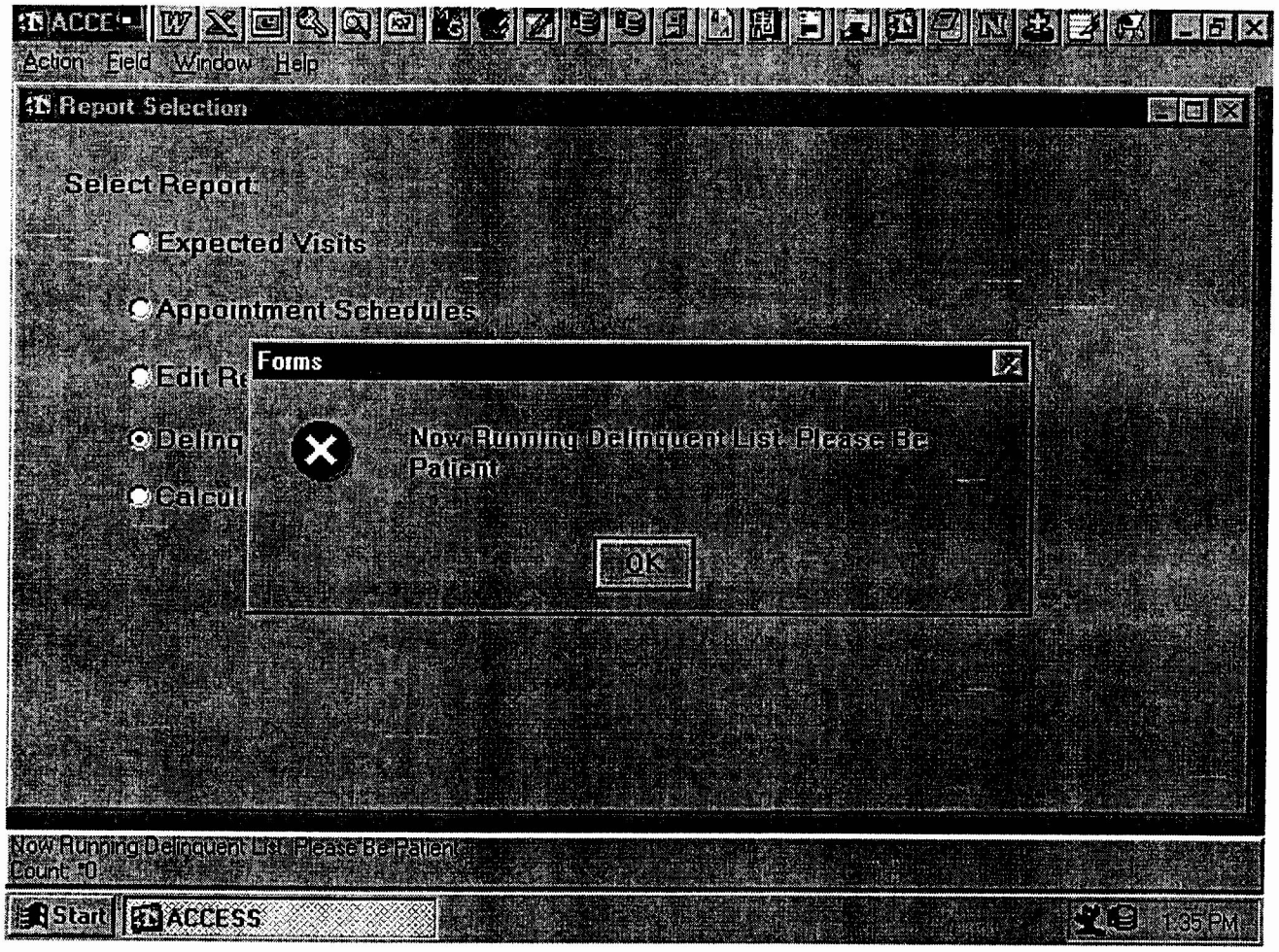


Figure 6-11

Sample Delinquent Forms Report

ACCESS
DELINQUENT FORMS
16-JUL-97

FORM	ID NUMBER	INITS	VISIT	DELINQUENT AS OF
13	9990001	AAA	EQ01	JAN-01-97
14	9990001	AAA	MQ01	JAN-01-97
19	9990001	AAA	SE01	JAN-01-97
24	9990001	AAA	PE01	JAN-01-97
26	9990001	AAA	CB01	JAN-01-97

Figure 6-12

Extraneous Forms Listing

ACCESS
EXTRANEOUS FORMS
LISTING
16-JUL-97

ID NUMBER	FORM	INITS	DATE OF VISIT	DELINQUENT AS OF
9990001	21	AAA	JAN-30-97	JAN-01-97
9990001	23	AAA	MAR-01-97	JAN-01-97

Figure 6-13

Report Selection Screen

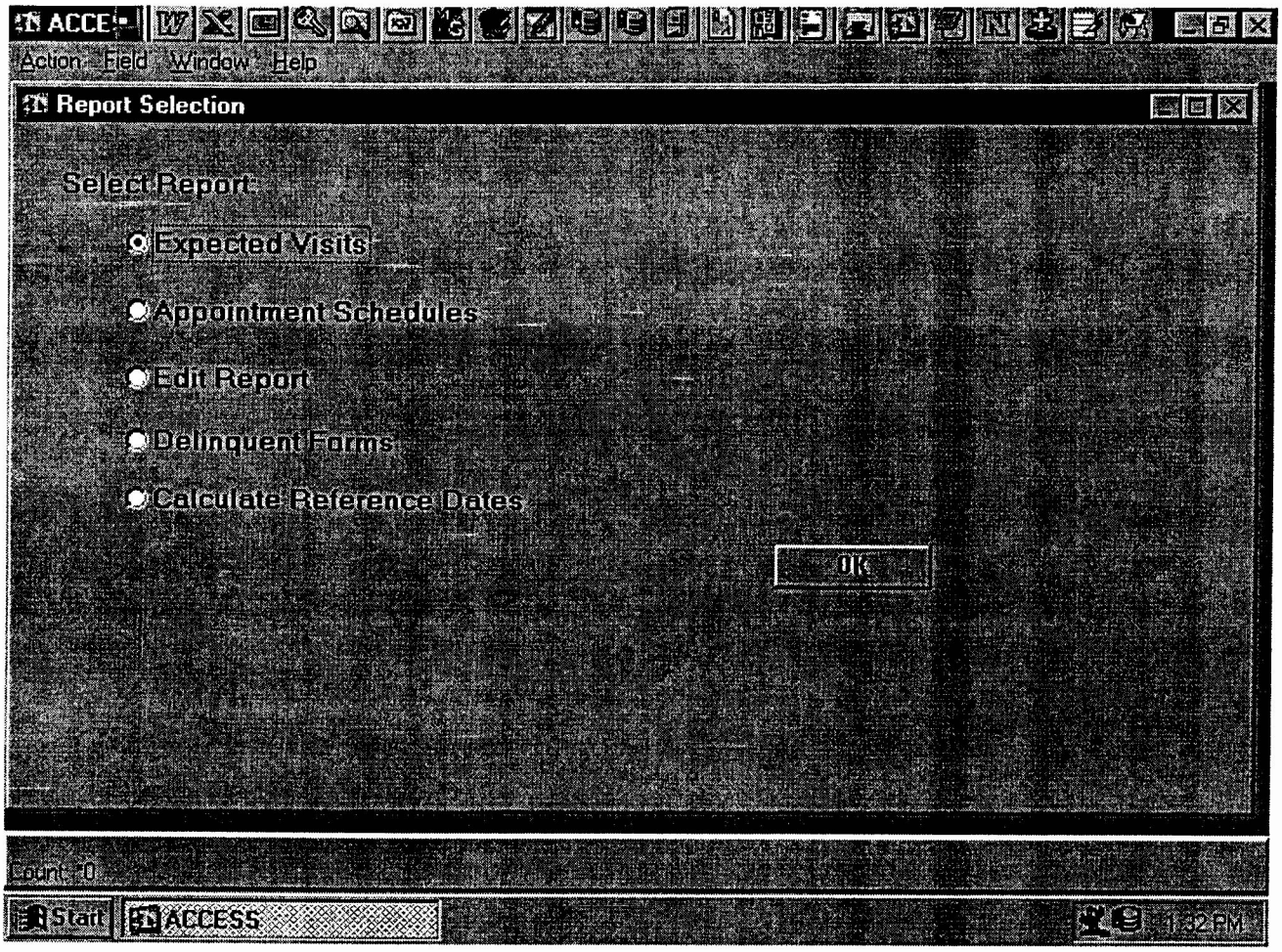


Figure 6-14

Calculate Reference Dates Screen (1)

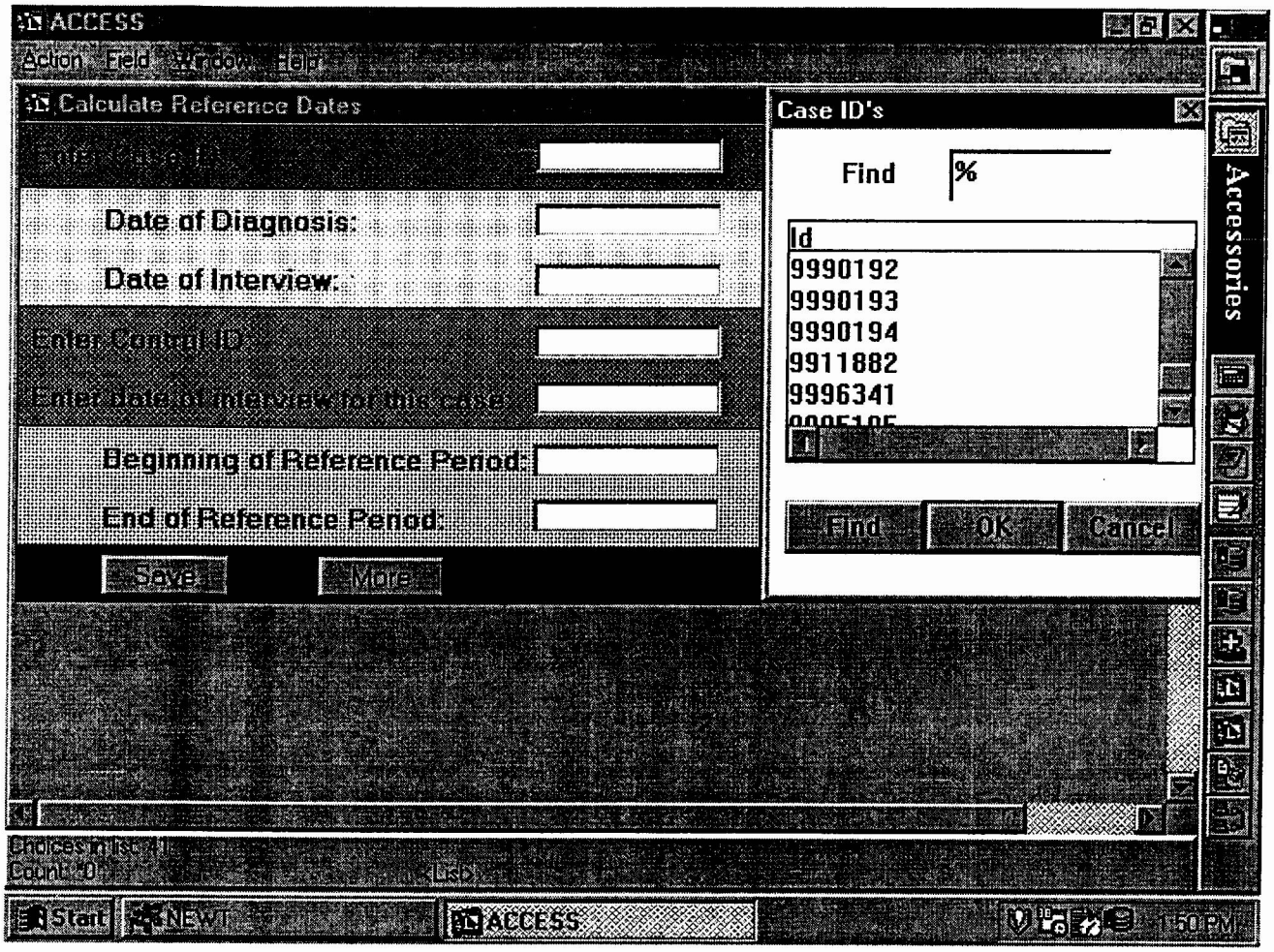


Figure 6-15

Reference Date Error Message Screen

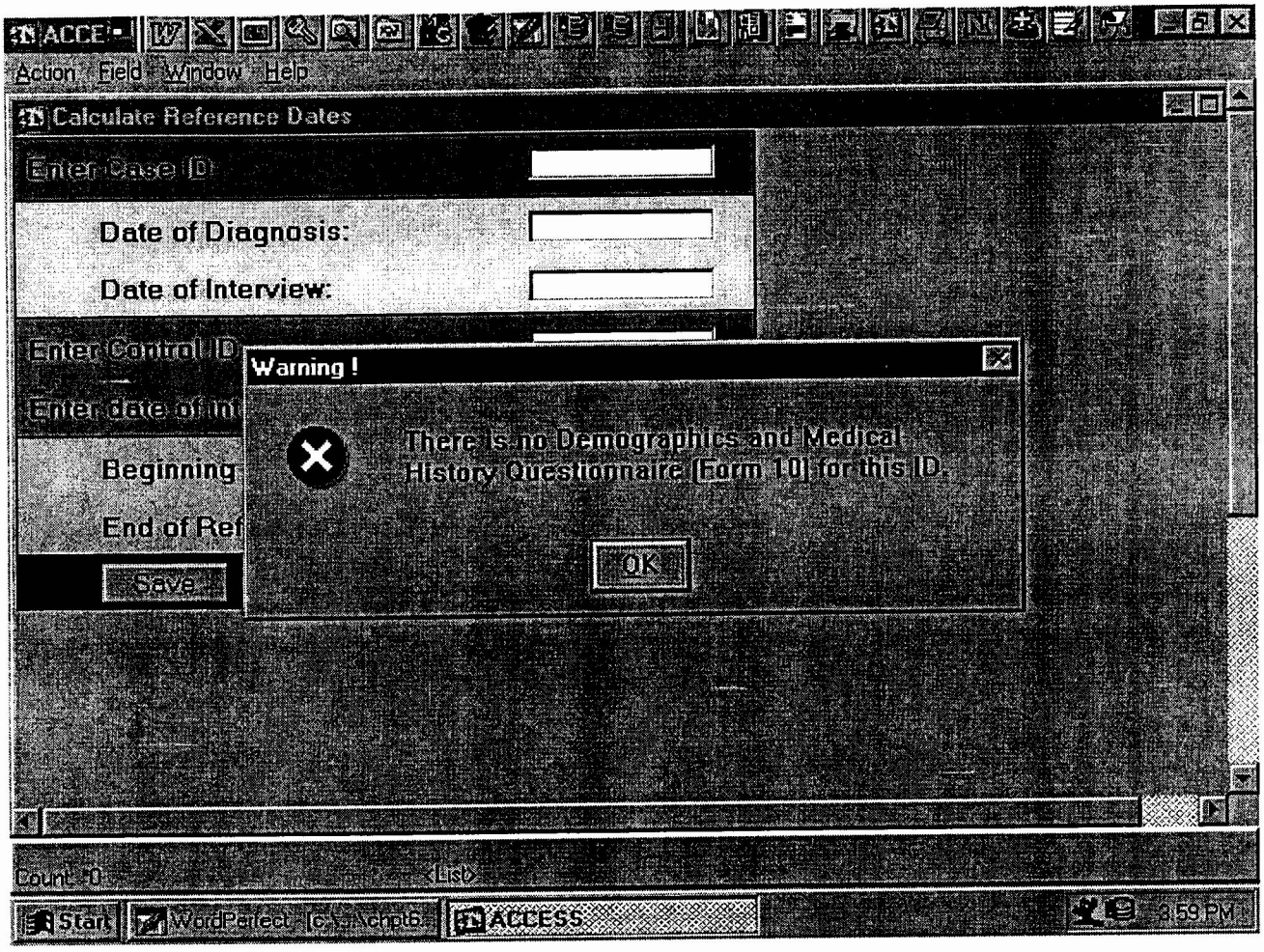


Figure 6-16

Calculate Reference Dates Screen (2)

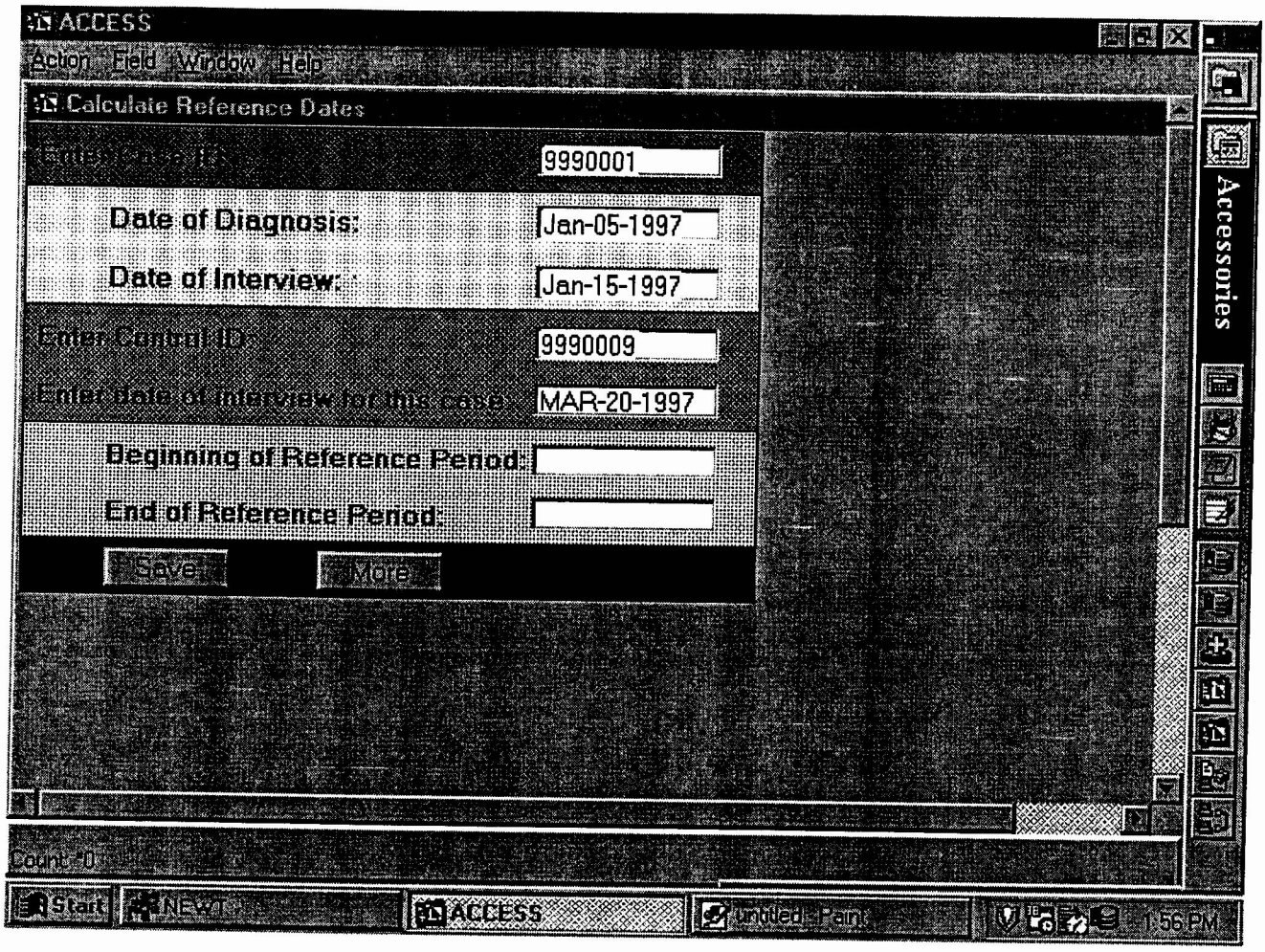


Figure 6-17

Calculate Reference Dates Screen (3)

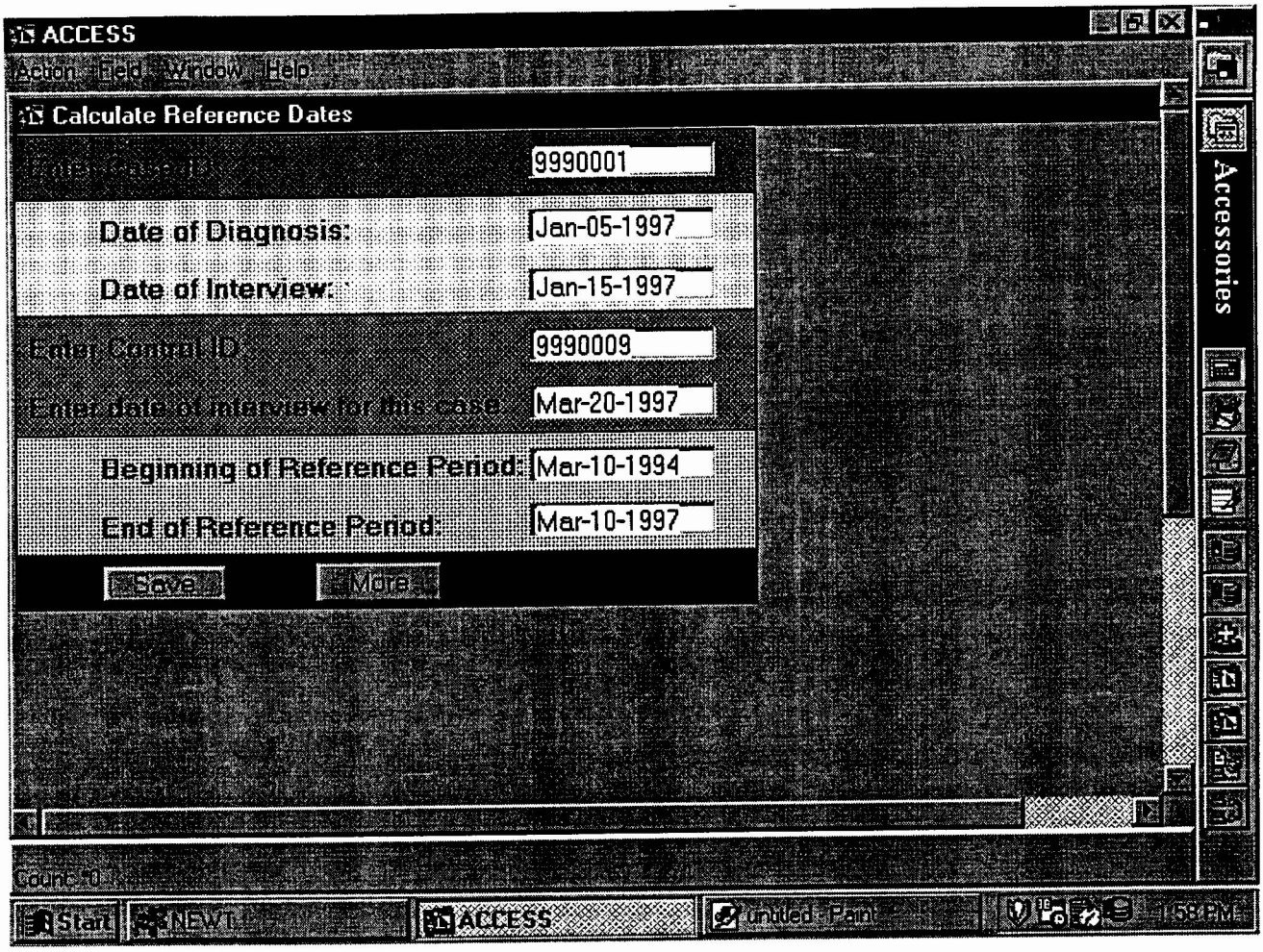


Figure 6-18

Reference Date Report Screen

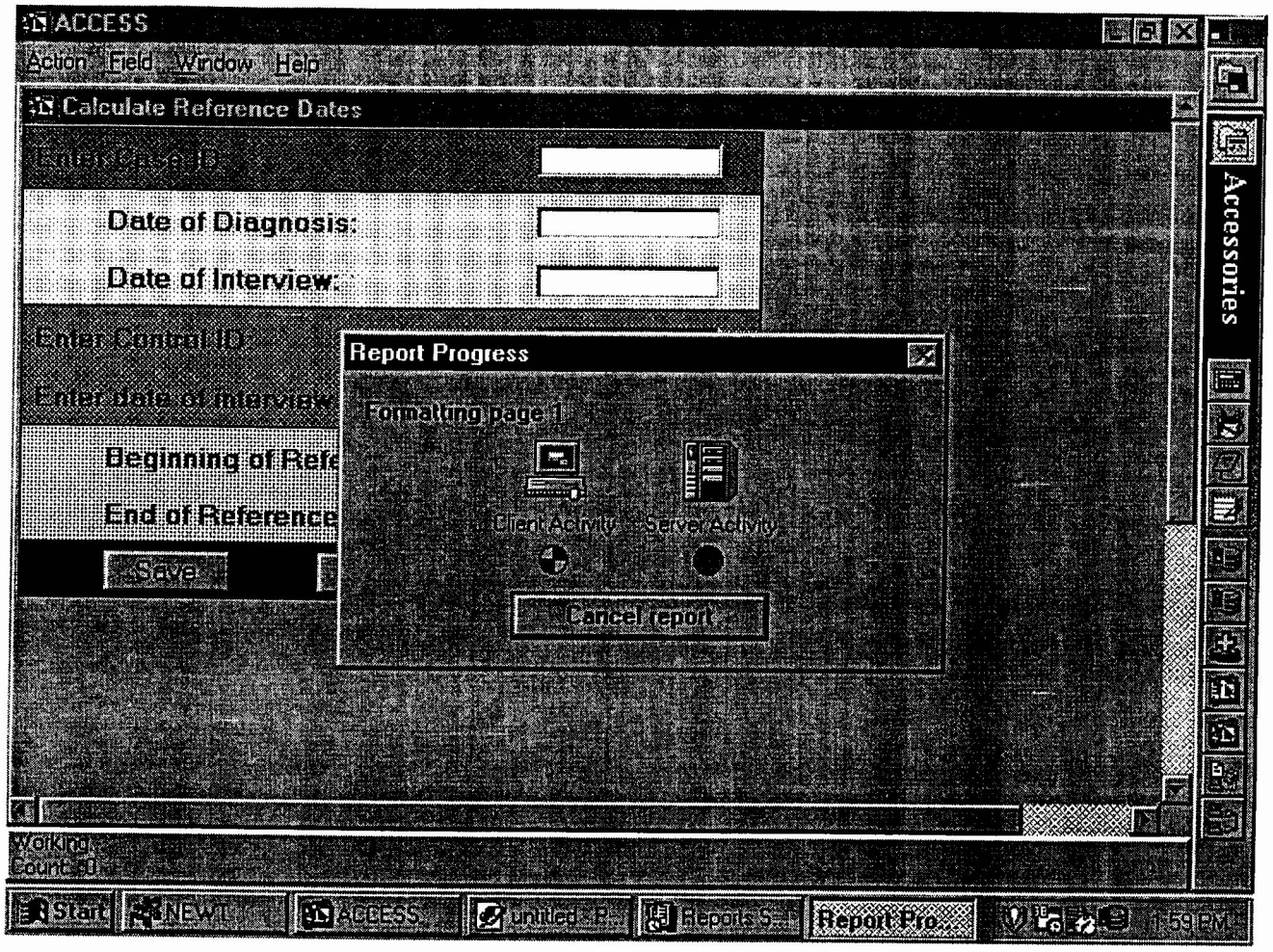


Figure 6-19

Reference Date Report

16-Jul-1997

ACCESS
Reference Date Calculations

Case ID	Case Diagnosis Date	Case Interview Date	Contol ID	Control Interview Date	Control Reference Date Start	Control Reference Date End
9990001	Jan-05-1997	Jan-15-1997	9990009	Mar-20-1997	*Mar-10-1994*	*Mar-10-1997*

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 7

SENDING DATA TO THE CLINICAL COORDINATING CENTER

7.1 OVERVIEW

Data will be extracted from the Clinical Center microcomputer by Clinical Coordinating Center staff on a scheduled basis. Most data will be extracted overnight by a script written by Clinical Coordinating Center staff. However, Clinical Center staff must set up their microcomputer for remote access to function. Clinical Coordinating Center staff use a software package called ReachOut for remote access to Clinical Center microcomputers for routine data transfer, software updates, and for troubleshooting problems experienced by Clinical Center staff. The system is configured when delivered to Clinical Centers for remote access including a special password that must be used for remote access. This protects the microcomputer from outside access by unauthorized persons.

7.1.1 Setting Up the Microcomputer for Remote Access Data Transmission

On a scheduled basis, Clinical Center staff will be asked to log on to their microcomputer as described in Section 2.2. The system should be left on for the evening in an active mode displaying the desktop as shown in Figure 2-4. At the beginning of business the next day, the system will be at the Window 95 log in prompt again so that ACCESS staff may perform their usual log in and begin their usual daily activities.

7.1.2 Setting Up the Microcomputer for Remote Diagnostics

In the event that remote diagnostics are required during the day, Clinical Coordinating Center staff may call Clinical Center staff and set up a time during the day when the microcomputer will

be available for remote access. The Window 95 log on will be different from the usual one. A sealed envelope will contain the log on and password required for this function.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 8

EDITS

8.1 OVERVIEW

Edits are queries to the Clinical Center about data that are out of range or inconsistent with other data on the form. The edit program is launched automatically when a data entry session has been completed, i.e., edit messages are generated when leaving the **Form Process Selection** function as described in Chapter 3, Section 5.6. Any newly keyed or corrected forms are edited. Corrections to the data are made on the form as described in Volume I, Chapter 8. Corrections to the electronic database are made as described in Chapter 3, Section 7 of this volume.

8.2 Review of the Edit Message

Figure 8-1 shows a sample edit message. The top of the message shows the date the edit was generated, the form number, and patient identification. The body of the message consists of 3 columns. The first column is the item number. The second column is the description of the item from the form. The third column lists the value in the database. Below the edit query, a custom message may be printed to further explain the nature of the problem. All edits can be resolved through corrections except when a value is outside of human ranges. In this case a custom message “Value cannot be verified.” is printed. If this is the only message for a form, call the Clinical Coordinating Center for central review of that item.

8.3 Making Corrections on the Paper Form

Forms that are failing edit should be pulled and corrections made on the form in red ink by crossing out the incorrect response and circling the correct response and the certified staff

member's initials and the date the correction is being made should be recorded on the form. If a write-in value is being changed, cross out the incorrect response, and write the correct response above it. Initial and date the correction. If a value that is out of normal range is to be verified as correct, circle, initial and date the item.

8.4 Preparing for Correction of the Form in the Database

By making all changes in red ink and dating each change, Clinical Center staff are able to rapidly correct electronic data from forms using the procedures described in Chapter 3, Section 6. Since forms are edited after correction again, there may be more edit queries based on the new values. Recording the date a form is corrected will enable staff to determine which corrections, if any, need to be made the second time the form is edited.

8.5 Running the Edit

The local edit is automatically executed when exiting from Forms Processing if the function chosen during that session was Data Entry or Correction. This allows newly entered forms and existing forms that have been corrected to be edited.

Figure 8-2 shows the first screen displayed as the edit begins. It is a reminder that the printer should be filled with paper. Click on [Run Edit]. The response message indicating that the edit is running is displayed (see Figure 8-3). Once the edit is completed, a response message indicating that the edit has been completed is displayed (see Figure 8-4). A new button is displayed on the screen called [Print Edit]. Click on [Print Edit] once. The edit message report is generated and the progress of the report generation is displayed as shown in Figure 8-5. Once the report is generated Form Processing will end and control is returned to the ACCESS Desktop. Messages will continue to print after the report has been generated. Note that "Reports Server" is displayed on the **Task Bar** at the bottom of the screen (see Figure 8-6). Once the messages

have finished printing, click on [Reports Server] to bring this function to the Desktop. Click on *Action*. Choose Quit.

8-6 Communicating Error Messages to the Coordinating Center

If an error occurs while the edit is running and another message is displayed other than "Edit Completed", please follow the following procedures so that Coordinating Center staff can diagnose and solve the problem.

Click on [Action].

Choose Print.

Click [OK] in the **Print Setup message Box** (see Figure 8-7).

Click [OK] in the **Print Message Box** (see Figure 8-8).

Click [OK] in the **Forms Print Capture Message Box** (see Figure 8-9).

Click [OK] in the **Forms Print Capture Complete Message Box** (see Figure 8-10).

Control is returned to the edit program. Click on [Print Edit] to print any messages processed before the error and follow the directions for generating the edit report in Section 8-5.

Figure 8-1

Access Edit Query
Feb-12-1997

Form/Rev:	02 /0	Initials:	FFF
Clinic:	999	Visit:	CA01
ID:	9992345	Visit Date:	Feb-11-1997

ITEM		OLD VALUE
This response is out of range		
5	Age	72
Please verify this response.		
This (These) response(s)		
5	Age	72
is (are) inconsistent with some or all of the following responses		
5A	Less than 18 yrs old	1
This (These) response(s)		
10D	Other biopsy	2
is (are) inconsistent with some or all of the following responses		
10D_rK	Specify other biopsy	Missing

Figure 8-1 (Continued)

Access Edit Query
Feb-12-1997

Form/Rev:	**02 /0**	**Initials:**	**FFF**
Clinic:	**999**	**Visit:**	**CA01**
ID:	**9992345**	**Visit Date:**	**Feb-11-1997**

ITEM		OLD VALUE
This (These) response(s)		
14	Any stops	2
is (are) inconsistent with some or all of the following responses		
5A	Less than 18 yrs old	1
8A	Tuberculosis	2
8B	MD-sarcoid 6 mo ago	2
8C	Biliary cirrhosis	2
8D	Crohns disease	2
8E	Histoplasmosis RX	2
8F	Beryllium	2
9	Specimen obtained	1
11B	Path rpt-sarcoidosis	2
11C	Any path exclusion	2
13	Culture positive	2

Figure 8-2

Run Edit Action Screen

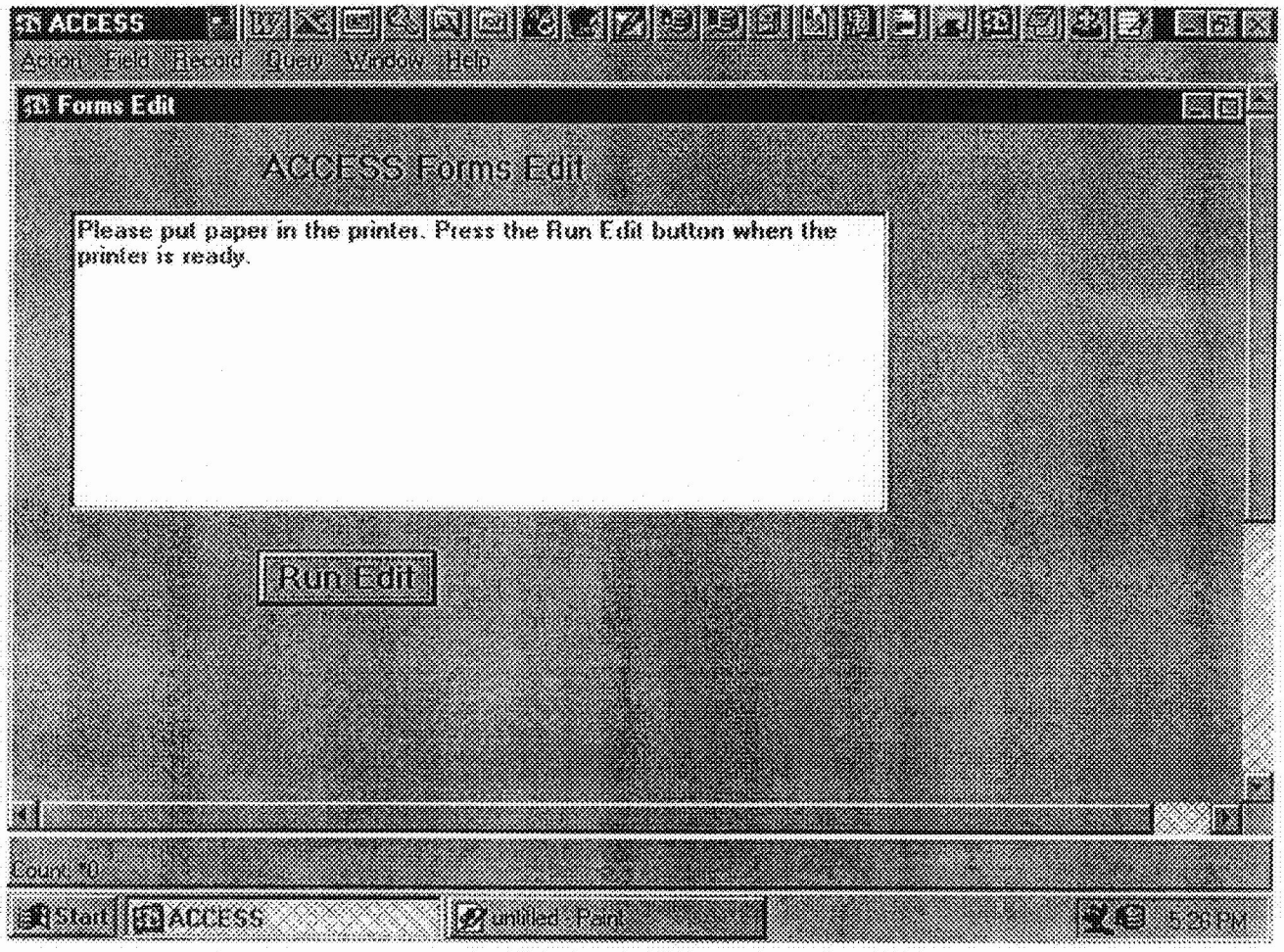


Figure 8-3

Edit Progress Screen

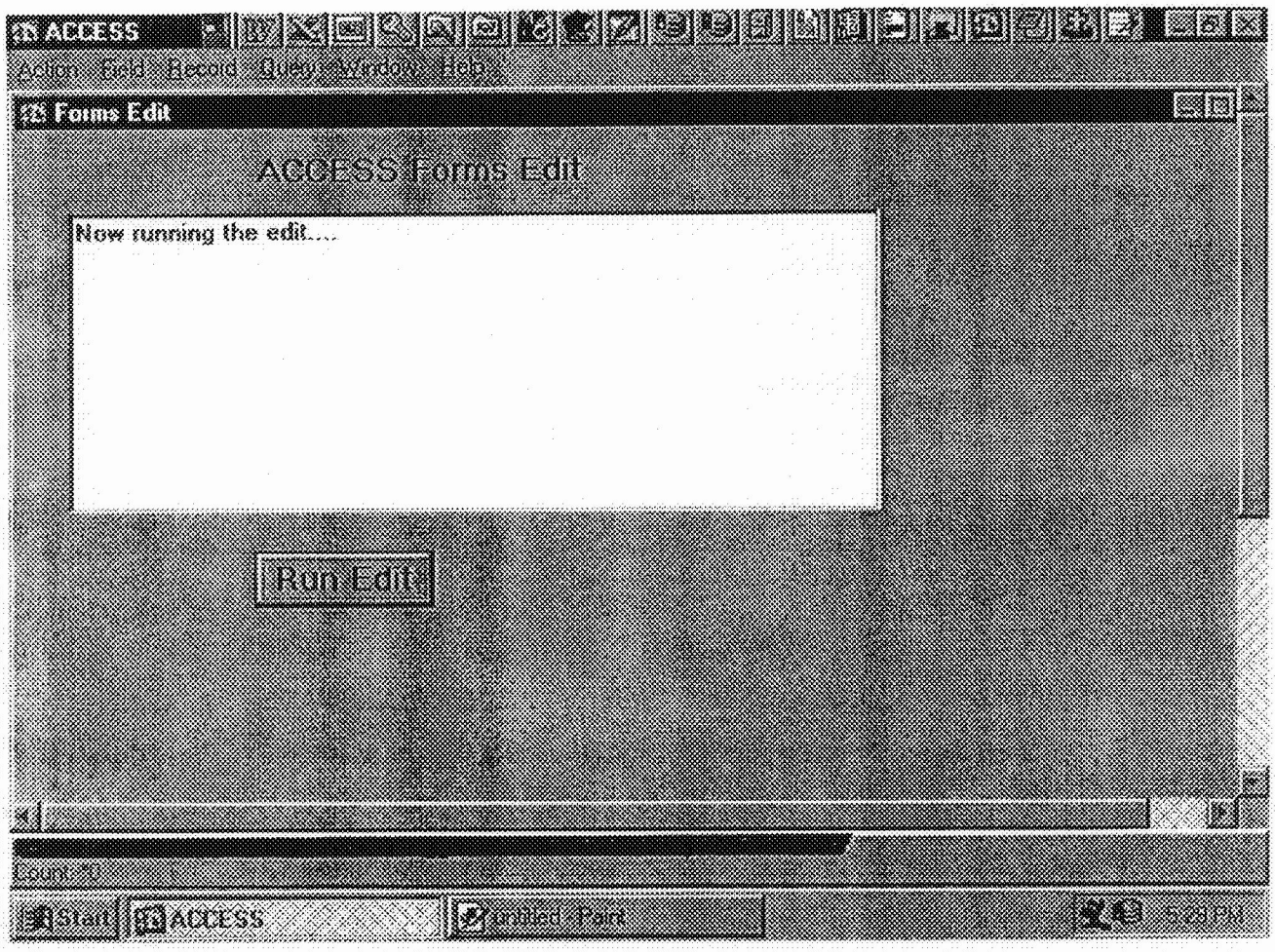


Figure 8-4

Print Edit Action Screen

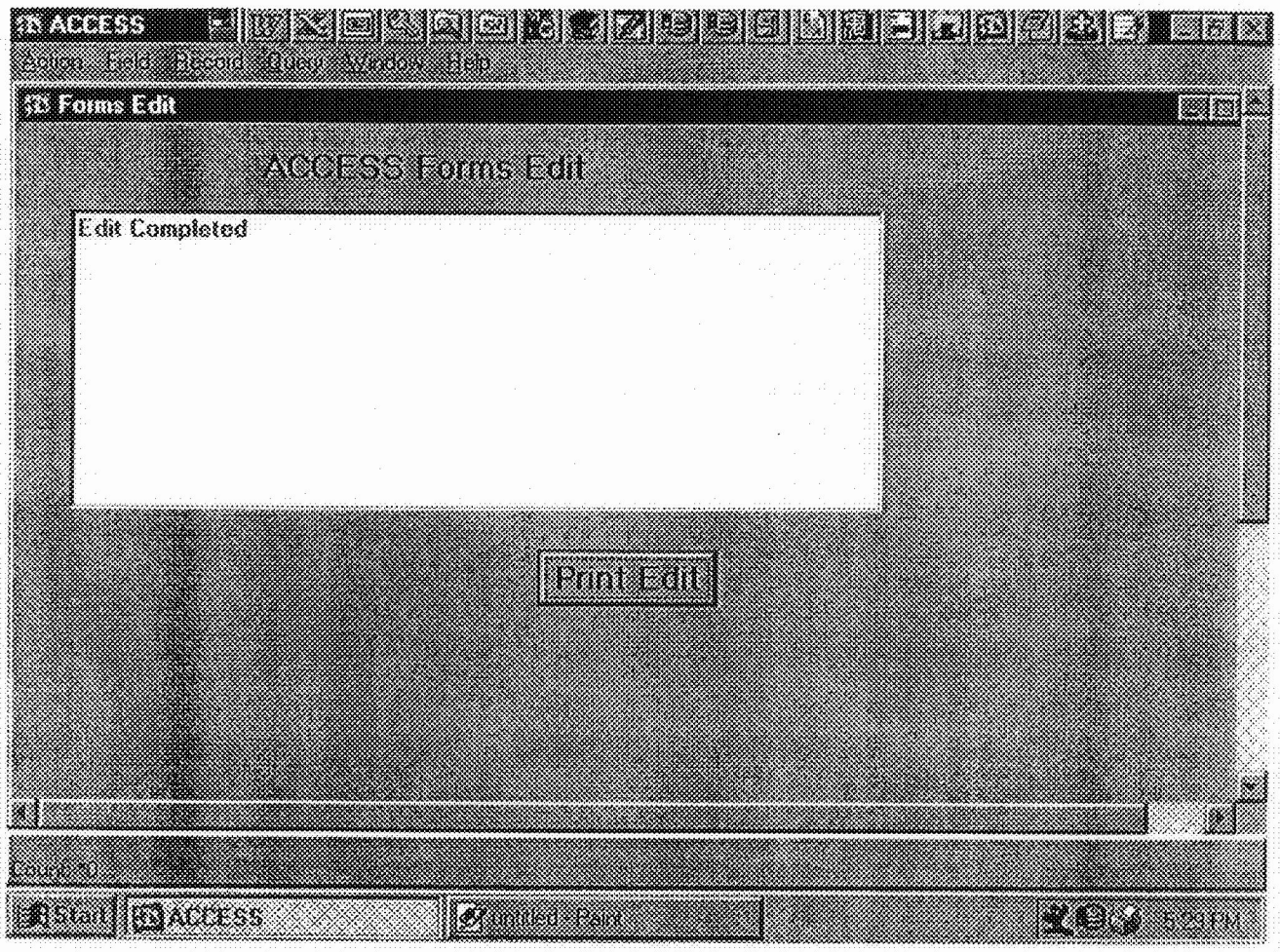


Figure 8-5

Edit Report Message Box

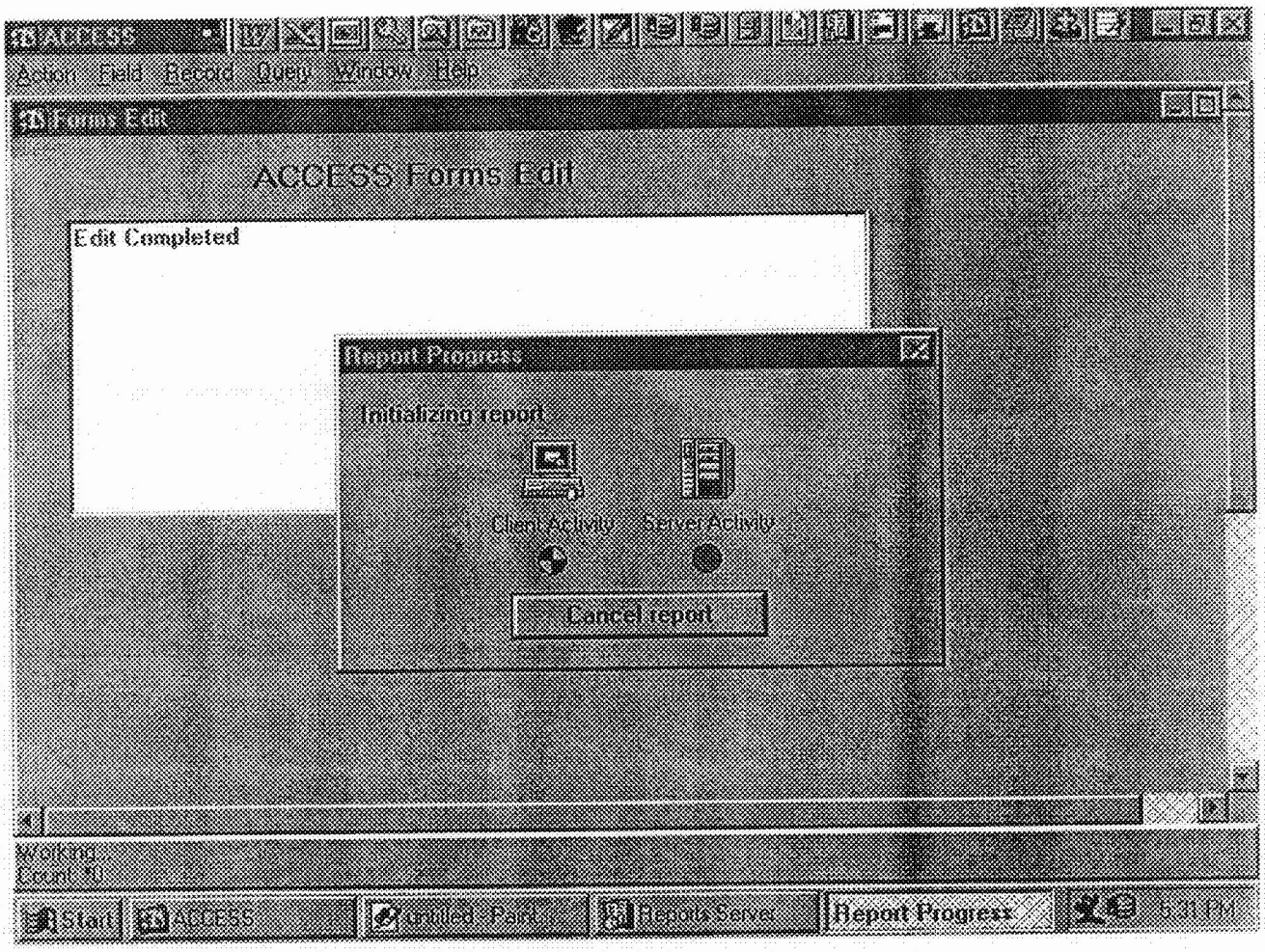


Figure 8-6

Reports Server Action Menu

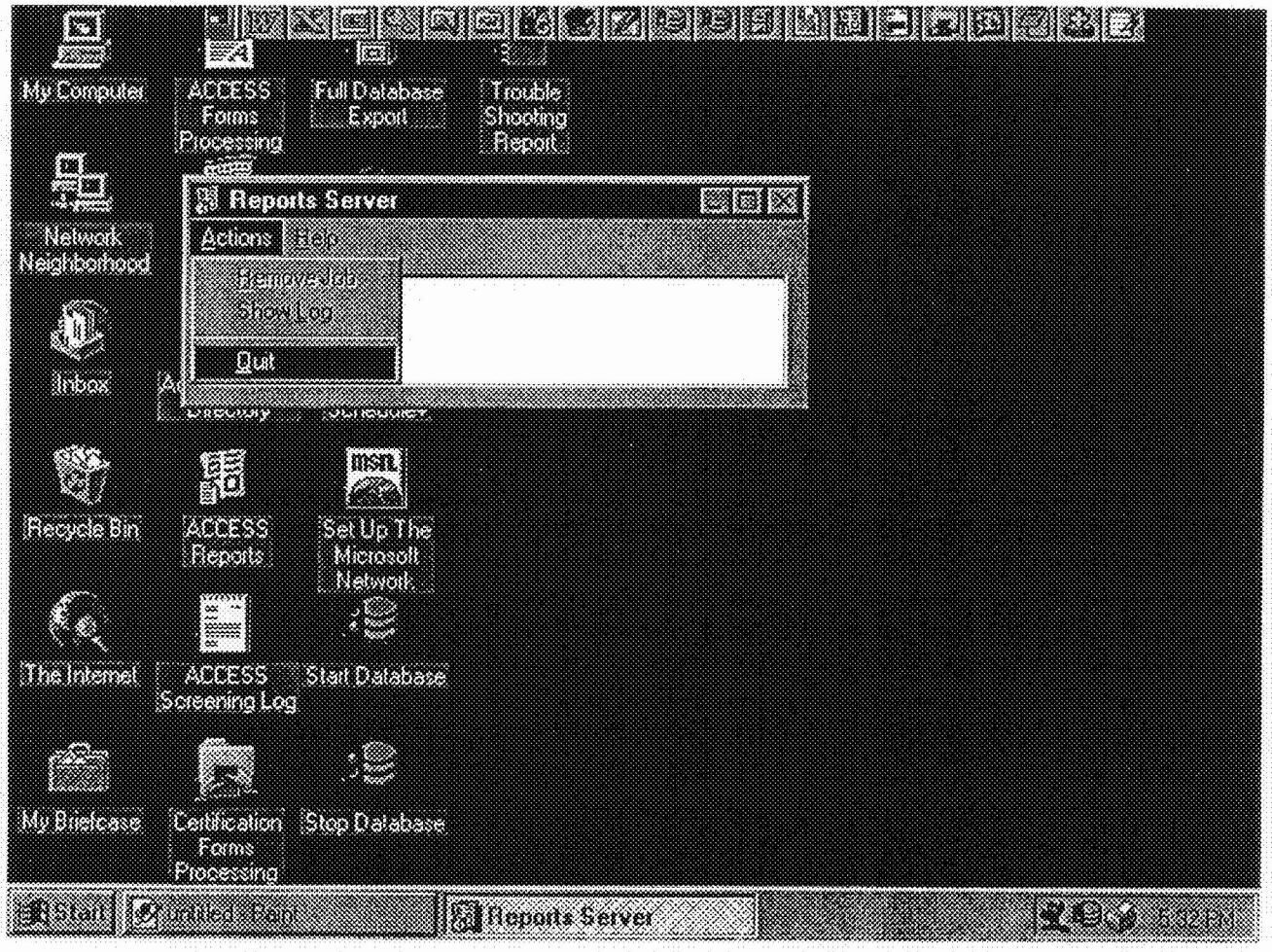


Figure 8-7

Print Setup Message Box

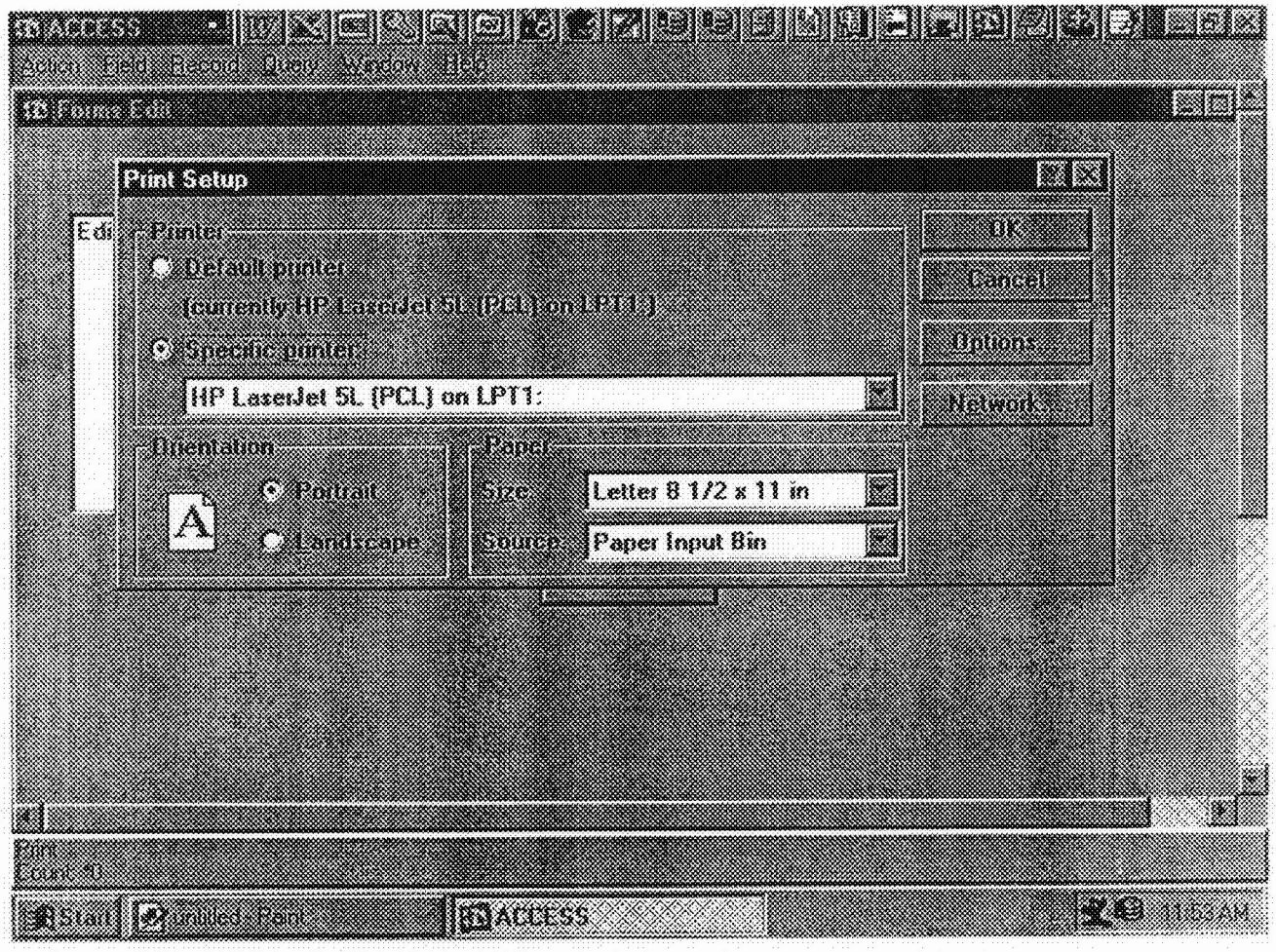


Figure 8-8

Print Message Box

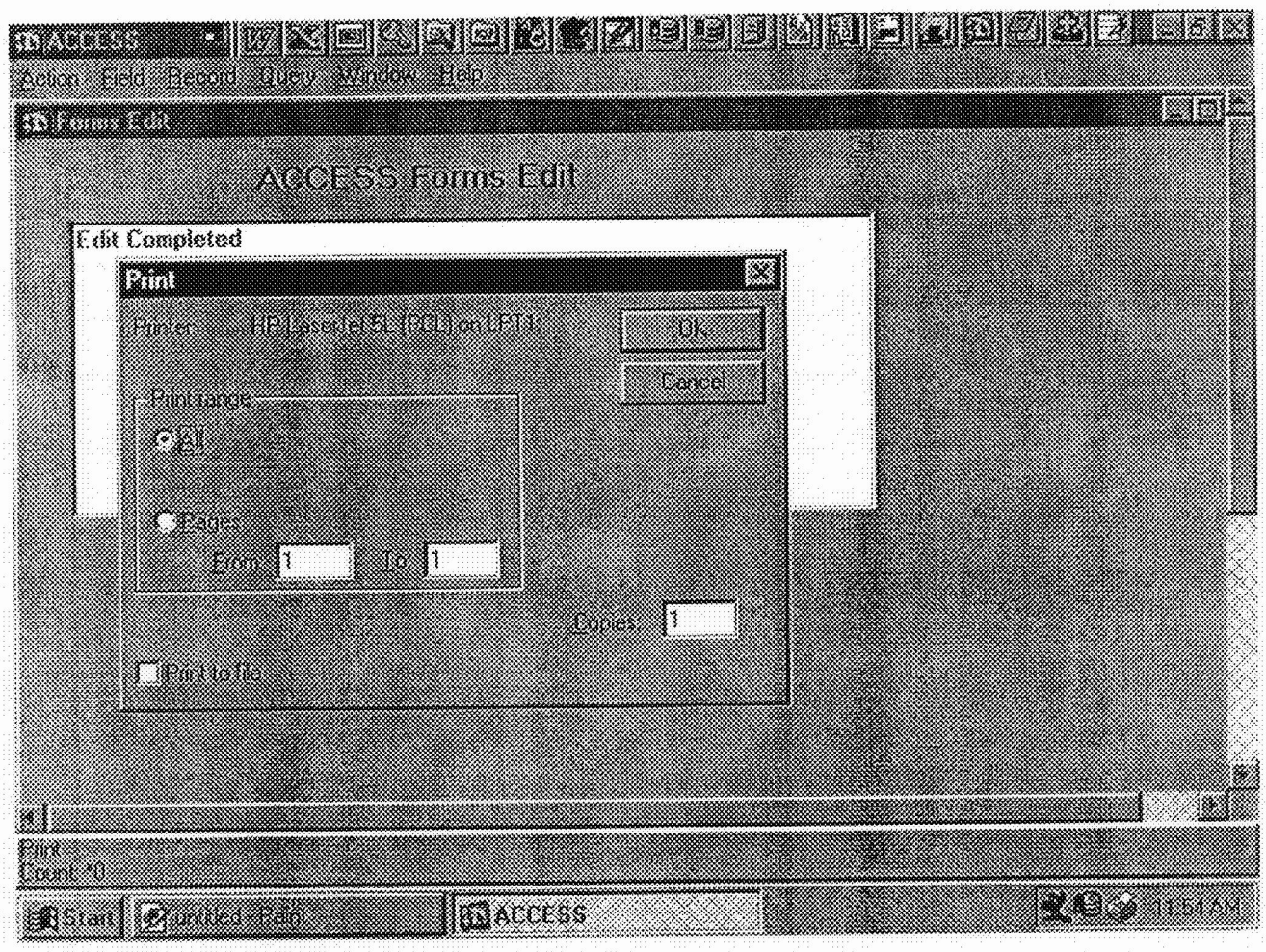


Figure 8-9

Print Capture Message Box

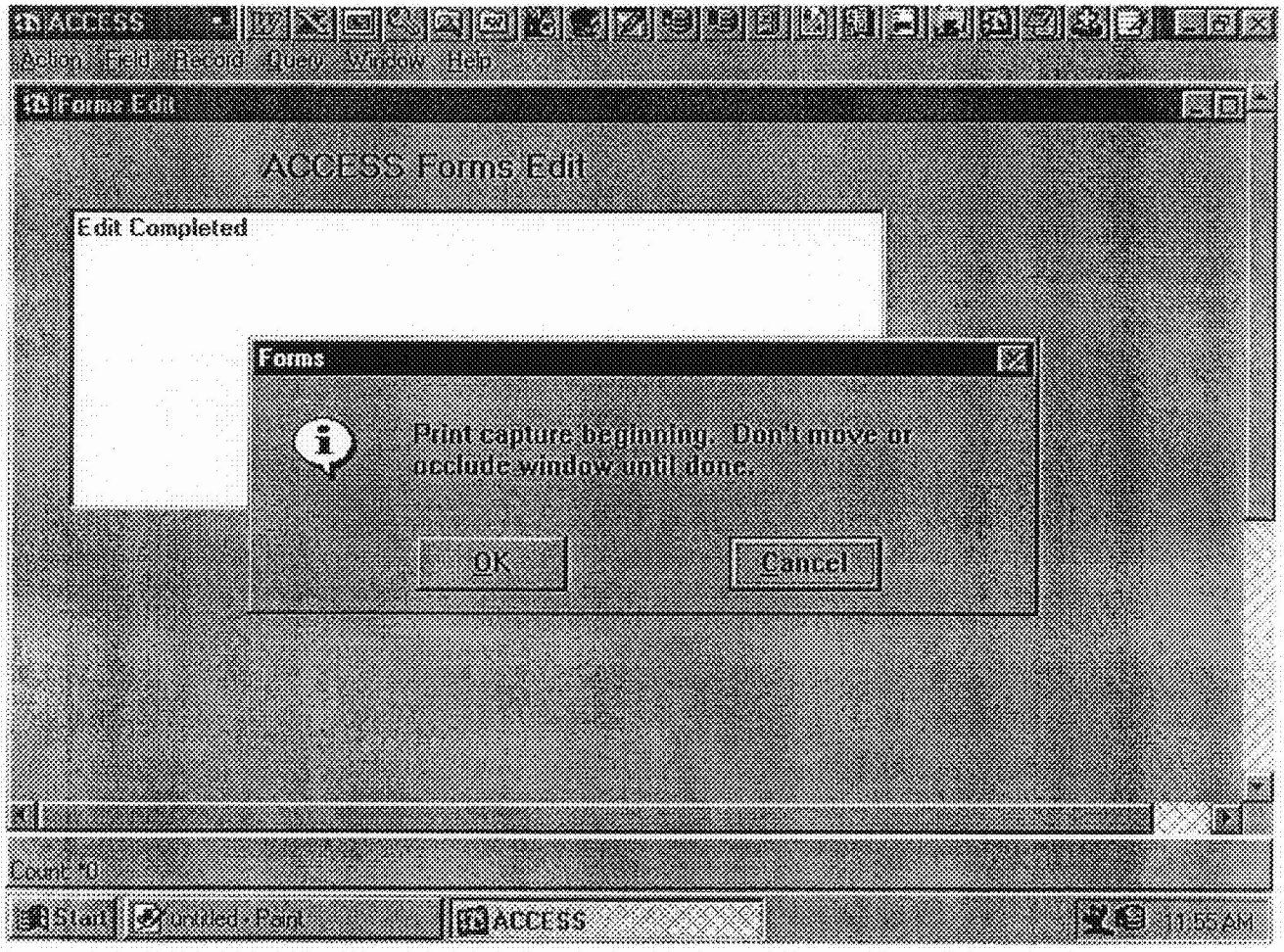
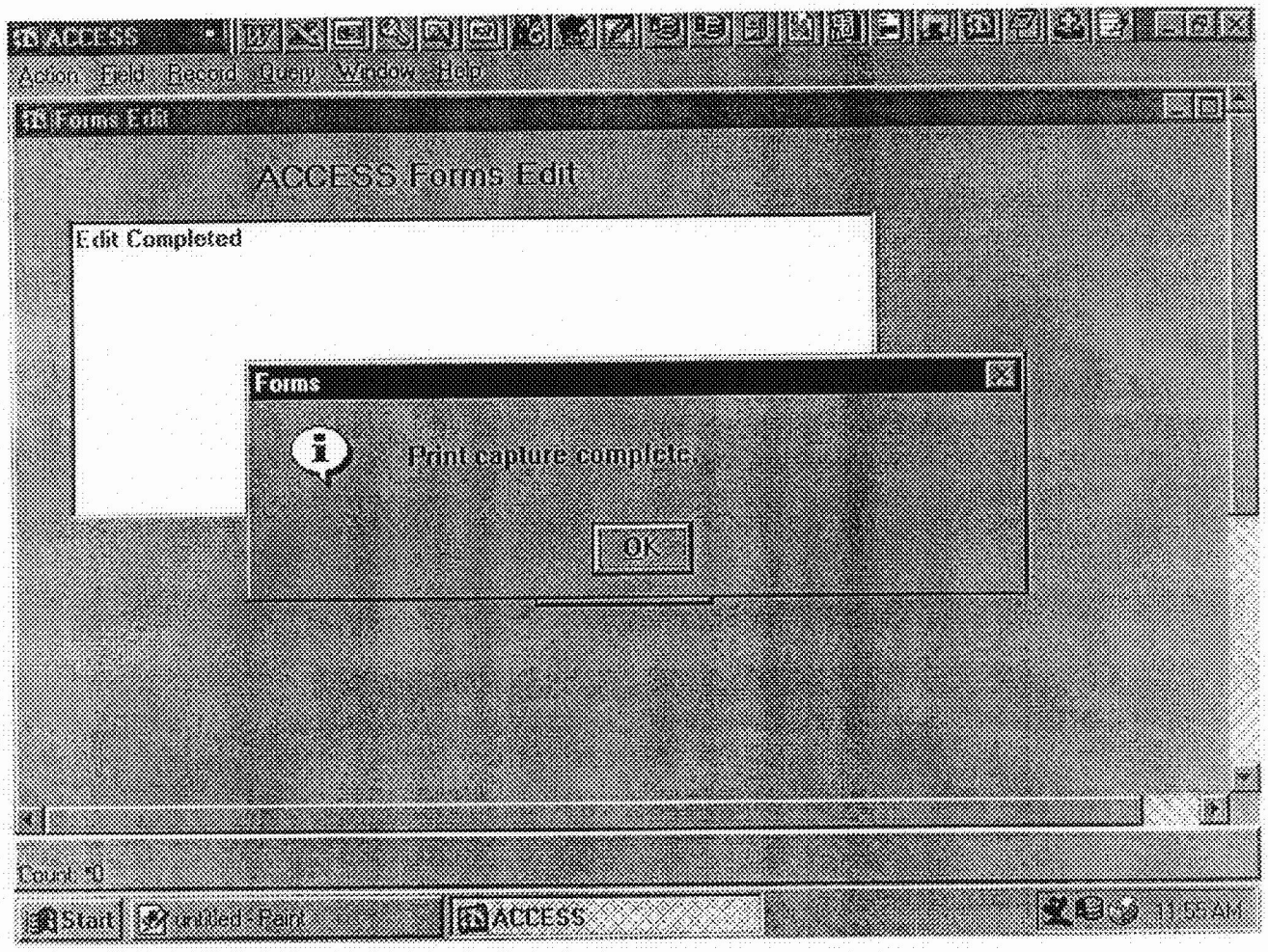


Figure 8-10

Print Capture Complete Message Box



A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume III

CHAPTER 9

PROBLEM SOLVING

9.1 OVERVIEW

Although staff are trained and certified for data management functions, unanticipated problems may occur or training may need to be reinforced. Coordinating Center staff are available to answer questions about the ACCESS data management system and solve unanticipated problems. A microcomputer at the Clinical Coordinating Center is configured like those at the Clinical Centers. Clinical Coordinating Center staff are able to "walk-thru" problems with Clinical Center staff by going through the same procedure as the Clinical Center staff member. If this approach does not work, then Clinical Center staff will be asked to set up their microcomputer for remote diagnostics as described in Chapter 7. Clinical Coordinating Center staff will then "take over" the Clinical Center microcomputer so that staff can "see" exactly what is being displayed on the Clinical Center microcomputer. Clinical Coordinating Center staff can peruse the database and system to diagnose the problem. The Clinical Coordinating Center Data Management Help Desk is always available to Clinical Center staff during normal business hours. See the Address Directory for staff names.

Clinical Coordinating Center staff will respond to e-mail messages within one to two working days. If there is a question about the protocol or any procedures, send it via e-mail and an e-mail response will be sent back to the originating Clinical Center. The general e-mail address is ctasc@clark.net. By using this method, questions and answers are documented in writing. This reduces the chance of a miscommunication.

9.2 Form Deletion or Participant Identity Problems

If an incorrect form is entered or the participant identification is entered and saved incorrectly, Clinical Center staff will want to delete the form. In previous distributed data management systems, allowing Clinical Center staff to delete forms has not been an optimum solution. In addition, incorrect participant identity usually means that other forms and the inventory and support files must also be changed. Thus any deletions or changes to participant identity are made by Clinical Coordinating Center staff via remote access. Problems should be reported by completing Form D1, Form Deletion - Participant Identification Correction and sending by facsimile transmission to the Clinical Coordinating Center. Figure 9-1 shows Form D1.

Figure 9-1

ACCESS Form D1
Rev. 0 8/30/96
Page 1 of 1

FORM DELETION -- PARTICIPANT IDENTIFICATION CORRECTION

ID:	____ ____ ____ - ____ ____ ____ ____
Form Number:	____ ____
Revision:	____
Form Type:	____ ____ ____ ____

		OLD (Incorrect)	NEW (Correct)
1.	Participants Initials:	__ __ __	__ __ __
2.	Item 2 Date (from form):	__ __ __ - __ __ - __ __ __ __ (Month - Day - Year)	__ __ __ - __ __ - __ __ __ __ (Month - Day - Year)

3. Form is to be . . . . . (1) Deleted
(2) Corrected

4. Person completing report:

A. Signature: . . . . . _____

B. Certification No.: . . . . . __ __ __ - __ __

C. Date report completed: . . . . . __ __ __ - __ __ - __ __ __ __ (Month - Day - Year)

5. Comments:

_____

_____

_____

_____

Please retain a copy of this form for your files and fax the original to:
410-435-0689
Attention: ACCESS Clinical Coordinating Center

A Case Control Etiologic Study of Sarcoidosis
(ACCESS)

Procedures Manual

Volume IV

June 1999

Notice: The contents of this Procedures Manual are confidential and are not to be cited or discussed except with individuals to whom it has been distributed on behalf of the ACCESS Steering Committee.

Prepared by:

Clinical Trials & Surveys Corp.
The Village of Cross Keys
350 West Quadrangle
Baltimore, Maryland 21210

Draft 06/18/99

A Case Control Etiologic Study of Sarcoidosis (ACCESS)
Procedures Manual Volume IV

Table of Contents

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

PREFACE

Volume IV of the ACCESS Procedures Manual details the procedures planned for the ACCESS DNA Core Laboratory, the Bronchoalveolar Lavage (BAL) Core Laboratory, and studies in seven specialized laboratories. The special laboratory studies were selected by the ACCESS Principal Investigators as most appropriate for the central goal of ACCESS -- to determine the cause(s) of sarcoidosis. Each chapter of Volume IV describes the procedures for a separate laboratory or special study. Chapter 1 describes the procedures of the DNA Core Laboratory to prepare genomic DNA, plasma and cell pellets for use by other investigators and for long term storage. Chapter 2 describes the procedures of the HLA Class II Typing Core Laboratory for analysis of genomic DNA to define the HLA Class II associations with sarcoidosis. Chapter 3 describes the procedures of the RNA Core Laboratory for the Molecular Analysis of Sarcoidosis-Specific Genes. Chapter 4 describes the procedures of the Ribosomal RNA Core Laboratory in searching for an Infectious Etiology of Sarcoidosis. Chapter 5 describes the procedures of the L-Forms Core Laboratory to determine the Role of Mycobacterial Cell Wall Deficient Forms in Sarcoidosis. Chapter 6 describes the procedures at the Johns Hopkins Hospital in Defining an Etiologic Antigen in Kveim Reagent. Chapter 7 describes the procedures in the BAL Core Laboratory. Chapter 8 describes the procedures for the Study of Pathogenic T Cells in Sarcoidosis. Chapter 9 describes the procedures for the Study of the Immunogenetics of Sarcoidosis. Chapter 10 describes the procedures for data transmission from Core Laboratories to the Clinical Coordinating Center. Although each of the special studies represents an independent effort, HLA Class II Typing requires DNA provided through the DNA Core Laboratory which will also provide DNA and plasma to the Central Repository. Also, the DNA Core Laboratory provides cell pellets to the Ribosomal DNA Core Laboratory for the Special Study, Searching for an Infectious Etiology for Sarcoidosis and DNA to the Medical University of South Carolina for the Special Study of Immunogenetics of Sarcoidosis.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 1

DNA CORE LABORATORY PROCEDURES

1.1 SAMPLE HANDLING

1.1.1 Core Facility Receipt

Blood samples shipped by express mail are received at the Henry Ford Health System (HFHS) - One Ford Place dock. Packages are received Monday through Saturday and are immediately delivered to the Core Laboratory for processing. Laboratory personnel are available Monday through Saturday to accept shipments and process samples. The originating institution must notify the Core Director that samples have been sent. If a sample is not received when expected, the sending institution is notified.

1.1.2 Sample Identification

Each blood sample has an identification number (provided by the Clinical Coordinating Center) which is printed on multiple computer labels resistant to tearing, moisture, freezing and aging. These labels are pasted on the original blood tubes and all other tubes containing the sample throughout the process to maintain the correct ID. These labels are also placed upon the final storage tubes.

1.1.3 Record Keeping and Quality Control

The following items are recorded in the database and on a Sample Tracking Form:

Date received

Label ID number

Originating institution

Sample volume

Final DNA concentration per aliquot

Number of aliquots of plasma and DNA

Cell count in cell pellet

Dates of shipment of aliquots to the Central Repository

Dates of shipments of cell pellets to the Ribosomal DNA Core Laboratory at the University of Iowa

Dates of shipments of DNA to the Immunogenetics of Sarcoidosis Special Study Laboratory at the Medical University of South Carolina.

1.1.3.1 Computer System and Database

An IBM PC computer is dedicated to this project. Information is stored for each patient using standard spreadsheets. The DNA Core Laboratory staff store in this database:

Label ID number

Originating institution

Date received

Blood sample volume

DNA concentration and total DNA

Quality assessment (acceptable, non acceptable)

Dates of shipments of aliquots to the Central Repository

Dates of shipments of cell pellets to the Ribosomal DNA Core Laboratory at the University of Iowa

Dates of shipments of DNA to the Immunogenetics of Sarcoidosis Special Study Laboratory at the Medical University of South Carolina

Identification of samples shipped

Number of DNA aliquots shipped

Number of plasma aliquots shipped

Number of cell pellets shipped

Cell count in each cell pellet

1.1.3.2 Security

The DNA Core Laboratory computer is in the DNA Core Laboratory Director's office, which is locked after working hours. It is accessible only to specified personnel. All logs and forms are stored in a locked file cabinet in the same office.

1.1.3.3 Back-up

All information is stored in the computer and backed up weekly using a tape drive. In addition to computer files, the following forms are kept as hard copy:

Sample Tracking Form

DNA Core Laboratory Sample Processing Log

1.1.3.4 Quality Control of Records

The DNA Core Laboratory Director is responsible for ensuring that all records are consistent and complete for each sample.

1.2 SPECIMEN PREPARATION FOR DNA EXTRACTION

Specimens are prepared for extraction of genomic DNA in the DNA Core Laboratory and for shipping of frozen, buffy coat derived cell pellets to the Ribosomal DNA Core Laboratory for extraction of organism DNA.

1.2.1 Preparation for Genomic DNA

Forty ml of blood are spun at 1500 rpm for five minutes at 20°C. Plasma is decanted and saved frozen at -70°C for later shipment to the Central Repository. Cellular constituents are used for genomic DNA isolation.

1.2.2 Preparation of Cell Pellets for Organism DNA

Ten ml of blood are centrifuged over Ficoll at 1500 rpm for 30 minutes at ambient temperature. The buffy coat is removed, washed once with phosphate buffered saline and centrifuged for five minutes at 1500 rpm. The cell pellet is resuspended in 1 ml phosphate buffered saline and cells are counted (1:100 dilution). Cells are again spun for five minutes at 1500 rpm. The supernatant is removed, and the cell pellet frozen at -70°C for shipment to the Ribosomal DNA Core Laboratory for extraction of organism DNA.

1.3 DNA PROCESSING

1.3.1 Record Keeping

All processing information is recorded in the DNA Core Laboratory Sample Processing Log which contains sample ID number and processing information including dates, yields, final

concentrations, total DNA and DNA quality control photograph. All information is maintained in the database with the exception of photographic results. The DNA Core Laboratory Director is responsible for ensuring that all records are consistent and complete for each sample.

1.3.2 DNA Isolation and Quantitation

A detailed description of procedures for isolation of genomic DNA is provided in Exhibit 1-1. All procedures and photographic results are recorded in the DNA Core Sample Processing Log.

1.3.3 Aliquoting and Storage

All purified DNA samples are diluted to a constant concentration and aliquoted into Biostor vials containing approximately 200 micrograms each to eliminate repeated freezing and thawing which may destroy the integrity of high molecular weight DNA. Sample tubes are labeled with identification number, DNA concentration and volume. DNA samples are stored in Tris-EDTA (TE) buffer at -70^{o}C for long term preservation. Plasma samples are stored in 1 ml aliquots at -70^{o}C until shipped.

1.3.4 Quality Control

If DNA levels are below the minimum requirement, or if the DNA is not of high molecular weight the originating institution is notified. If an additional sample is provided, this sample is numbered identically to the first with the addition of a letter to indicate repeat sampling.

1.4 SHIPPING PROCEDURES

All samples are shipped in batch biweekly to repository sites. The repositories are notified of the date of shipment. Frozen pellets of cells prepared from buffy coat of blood cells are shipped to the ACCESS Ribosomal DNA Core Laboratory for isolation of organism DNA. Plasma and purified DNA are shipped by overnight mail on dry ice in biomailers approved for biological material. Accompanying information includes a copy of the DNA Blood Specimen Shipping Form.

1.5 DETAILED PROCEDURES FOR GENOMIC DNA ISOLATION

1.5.1 Sample Collection

Blood is drawn into anticoagulant-containing Vacutainer tubes. For highest yield, EDTA or acid citrate is preferable to heparin as an anticoagulant (Gustafson, et al., 1987; Madisen et al.,1987; Ross et al., 1990; Kendall, et al.; 1991). Blood should be maintained and shipped in biomailers approved for biohazardous material at room temperature after drawing.

1.5.2 Genomic DNA Isolation

Samples are processed at time of receipt. DNA is prepared by detergent lysis and organic solvent extraction (Zoghbi, et al., 1989). First, samples are spun 5 minutes at 1500 rpm at 20^{o}C and plasma removed to be frozen at - 70^{o}C. The remaining sample is diluted 1:2 (original volume) with Triton-lysis buffer (10 mM Tris-HCl pH 7.50, 5 mM $MgCl_2$, 0.32 M sucrose, 1% Triton X), mixed by gentle inversion, and left at 4 ^{o}C for 30 minutes. A nuclear pellet is obtained by centrifugation at 4^{o}C., the supernate is decanted and nuclei lysed using 75 mM NaCl, 25 mM EDTA, (pH 8.0), 0.5% sodium dodecyl sulfate (SDS) and Proteinase K. After overnight digestion at 65^{o}C, the DNA is extracted with one volume phenol (pH 8.0) and one volume chloroform. DNA is precipitated from the aqueous layer using isopropanol and ammonium acetate. Typical DNA yields range from 300 micrograms to 2000 micrograms and largely depend on the white blood count at the time the sample is obtained. All DNA samples are rehydrated after isolation in 10 mM Tris, 1 mM EDTA (TE). All dilutions from a concentrated stock are made in this same buffer. The physical handling (i.e., pipetting) of genomic DNA is minimized.

1.5.3 Quality Control

Five microliters of DNA are run on a 0.6% agarose gel and compared to ethidium bromide stained high molecular weight (over 23 kb) DNA standards to ensure that the DNA is of high molecular weight and not degraded. Five microliters accounts for 0.25% to 1% of the sample, or 0.25 - 1 microgram. The quality of DNA and concentration of the stock are determined and recorded using a UVP digitizing system. If the sample contains significant degraded material, or less than 400 micrograms are obtained, the originating center is notified to request additional blood.

EXHIBIT 1-1

DETAILED PROCEDURE: GENOMIC DNA ISOLATION

Day 1:

1) Record patient identifier, date of receipt, date of draw and source in DNA Core Sample Processing Log.

2) All laboratory procedures are recorded in the DNA Core Sample Processing Log including sample volume, yields and quality test results.

3) Spin tubes 5 minutes at 1500 RPM to separate plasma. Remove plasma layer and divide into 1 ml aliquots in Biostor vials. Store at -70°C until shipped.

4) Pour remaining blood from glass tubes into two 50 ml tissue culture conical tubes, rinsing tubes with a small amount of Triton-lysis buffer. Dilute the blood in each tube 1:2 with Triton-lysis buffer. Mix gently and leave at 4°C for 30 minutes. Rinse the glass tubes in 50% bleach and dispose of in sharps container.

5) Spin at 3500 RPM for 25 minutes at 4°C.

6) Decant supernatant gently into a beaker being careful not to disturb the pellet, which contains cell nuclei. Retain the supernatant and store at 4°C until finished with the extraction. To a new 50ml conical tube add 19 ml Nuclei Lysis Buffer, 1 ml 10% SDS and 100 Fl Proteinase K (25 mg/ml). Add this to the pellet in one tube. Invert to dislodge the pellet. Add the broken up pellet to the second tube. Pipette up and down to break up the pellet. Incubate the sample in a 65°C water bath overnight to digest.

Day 2:

1) In a fume hood, add an equal volume (20 ml) phenol pH 8. Pipette under the layer of 0.1M Tris-HCl pH 8 to get to the phenol. Invert the tube to mix. Spin at 3500, RPM, 4°C, for 20 minutes.

2) Using a dispopipette and being very careful not to disturb the undigested protein at the interface, transfer the upper phase to a clean 50ml tube. Add an equal volume (20ml) of chloroform and mix. Spin at 3500 RPM, 4°C, for 10 minutes.

3) Transfer the upper phase to another tube. Add 10 ml 7.5M ammonium acetate to this tube and then divide the sample in half. Add 1.5 volume (of the original sample) of isopropanol to the sample. (If original sample = 20ml, add 30 ml total of isopropanol or 15 ml isopropanol to each tube). Invert until DNA precipitates.

4) Dip the end of a heat-sealed capillary tube into 70% ethanol and then flame. Swirling this rod through the sample, collect the precipitated DNA on the capillary tube tip by swirling. Be careful not to collect too far down the rod. Dip in 70% ethanol and air dry for about 10 minutes.

5) Stand the rod in an Eppendorf tube containing 0.5-1.0 ml of Tris- EDTA buffer pH 8.0. The volume depends on the yield of DNA. Put the sample at 4°C to rehydrate overnight, removing the rod.

EXHIBIT 1-1

DETAILED PROCEDURE: GENOMIC DNA ISOLATION (Continued)

NOTE: If for some reason there is a low yield of DNA, add ½ volume more of isopropanol at step 3. Leave at -20°C. overnight. Decant gently and add 70% ethanol to wash pellet. Spin 20 minutes at 3500 RPM. Pour off the supernatant and air dry pellet. Add 400 Fl of TE buffer.

DNA Quantitation and Quality Control

The amount of DNA is estimated using ultraviolet-induced fluorescence emitted by ethidium bromide molecules inserted into the DNA. The amount of fluorescence is proportional to the total mass of DNA. The quantity of DNA in the sample can be estimated by comparing the fluorescent yield of the sample with that of a series of standards.

CAUTION: Ethidium bromide is a powerful mutagen. Gloves should be worn. Ultraviolet radiation is harmful to eyes. Wear a safety mask to block the light. Dispose of ethidium bromide gels in hazardous waste.

1. Prepare a 0.6% agarose gel by adding 0.6g agarose/100 ml 1x Tris - acetate-EDTA buffer with 0.5 microgram/ ml ethidium bromide.

2. Make a 1:5 dilution of DNA in 1x Tris - EDTA buffer, pH 8.0. (5Fl DNA + 20Fl 1x TE buffer).

3. Mix 5Fl of the diluted DNA sample with 1 Fl of 6x tracking dye. Load this sample on the gel. (Since this is a 1:5 dilution, 5Fl of the sample represents 1Fl of the original DNA). Load 4Fl of *lambda* DNA digested with Bste II marker at 100 ng per Fl adjacent to the samples.

4. Run the gel at 110-120 volts until the dye migrates about 1.5 inches into the gel.

5. Photograph the gel using UV illumination and the UVP photographic system. Save photo to diskette for future use and print out the photograph. Compare the intensity of the fluorescence of the unknown DNA with that of the marker. The high molecular weight band of the marker is equal to 250ng of DNA.

6. Confirm concentration by running a second agarose gel. Load this next to 2 Fl (200ng) and 6Fl (600ng) of marker. The 5 Fl sample should compare to 600ng of marker. If the DNA concentration is 300 ng/Fl, aliquot sample.

7. Record the total volume, concentration and yield of DNA (micrograms/ml) in the Sample Processing Log.

8. Aliquot the stock DNA into 200 microgram samples in Biostor vials. Store at -70°C until shipped

EXHIBIT 1-1

DETAILED PROCEDURE: GENOMIC DNA ISOLATION
(Continued)

REAGENTS

Triton-Lysis Buffer

For any volume:
- 0.32M Sucrose
- 10mM Tris-HCl pH 7.50
- 5mM $MgCl_2$
- 1% Triton X

For 1 liter:
- 109.54g Sucrose
- 10 ml 1M Tris-HCl pH 7.50
- 10 ml Triton X - 100
- adjust pH to 7.5
- add 5 ml 1M $MgCl_2$
- Bring to 1000 ml with ddH_20

This buffer can not be autoclaved or filter sterilized. Store at 4°C. Make up fresh solution every month.

Nuclei Lysis Buffer

For 500 ml:
- 2.2g NaCl
- 4.5g EDTA
- adjust pH to 8.0
- Bring to 500 ml with ddH_2O
- Autoclave. Store at room temperature.

1M Tris-HCl pH7.5

For 500 ml:
- 60.56g Tris
- adjust pH to 7.5 with HCl
- Bring to 500 ml with ddH_2O
- Autoclave. Store at room temperature.

Proteinase K in 50mM Tris-HCl pH8, 1% SDS (25 mg/ml)

For 4 ml:
- 100 mg Proteinase K
- 2 ml 0.1 M Tris-HCl, pH8
- 0.4 ml 10% SDS
- 1.6 ml ddH_2O
- Aliquot and store at -20°C.

A Case Control Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 2

HLA CLASS II TYPING

2.1 OVERVIEW

HLA genes are the most notable candidate susceptibility genes in sarcoidosis. In previous studies, HLA Class I and II genes have been associated with various presentations of sarcoidosis (i.e. age, extent of disease, ethnic groups) and prognosis (Pasturenzi et al.,1993; Martinetti et al.,1995; Ishihara et al.,1996). Importantly, HLA gene products play a direct role in the immune response. CD4+ and CD8+ T lymphocytes only respond to antigenic peptides that are bound to HLA Class I and II proteins (Babbitt et al.,1985). Thus the ability to develop a CD4+ or CD8+ T cell immune response to specific antigens is dependent upon specific immunogenic peptide sequences binding to HLA Class I or II molecules and then being presented to T lymphocytes.

Sarcoidosis has been characterized as disease with an increased number of CD4+ T lymphocytes at the site of disease activity (Hunninghake and Crystal,1981). CD4+ T lymphocytes only respond to antigenic peptides that are bound to HLA Class II molecules. Thus the ability of specific HLA Class II molecules to bind antigenic peptides, may determine the antigens (i.e., environmental agents) associated with sarcoidosis. Therefore, this study investigates HLA Class II associations with sarcoidosis and correlates any associations with environmental exposure history.

Since the major heterogeneity of HLA Class II molecules resides in the â chains, the molecular sequence of HLA Class II DP, DQ and DR beta chains is determined by polymerase chain reaction (PCR) amplification of genomic DNA and hybridization with sequence specific oligonucleotide probes (SSOP). In addition, specific alleles are also identified by their ability to be amplified by PCR using sequence specific primers (SSP). If any molecular sequence is ambiguous by these methods, then the allele is sequenced (Dyer et al., 1993). Less than 5% of all samples are expected to need sequencing. Associations are made not only with specific HLA Class II alleles, but also with specific hypervariable amino acids that are crucial for peptide binding. This study not only investigates a larger number of individuals than previous studies of HLA Class

II associations in sarcoidosis, but also is the first study to correlate HLA Class II alleles and hypervariable amino acid positions with a detailed environmental exposure history.

DNA is extracted for these studies in the ACCESS DNA Core laboratory. Four aliquots of 5 Fmol DNA are coded for each individual case and control. These samples are sent from the DNA Core Laboratory to the Central Repository for storage. Every month approximately 48 samples are sent from the Central Repository to the HLA Class II Typing Core Laboratory. Only after the DNA sequences have been determined is the code be broken to determine whether samples are from cases or controls. Five percent of all samples are analyzed blindly a second time to estimate reproducibility. The standard for reproducibility of the Class II typing is greater than 99%.

2.2 CASE AND CONTROL POPULATIONS

Identification of cases and controls is performed according to the ACCESS Protocol, and standard data collection includes staging of disease, environmental exposure questionnaire, and family history. In a sub-population of 252 cases, the two-year outcome of sarcoidosis is determined to further define the phenotype of these patients.

2.2.1 Statistical Considerations

Power analysis indicates that the first aim of the study to test whether Class II alleles are associated with sarcoidosis can be accomplished with 180 patients. With this population, an odds ratio of 5 is detected with a power of 90% if the correlation between cases and controls is 0 (a conservative lower bound). This analysis is performed after the first 180 cases and controls have been analyzed. However, to determine whether sarcoidosis is associated with specific environmental exposures in the presence of a given HLA Class II allele requires these studies to be performed on 480 cases and controls. Assuming 10-15% of the cases have a given allele, 48-72 cases with the allele would be compared to their controls for environmental associations. The odds ratios of cases with the allele would be compared to the odds ratios for the environmental exposures in the 408-432 cases who do not have that allele. Under these assumptions, the prevalence of an exposure of interest would have to be at least 5-15% in order to have 80% power

to determine whether the presence of the allele elevated the exposure associated risk of sarcoidosis 3-5 fold. Similar analyses are performed evaluating specific HLA Class II beta chain amino acids at polymorphic amino acid positions related to the binding pockets for peptides. This analysis increases the sensitivity of ACCESS to detect associations between environmental exposures and sarcoidosis.

2.2.2 Strategy for Molecular Typing of Exon 2 of the HLA-DRB1, -DQB1 and –DPB1 Genes of Class II Molecules

DNA Extraction (performed by the DNA Core Laboratory).

DRB1 Typing

First Level Evaluation (Generic typing)

Amplify genomic DNA with generic DRB primers.

DRB AMP – 1A

DRB AMP – B

DRB AMP GH46A

Perform hybridization with generic DRB1 SSO probes.

Identify alleles and allele groups.

DRB1*09

DRB1*10

DR1 Group

Identify by DRB SS0 probes for DR1 group.

Proceed to Second Level DR1 Group Evaluation.

DR2 Group

Identify by DRB SS0 probes for DR2 group.

Proceed to Second Level DR2 Group Evaluation.

DR4 Group

Identify by DRB SS0 probes for DR4 group.

Proceed to Second Level DR4 Group Evaluation.

DRw52 Group

Identify by DRB SS0 probes for DRw521 group.

Proceed to Second Level DRw52 Group Evaluation.

Second Level Evaluation

Basic approach

Amplification of DNA with group specific primers.

Hybridization with group specific SSO.

Identification of group specific alleles.

DR1 Group

Amplification primers.

DRB AMP-1A

DRB AMP-B

Hybridization with DR1 Group specific SSO probes.

Identification of DRB1.*01 alleles.

DR2 Group

Amplification primers

DRB AMP-1A

DRB AMP-B

Hybridization with DR1 Group specific SSO probes.

Identification of DRB1*01 alleles.

DR4 Group

Amplification primers

DRB AMP-4

DRB AMP-B

Hybridization with DR4 Group specific SSO probes.

Identification of DRB1*04 alleles.

DRw52 Group

Amplification primers

DRB AMP-3

DRB AMP-B

Hybridization with DRw52Group specific SSO probes.

Identification of DRB1*03, *11, *12, *13, *14, *08 alleles.

Third Level Evaluation (PCR Amplification using SSP)

Dynal (Dynal A.S., Oslo, Norway) DRB1*01 – SSP

Dynal (Dynal A.S., Oslo, Norway) DRB1*03 – SSP

Dynal (Dynal A.S., Oslo, Norway) DRB1*04 – SSP

Dynal (Dynal A.S., Oslo, Norway) DRB1*15/16 – SSP

Fourth Level Evaluation

PCR amplification and sequencing.

DQB1 Typing

First Level Evaluation

Amplify genomic DNA with DQB1 primers.

Amplification primers

DQB AMP-A

DQB AMP-B

Perform hybridization with specific SSO probes.

Identification of DQB1* alleles.

Second Level Evaluation (PCR Amplification using SSP)

Dynal (Dynal A.S., Oslo, Norway) DQB1* – SSP

Third Level Evaluation

PCR amplification and sequencing.

DPB1 Typing

First Level Evaluation

Amplify genomic DNA with DPB1 primers.

Amplification primers

DPB AMP-A

DPB AMP-B

Perform hybridization with specific SSO probes.

Identification of DPB1* alleles.

Second Level Evaluation (PCR Amplification using SSP)

Dynal (Dynal A.S., Oslo, Norway) DPB1* – SSP

Third Level Evaluation

PCR amplification and sequencing.

2.3 SPECIFIC METHODS

2.3.1 DNA Isolation

DNA is extracted and supplied by the DNA Core Laboratory.

2.3.2 PCR Amplification

DNA is amplified on a thermocycler (Gene Amp. PCR System 9600 Perkin-Elmer) according to standard methods (Saiki et al.,1988; Vaughan et al.,1990; Mickelson et al., 1993) using 50 pmol of each primer, 25 pmol of each dNTP, and 2.5 units of Taq Polymerase (Perkin-Elmer Cetus) in a final volume of 100 lambda. The sequence of the primers used are the same as described in the II International Histocompatibility Workshop: DRBamp-A (5'), DRBamp-B (3'), and DRB-G46 to amplify all DRB loci, including DRB1, DRB3, DRB4 and DRB5. For DPB1: DPBamp-A (5'), and DPBamp-B (3'). ForDQB1: DQBamp-A (5'), and DQBamp-B (3'). The PCR cycle profile for DRB generic, and DQB1 is 20 sec. Denaturation step at 96^{o}C followed by 20 sec. annealing at 57^{o}C, and 75 sec. Extension at 72^{o}C. For DPB1, DRw52, DR2, and DR4, the cycle profile consists of a 20 sec. Denaturation step at 96^{o}C, 10 sec. annealing at 62^{o}C, and 60 sec. extension at 72^{o}C. A 270 base pair amplified DNA product is verified by 2% agarose gel electrophoresis.

2.3.3 Oligonucleotide Probes and Primers

Synthesis is performed on a MilliGen/BioSearchSyslone 8400 DNA Synthesizer in the Nucleic Acid Facility of the Biochemistry Laboratories at the University of Pennsylvania.

2.3.4 SSOP Hybridization

Hybridization is performed as described elsewhere (Bugawan et al., 1990; Teodorica et al., 1990; Obata et al., 1991) with some modifications. Amplified DNA is diluted in water and dot blotted into Hybond N+ nylon transfer membranes (Amersham Corp., Arlington Heights, Il) using a Micro 96 Dot Blot Apparatus (Robbins Scientific Corp., Sunnyvale, CA). The DNA is bound to the membrane by UV irradiation in a STRATALINKER 1800 (Stratagene, La Jolla, CA.). A panel of sequence-specific oligonucleotide probes (SSOP), described earlier (Kimura and Saszuki, 1992),

is used with some modifications. The oligonucleotide probes are labeled with digoxigenin-11-dUTP (Boehringer Mannheirm Corp., Indianapolis, IN) using terminal deoxynucleotidyl transferase (Boehringer Mannheirm) according to the manufacturer's instructions. The labels are detected by sheep anti-digoxigenin antibody fragments (Fab) conjugated to alkaline phosphatase (Boehringer Mannheim) diluted at 150 mU/ml. Nitro blue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate (Sigma Chemical Co., St. Louis, MO) are used as the chromogenic substrates.

2.3.5 SSP Analysis

The SSP analysis is performed using commercially available kits (Dynal A.S., Oslo, Norway). The specific kits employed are Dynal DRB1*01 – SSP, Dynal DRB1*03 – SSP, Dynal DRB1*04 – SSP, Dynal DRB1*15/16 – SSP, Dynal DQB1*– SSP, and Dynal DPB1*– SSP.

2.3.6 Sequencing

When specific alleles cannot be determined by SSOP or SSP analysis, the DNA is sequenced. Specific primers are utilized to amplify the allele of interest. The DNA is prepared for sequencing using the PRISM ready reaction dye deoxy terminator cycle sequencing kit. The sample is immediately loaded into an automatic sequencer at the University of Pennsylvania Cancer Center's Sequencing Laboratory. All sequences are analyzed in both forward and backward directions .

2.3.7 Nomenclature

The nomenclature for HLA alleles identified in this project are those identified in 1995 (Bodmer et al., 1995).

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 3

MOLECULAR ANALYSIS OF SARCOIDOSIS-SPECIFIC GENES

3.1 INTRODUCTION

With the striking advances that have occurred in molecular biology, novel approaches applicable to identifying an infectious etiology of sarcoidosis have recently become available that could be applied either to blood or to tissue specimens. One powerful method is potentially capable of not only discerning an infectious etiology, but also providing additional information about genetic, environmental, and immunologic contributions to sarcoidosis. This technique involves the differential display of reverse transcribed (RT) polymerase chain reaction (PCR) products, and is termed differential display PCR (DD-PCR).

DD-PCR involves the use of arbitrary oligonucleotide primers to amplify most mRNAs found in the cell using reverse transcriptase PCR, with modifications to target cDNA coding regions (Liang and Pardee, 1992; Liang et al., 1992; Amac et al., 1994; Brenner et al., 1994; Gullans et al., 1994; Kojima et al., 1994; Randall et al., 1994;). For the ACCESS study, the DD-PCR reaction is performed using RNA from cases and controls, and the PCR products from each reaction are compared on polyacrylamide sequencing gels.

DD-PCR detects bands that are consistently observed in one group (either cases or controls), but are absent in the other group of paired samples. Alternatively, bands may be selected on the basis of either increased or decreased intensity. Using recent modifications, including the normalization of background noise, the unique bands that are present in cases but not controls are presumed to represent candidate genes specific for sarcoidosis. Such candidate genes could be of host origin or could represent genetic material from an infectious agent that is causally related to development of sarcoidosis. To identify and characterize the genes, unique bands are eluted from the gel, reamplified, and cloned into plasmids. The clones are sequenced and subjected to computer analysis in the GenBank to identify the genes and determine whether, for example, there is a specific gene of viral or bacterial origin.

Although DD-PCR is a technique that has been developed only recently, it has already been used successfully to identify genes differentially expressed in a variety of conditions applicable to human disease, including oncogenes, tumor suppressor genes, and transplantation associated genes, as well as metabolically or developmentally induced genes (Brunet et al., 1991; Liang and Pardee, 1992; Liang et al., 1993; Aiello et al., 1994; Nishio et al.1994; Russell et al., 1994; Utans et al., 1994; Zimmermann et al., 1994). In humans, there is precedent for this technique using both peripheral blood specimens and small tissue samples, such as those obtained by renal biopsy (Gullans et al., 1994). Recent improvements have allowed comparisons of gene expression from individuals representing eight different ethnic groups (Brenner et al., 1994). Reproducibility for this technique has been shown in experiments identifying novel breast cancer tumor suppressor genes; the bands were reproducible (>95%) for a given pair of primers and mRNA samples in more than three independent experiments (Liang and Pardee, 1992; Liang et al., 1993).

Given that sarcoidosis may be a multifactorial disease, there is an advantage in selecting an approach which screens for several types of etiologic agents simultaneously. Using DD-PCR with arbitrary primers, all types of non-infectious and infectious etiologies, including viral and fungal as well as mycobacterial, can be detected. Furthermore, since previous successful laboratory studies have shown that paired samples and good controls are essential for interpreting DD-PCR (Sunday, 1995), the case control method of study using differential display with human samples is an ideal approach.

3.2 SPECIFIC METHODS

3.2.1 Subjects

An initial pilot study (Phase I) includes 20 patients with sarcoidosis and 20 matched controls to generate 50 candidate gene markers of sarcoidosis. Confirmatory studies will be done with an additional 20 cases and controls. Depending upon the results from these initial pilot studies, a larger group of cases and controls may be screened using semi-quantitative PCR with primers specific for the candidate genes identified.

3.2.2 Specimens

3.2.2.1 Collection and Processing of Specimens

Twenty ml of peripheral blood are drawn from each case and control. Peripheral blood mononuclear cells are harvested using Ficoll-Hypaque centrifugation. Allowing for variability in processing and yields from case to case, we estimate that 20 ml of peripheral blood will yield 20 Fg of high quality RNA.

3.2.2.2 Cell Storage and Shipping

After peripheral blood mononuclear cells are obtained, the cells are counted and redistributed so that 10×10^6 cells are resuspended in 1 ml of solution D (containing 4M guanidinium thiocyanate, 0.75 M Na citrate, pH 7, 10% sarcosyl and DEPC treated distilled water). The pellets which have been suspended in solution D (estimate of 2 ml) are frozen for future insolation of RNA.

3.2.2.3 Isolation of mRNA

The pellets which have been suspended in solution D are processed for RNA at Brigham and Women's Hospital. The RNA is isolated from the pellet according to the guanidinium thiocyanate phenol-chloroform extraction method (Chomczynski and Sacchi, 1987). A uniform approach is to use the RNA isolation kit (Stratagene, cat #200345) based upon this method. Isolation of poly (A)+ RNA is used for confirmatory Northern blot analysis with oligotex-dt (Qiagen). Quantity of RNA is ascertained by optical density (O.D.), followed by ascertainment of RNA quality by visualization on a 4% agarose ethidium bromide stained paraformaldehyde gel.

3.2.3 Differential Display PCR

3.2.3.1 Overview

Differential display PCR involves the use of arbitrary oligonucleotide primers to amplify most mRNAs found in the cell using reverse transcriptase PCR, with modifications to target cDNA coding regions (Liang and Pardee, 1992; Liang et al., 1992; Amac et al., 1994; Brenner et al., 1994; Gullans et al., 1994; Kojima et al., 1994; Randall et al., 1994;). Differential display PCR detects bands that are consistently observed in one group (either cases or controls), but are absent in the other group

of paired samples. Using recent modifications that target coding sequences and greatly reduce false positives, the unique bands that are present in cases but not controls are identified and presumed to represent candidate genes specific for sarcoidosis. To identify and characterize the candidate genes, unique bands are eluted from the gel, reamplified, and cloned into plasmids. The clones are sequenced and subjected to computer analysis in the GenBank to identify the genes and determine whether, for example, there is a specific gene of viral or bacterial origin.

3.2.3.2 Differential mRNA Expression Analysis

For the reverse transcriptase (RT) reaction, a 20 ml volume containing 2 mg total RNA, 10 U RNase inhibitor (Promega), 2mM diothiothreitol, 50 mM KCl, 10 mM Tris-HCL (pH 8.3), 5 mM Mg Cl_2, 100 mM dNTPs, 2.5 mM oligo-dT primer and 200 MMLV reverse transcriptase (Life Technologies) is incubated for 1 hour at 37^o C, heated to 99^o C for 5 minutes, and chilled on ice. RNA is treated with DNase to reduce genomic contamination.

To perform PCR, 1 ml of the cDNA reaction mixture is added to 1.25 mM Mg Cl_2, 50 mM KCl, 10 mM Tris-HCL (pH 8.3), 2.5 mM of each primer, 5 mCi ^{35}S-dATP. and .3 U *Taq* polymerase. The primers included in the PCR reaction are the arbitrary oligonucleotides previously found to be most effective (Oligos Etc, Portland, OR) (Kojima et al., 1994). The samples are run on a Biomek 2000 Robotic work station capable of performing high throughput differential display PCR.

The PCR products are separated by electrophoresis on a 6% polyacrylamide-urea gel prepared using a long-range thermoregulated electrophoresis system (Genoymx). This system is computer controlled and provides high resolution of differential display PCR of large cDNA fragments. Samples are run for 2-3 hours at 1500 V, transferred to filter paper, and autoradiographed.

3.2.3.3 Cloning the cDNA Fragments

The cDNA fragments are excised from the gel, eluted into 0.5 ammonium acetate /1mM EDTA (pH 8.0), precipitated, and washed. Using PCR, the cDNA product is reamplified in the presence of 2 mMg Cl_2, 50 mM KCl, 10 mM Tris-HCL (pH 8.3), 20 mM dNTPs, 12.5 mM primers, and 2 U *Taq* polymerase.

Reamplified cDNA fragments are separated on a 2% agarose gel, isolated, blunt-end ligated into a plasmid vector (pBluescript SK+) and cloned. Plasmid DNA is isolated (Qiagen) and the cDNA inset is sequenced at Brigham and Women's Hospital.

3.2.3.4 Computer Analysis

DNA sequences are analyzed using standard DNA search algorithms (e.g., BLASTN, BLASTX). cDNAs are of three types: 1) a known gene, 2) a homologue of a known gene or a 3) a completely novel gene. Current experience indicates that at least 50% are known genes (e.g., transcription factors, cytokine receptors), so that we anticipate correlation with functional significance. Moreover, should we isolate a viral or bacterial gene, this will be readily evident in the homology search. In addition, the current databases contain most human mRNA sequences, so that we are likely to be able to readily obtain a full-length clone.

3.2.3.5 Northern Blot and Semi-Quantitative/Quantitative PCR Analysis

In the confirmatory studies, the RNA isolated as described above is analyzed by Northern blot and semi-quantitative PCR analysis using standard methods (Ausubel et al. 1991). The cDNAs identified can be utilized directly as probes for Northern blot analysis in future studies to confirm the desired differential expression and to provide information about the molecular weight of the identified transcripts. The same cDNA fragments (generally between 100 and 500 base pair (bp) in length) can be rapidly screened by sequencing. Semi-quantitative PCR is performed using primers specific for the candidate genes identified by the original screening. For quantitative PCR, an exogenous competitor template is prepared as described (Schneeberger and Zeillinger, 1996) and used for quantification. Given the sample numbers, quantitative PCR is performed on a subgroup of samples for confirmatory studies.

3.2.4 Controls for Experimental Procedures and Quality

3.2.4.1 mRNA and Differential Display

mRNA is extracted as described above, analyzed for quality on an agarose gel, and subjected to DNase treatment prior to the RT reaction. DNase treatment has been shown to reduce background noise in differential display PCR due to sequences generated from contaminating DNA.

Each PCR reaction is done in quadruplicate, using an additional non reverse transcribed control. On the sequencing gel, adjacent lanes for the PCR reaction run in quadruplicate are run comparing samples from cases versus controls. Obtaining a second independent blood sample from each case and control may not be feasible, so this issue is addressed in the following ways. First, when mRNA is originally made, it is stored in multiple aliquots. Comparison analyses of different mRNA aliquots by differential display PCR in quadruplicate analyses are made. Second, if cases return for follow up studies, consideration to draw a blood sample at that time could be made. Finally, the case control study design is totally appropriate for differential display analysis, because each case has a control matched for multiple parameters. Our analyses are designed to confirm or eliminate our candidate genes specific for sarcoidosis.

3.2.5 Northern Blot Analysis

To rule out false positive cDNAs, candidate genes are subcloned into plasmid vectors, and Northern blots are performed using random-primed cDNA probes of the candidate genes with the RNA from the cases and controls.

3.2.6 Semi-Quantitative/Quantitative PCR

As with all PCR analyses, excellent laboratory technique is maintained, including previously well defined procedures to eliminate sample contamination, e.g., use of gloves and plugged micropipettor tips. Controls include non reverse transcribed samples and samples without RNA.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 4

SEARCHING FOR AN INFECTIOUS ETIOLOGY FOR SARCOIDOSIS

4.1 INTRODUCTION AND BACKGROUND

Sarcoidosis is a systemic disorder of unknown cause. It is likely to be a consequence of an environmental exposure in a genetically susceptible host. This notion is based upon several observations--the Isle of Man epidemiology studies (Hills et al., 1987; Parkes et al., 1987), the occurrence of the disease in clusters of time and place (Sharma and Kadakia, 1986; Kern et al., 1993), and the loss of the capacity to trigger granuloma formation in mice using injected human sarcoid tissue, when the tissue is pre-treated with autoclaving, stored at -20^{o} C for one week or exposed to irradiation (Mitchell et al., 1976). In addition, there are case reports of possible transmission of sarcoidosis via allogenic bone marrow transplantation (Heyll et al., 1995) and by cardiac transplantation (Burke et al., 1990). Also sarcoidosis has occurred in the lungs that have been transplanted into patients with the disease (Kazerooni and Cascade, 1995; Martinez et al., 1994). These observations suggest that sarcoidosis may be triggered by an infectious agent.

There are many known infectious agents that can cause granulomas that are typical of sarcoidosis, including mycobacteria, herpes viruses, histoplasmosis, treponematosis, sporotrichosis, coccidiomycosis, schistosomiasis, listeria, the agent of Whipple's disease and Rhodococcus sp. (Bisaccia et al., 1983; van Etta et al., 1983; Cho et al., 1984; Ghossein et al.; 1987; Southern et al., 1989; Spapen et al., 1989; Wright et al., 1989; Lyons et al., 1991; Bocart et al., 1992; Gerdes, et al., 1992; Graham et al., 1992; Joyce-Brady, 1992; Mitchell et al., 1992; Saboor et al., 1992; Su et al., 1992; Thakker et al., 1992; Fidler et al., 1993A; Fidler et al., 1993B; Lisby et al., 1993; Ehlers et al., 1994; Impraim et al., 1994; Nikkels et al., 1994; Popper et al., 1994; Mangiapan and Hance, 1995). Because sarcoidosis has a world-wide distribution, it is necessary to postulate that the putative agent that causes sarcoidosis is also widely distributed, if there is

indeed a single infectious disease as a cause. It is also possible that sarcoidosis may be the result of several different infections.

Although granulomas may occur in direct response to an infection and the presence of the whole organism, they may also occur as a response to an infectious agent product such as the cell wall. This appears to be the case in some instances of herpes zoster related cutaneous granulomas (Langenberg et al., 1991; Nikkels et al., 1994) in which viral nucleic acid is not found in the granuloma. Alternatively, the granulomas may be in response to a host antigen that has been altered by the infection. Thus, it is conceivable that the sarcoid granuloma does not contain infectious organism DNA or viable organisms. In searching for an infectious etiology for sarcoidosis there have been attempts to identify unusual objects (either foreign body or infectious agents) using light and electron microscopy on granulomas. Structures resembling leptospiral or large mycobacteriophage microorganisms have been identified in bronchoalveolar lavage (BAL) fluid from subjects with sarcoid (Williams and Davis, 1986) and from the center of the sarcoid granuloma (Wang et al., 1981). Similar structures have also been identified in the newly recognized syndrome of familial granulomatosis disease (Chadarevian et al., 1992). While these unusual bodies may be an infectious agent, one study has identified them as likely damaged platelets (Williams and Davis, 1986), raising the intriguing possibility of an altered platelet, perhaps associated with an infectious agent.

Clinically the granulomas of sarcoidosis are diffusely spread throughout the body, implying strongly that an etiologic agent is distributed through the blood stream, at least at some point in the disease. It is therefore reasonable to look for a probable infectious agent by examining the blood from subjects with sarcoidosis. Indeed many infectious agents that appear clinically organ specific, can now be detected in blood specimens using molecular techniques (Nichols et al., 1991; Chryssanthou et al., 1994; Murakami et al., 1994; Schluger et al., 1994; Goodman et al., 1995; Patel et al., 1995); this list includes many of the mycobacterial sp., as well as viruses and fungi. Moreover, the DNA from infectious organisms is also very likely to be in the plasma as well as in the cells of the blood, as has been demonstrated for instance for cytomegalovirus (CMV) and candida.

It is, therefore, a reasonable suggestion that blood samples be examined for any putative infectious agent(s) in sarcoidosis, and that infectious organism DNA is likely to be present in the blood, at least at some point in the disease, presumably most likely in acute, early cases.

Our overall hypothesis—is therefore that sarcoidosis is the result of a response to an infection. Our working hypothesis is that the DNA from this infectious agent will be present in the blood of sarcoidosis subjects.

There are now novel methods for examining for micro-organism DNA in tissues such as blood, and these methods have been the subject of recent reviews (van Belkum, 1994; Christie and Callihan, 1995). The first technique that is available examines for a candidate micro-organism DNA, using PCR primers that are specific to that particular candidate micro-organism. Such PCR primers are available for many infectious agents including mycobacteria, and the other agents, listed above, that have been associated with granuloma formation. This technique is well established, sensitive, and specific for the candidate micro-organism.

A second technique is to examine tissues for the presence of DNA coding for micro-organism related ribosomal RNA (r-RNA). This relatively new technique is very powerful in its capacity to identify micro-organism DNA in tissue samples, such as blood. DNA coding for r-RNA varies little within species. Indeed, differences in this DNA have been used over the last few years to construct a whole new phylogenic tree for micro-organisms. Micro-organisms have been classified, with this new system, into three main domains - Bacteria, Archaea and Eukarya (Stackebrandt and Woese, 1991). These domains account for all of the known micro-organisms, as well as unknown micro-organisms. Using PCR techniques to amplify for micro-organism DNA, it has been recently demonstrated, for instance, that less than 10% of the microorganisms in the soil (Liesack and Stackebrandt, 1992) and in the ocean (Britschgi and Giovannoni, 1991) have been previously identified. The domain Archaea has not been found to have any human pathogens at this time (Schmidt and Relman, 1994), whereas human pathogens do come from the Bacteria and Eukarya domains. This approach of examining for 16S ribosomal DNA has recently been applied to examine for the putative agent of Kawasaki's disease (Rowley et al., 1994), as well as to

demonstrate very successfully the causative organisms in Whipples' disease (Relman et al., 1992) and a probable infectious agent in Crohn's disease (Sanderson et al., 1992). This technique of broad-based 16S ribosomal DNA searches has recently been reviewed (Relman, 1993). Viruses are the only organisms that are not detected using this approach.

4.2 AIMS

Given this background the proposed studies have three major aims:

Aim 1: to determine the prevalence of micro-organism DNA using broad based PCR for the detection of 16s-DNA for micro-organisms in the domain Bacteria, Eukarya and Archaea, in blood samples from both normal and sarcoidosis subjects.

Aim 2: to determine the prevalence of specific viral and bacterial DNA in blood samples using micro-organism specific primers for CMV, the agent of Whipples' disease, and mycobacteria including M. tuberculosis and M. avium in blood samples from both normal and sarcoidosis subjects.

Aim 3: to compare the type and prevalence of micro-organisms identified in blood samples from normal controls and sarcoidosis subjects.

4.3 RESEARCH DESIGN AND METHODS

4.3.1 DNA Preparation

Cell pellets are prepared in the DNA Core Laboratory from blood samples obtained from cases with sarcoidosis and controls as part of the ACCESS Protocol and shipped, frozen, to the University of Iowa for DNA extraction. The DNA is prepared in Iowa from the cell pellet. Buffy coats are removed from blood in a sterile hood and spun at 1500-2000 rpm to pellet. Pellets are washed once with normal saline, cells counted and cell counts are recorded. Five million cells are separated to extract DNA and the rest are frozen at -135°C. Separated cells are respun to pellet; 120 Fl 10% SDS, 80 Fl TE Buffer pH 7.0, and 20Fl Proteinase K are mixed with cells and the mixture is heated to 56EC for one hour or to 95EC for 10 minutes. An equal volume of Phenol:Chloroform:Isoamyl Alcohol (25:24:1) is added to the cells. The cells are shaken and then spun at 14000 rpm for 10

minutes at 4°C. The aqueous layer is removed. An equal volume of Chloroform:Isoamyl Alcohol (24:1) is added and the mixture is spun at 14000 rpm for 10 minutes at 4°C.

DNA is precipitated by adding 10% of aqueous volume 3M Sodium Acetate at pH 6.0 and two volumes of cold 100% ethyl alcohol. The mixture is incubated at -20°C for 30 minutes, and then spun at 14000 rpm for 10 minutes at 4°C. The pellet is washed with cold 80% ETOH and resuspended in 50Fl Sigma RNase free water (#W-4502), Proteinase K (stock 10 mg/ml) using Gibco BRL Pro K catalog #25530-015, to reconstitute according to the manufacturer's recommendation. The DNA prepared in this way is stored in DNA/RNase free water at -70°C

4.3.2 PCR

The DNA is screened for known pathogens and unknown pathogens using PCR in conjunction with appropriate primers (see primer section to follow). Briefly DNA amplification is performed as follows: all reactions contain 50 mM KCI, 10 mM Tris-HC1, 1.5 - 5.0 mM $MgCl_2$, 0.1 mg/ml BSA, 0.4 mM of each oligonucleotide primer (Res. Gen., Huntsville, AL), 0.2 mM each of dNTP (Boehringer Mannheim, Indianapolis, IN), 2.0 U AmpliTaq DNA polymerase (5U/ml, Perkin Elmer Cetus, Forest City, CA) and l00 ng of DNA template or water. Thirty-five amplification cycles are performed with denaturation at 94°C for 45 seconds, annealing at 55-68°C for 45 seconds and extension at 72°C for 2 minutes, using an automatic thermocycler (Geneamp 9600, Perkin Elmer Cetus, Forest City, CA). Samples are run on a 1.5% agarose gel in 1X Tris-Borate-EDTA buffer with 0.5 mg/ml ethidium bromide.

To address Aim 1, aliquots of DNA prepared from cell pellet samples are examined for the presence of Bacteria domain DNA using specific primer pairs. Prior to the blood samples being evaluated, the specificity and sensitivity of each primer pair are evaluated using a panel of known organisms in the Bacteria and Eukarya domains. A positive result is the detection of a well defined PCR product of the correct size for the primer pairs, in the presence of no product for the negative control and well-defined product for the positive control. If the PCR assay does not give good quality results for the negative and positive controls, it is re-run until an adequate reaction has occurred.

Positive PCR products for organisms in the Bacteria and Eukarya domains are noted in samples from both controls and cases and the PCR band kept for later sequence analysis.

To address Aim 2 aliquots of DNA prepared from the cell pellet samples are examined for the presence of specific viral and bacterial DNA using primer pairs. These primers have been used in previous studies, and are considered specific for these organisms, and have been selected as they usually represent repeating motifs in the organism genome. However, sensitivity and specificity assessments are conducted using a known panel of organisms. Again we accept a positive PCR product only in the presence of adequate negative and positive controls in the same PCR reaction. In preliminary results, we have demonstrated that the primers that are specific for M. tuberculosis are more sensitive than the primer to detect broad based 16s r-DNA, and for that reason believe that the two assays for candidate bacteria are complementary. Positive PCR products for specific organisms are so recorded.

In both Aims 1 and 2 experiments, great care is necessary to prevent cross contamination of blood samples with PCR products, especially PCR products from positive control organisms. To reduce the possibility of cross contamination all bacterial and viral cultures are stored and handled in another laboratory. The PCR reactions are performed in a sterile environment within our main laboratory from DNA aliquots derived from cell pellets provided by the DNA Core Laboratory.

Aim 3 is addressed with the assistance of the statisticians associated with the ACCESS study, after 50 sarcoidosis cases and 50 controls have been tested. To improve the chances of finding organisms in the sarcoidosis, cases with advanced pulmonary fibrosis sarcoidosis are excluded. This group, in our opinion, is less likely to have a circulating infectious agent.

We intend to spend the first several months of this study further examining the efficacy of the various methods for extraction of organism specific DNA from cell pellets and establishing that the host DNA does not unduly interfere with the organism DNA PCR amplification for all primer pairs. The optimal PCR conditions for each primer pair are obtained by establishing sensitivity and specificity for each primer pair. Then the ACCESS study samples are analyzed.

4.4 DETAILED METHODS OF DNA PCR STUDIES

DNA amplification will be performed as follows. All reactions contain PCR Master Mix with the following: 50 mM KCL, 10 mM Tris-HCL, 3 mM MgCL2, 0.1 mg/ml BSA, 0.4 mM each oligonucleotide primer (Research Genetics, Huntsville, AL), 0.2 mM each dNTP (Boehringer Mannheim, Indianapolis, IN), 2.0 U Amplitaq DNA Polymerase 5U/Fl (Perkin Elmer Cetus, Forest City, CA) and 100 ng/Fl of DNA template or water. For each sample, tubes contain 40 Fl of Master Mix, 0.4 µM each of 3' and 5' primers for a 50 Fl reaction. Thirty-five cycles of amplification are performed by denaturation at 94°C for 45 seconds, annealing at 60°C for 45 seconds and extension at 72°C for 2 minutes. One additional extension cycle of 72° for 7 minutes is performed (Gene Amp 9600 Thermocycler Perkin Elmer Cetus, Forest City, CA). Samples are run on a 1.5% agarose gel in 1X Tris-Borate-EDTA buffer with 0.5 Fg/ml ethidium bromide.

To determine the specificity of each of our primer pairs the following experiments are performed: To determine the specificity we test bacterial primer pair P515FLP and P13B with 100 ng/Fl DNA from M. tuberculosis, pseudomonas species, saccharomyces species and CMV in a 50 Fl PCR reaction. M. tuberculosis and pseudomonas DNAs are positive for a 904 bp product. The CMV and Saccharomyces species are negative for a 904 bp product. The M. tuberculosis specific primer pair, IS6110, is tested with 100 ng/Fl DNA from E. coli, pseudomonas, CMV and Saccharomyces in a 50 Fl PCR reaction. All DNAs are negative for a 123 bp product. The M. tuberculosis DNA is positive for a 123 bp product.

Fungal specific primer pairs NS3 and NS4 are tested with 100 ng/Fl DNA from E. coli, pseudomonas, CMV and M. tuberculosis. All DNAs are negative for a 597 bp product. Saccharomyces DNA are positive for a 597 bp product.

CMV IE specific primers are tested with 100 ng/Fl DNA from E. coli, pseudomonas, Saccharomyces and M. tuberculosis. All DNAs are negative for a 435 bp product. CMV DNA are positive for a 435 bp product. CMV LA primers are tested with 100 ng/Fl DNA from E. coli, pseudomonas, Saccharomyces and M. tuberculosis. All DNAs are negative for a 400 bp product. CMV DNA are positive for a 400 bp product.

To determine the sensitivity of the bacterial primer pairs fD1 and rP2 we test 1:10 serial dilutions of 100 ng/Fl M. tuberculosis DNA in a 50 uL PCR reaction. Our sensitivity should range from 100 ng to 0.01 ng.

To determine the sensitivity of bacterial primer pair fD1 and rD1 we test 1:10 serial dilutions of a 100 ng/Fl DNA from Pseudomonas agarici in a 50 Fl PCR reaction. Our sensitivity should range from 100 ng to 0.01 ng.

To determine the specificity of the fungal primer pairs NS3 and NS4 we test 1:10 serial dilutions of 100 ng/Fl DNA from Saccharomyces in a 50 Fl PCR reaction. Our sensitivity should range from 100 ng to 0.01ng.

To determine the sensitivity of the M. tuberculosis specific primer pair IS6110 we test 1:10 serial dilutions of 100 ng/Fl DNA from M. tuberculosis in a 50 Fl PCR reaction. Our sensitivity should range from 100 ng to 0.001 ng. To test for bacteria in blood we draw 10 ml of blood from a normal volunteer in a 15 ml Venoject tube containing 22.5 ml dry EDTA. The tube is spun at 2000 rpm for five minutes. The buffy coat is removed, the cells are counted by Coulter Counter (Coulter Corp., Hialeah, FL) and DNA extracted. DNA is quantitated by OD 260/280 and diluted to 100 ng/Fl.

PCR is performed as above using primers P515FLP and P13B and 100 ng/Fl of blood in a 50 Fl PCR reaction. Added to the PCR tubes containing the 100 ng of blood DNA are 1:10 serial dilutions of M. tuberculosis DNA beginning with 10 ng/Fl. The sensitivity should range from 10 ng to 0.0001 ng.

Repeating the above experiment using primers P8FLP and P806R our sensitivity should range from 100 ng to 0.1 ng. The blood sample with no added bacteria should be negative.

Blood DNA is spiked with M. tuberculosis DNA in the same manner as above and tested with M. tuberculosis specific primers IS6110. The sensitivity should range from 10 ng to 0.0001 ng. The blood sample with no bacteria added should be negative.

Enzyme concentration is determined by the presence or absence of nonspecific background or insufficient product. To determine optimal magnesium chloride concentration we test concentrations between 0.5 to 2.5 mM. Primer annealing temperature and time are determined

based upon base composition, length and concentration of primers. Temperature is determined by starting with 5ºC below the true T_m of the primer. The number of cycles starts at 30 and increases by 2 cycles until the optimal cycling is reached.

4.5 PROCEDURES FOR ASSESSING INFLUENCE OF SHIPPING SAMPLES

In the event of organism DNA being recovered from specimens there will need to be a study to assess whether organism DNA is truly part of the sample or has been a contaminant introduced through shipping and/or processing in the DNA Core Laboratory. This will be addressed by taking samples in the Iowa center and splitting the sample into two, shipping one-half of the sample to the DNA Core Laboratory and retaining the other half of the sample in Iowa, then analyzing and processing as usual at the DNA Core Laboratory, and shipping the sample back to Iowa. Independently, the sample retained in Iowa will be processed similarly to the DNA Core Laboratory and analyzed for organism DNA. This will demonstrate if any organisms are collected or added from the sample processing and shipping steps. This will only be necessary in the event of organism DNA being found in the study.

A spiking study is underway. This spiking study involves specimens of normal blood drawn in Iowa under study conditions, spiking those specimens with known amounts of bacterial DNA in a variety of dilutions. The sample is shipped to the DNA Core Laboratory where it is processed under study conditions, and returned back to Iowa to see if the organism DNA added to the sample in Iowa can be recovered. There are appropriate controls kept in Iowa. The DNA used includes heat killed bacteria. This study is expected to be completed towards the end of ACCESS after other samples are processed.

It is understood that these additional studies (i.e., the search for any potential contamination and the spiking study), do not fully replicate the pathophysiological conditions that might be seen in sarcoidosis. For example, the spiking study will involve adding organism DNA and heat killed organisms to human blood samples. The recovery of spiked DNA depends upon incorporation of that DNA into the cell pellet which is different from the process by which organism DNA comes to be present in circulating cells and plasma in the course of infectious diseases.

4.6 FLUORESCENT DNA SEQUENCING

DNA sequencing is performed using fluorescent dye terminator chemistry and analyzed on one of two Applied Biosystems 373 Automated DNA Sequences (Stretchliner). Investigators provide the facility with the DNA templates for analysis. Templates can be double-stranded plasmic DNA, single-stranded M13 DNA, purified restriction fragments or PCR products. Reactions are performed using either standard sequencing primers provided by the facility or custom sequencing primers provided by the investigator. Most sequencing reactions employ the use of AmpliTaq FS DNA polymerase and a cycle sequencing protocol. The use of four different fluorescent dye dideoxynucleotide terminators permits single lane analysis for each template. Quality templates generate 400-700 bases of sequence information per reaction.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 5

ROLE OF MYCOBACTERIAL CELL WALL DEFICIENT FORMS IN SARCOIDOSIS

5.1 HYPOTHESIS

The working hypothesis is that sarcoidosis is caused by a mycobacterial or mycobacterial-like cell wall deficient organism.

5.2 SPECIFIC AIMS

The specific aims of the study are to:

1. Culture acid-fast cell wall deficient forms (CWDF) from blood and available tissue samples from cases with sarcoidosis and to compare findings with those obtained from controls.
2. Determine the structure of DNA isolated from CWDF grown from the blood of cases with sarcoidosis.

5.3 BACKGROUND AND SIGNIFICANCE

Despite intensive research efforts for nearly 90 years, the etiology of sarcoidosis remains uncertain. However, cumulative findings from a diverse array of sources including microscopy, culture, animal, and DNA studies implicate mycobacteria as causative factors in the development of the disease. In addition, several microscopy and culture studies suggest the etiological factor may be a mycobacterial cell wall deficient form (CWDF).

5.3.1 Microscopy Studies

Numerous reports have appeared in the literature describing the presence of acid-fast organisms in lymph node tissue of patients with sarcoidosis (Schaumann, 1941; Koch and Cote, 1965; Vanek, 1968; Baro and Butt, 1969; Richter et al., 1969; Vanek and Schwarz, 1970; Moscovic, 1978; Barth et al., 1979). In the most detailed light and electron microscopy study to date, Moscovic described "pleomorphic chromogens" with unique morphologic and histochemical properties in lymph node tissue from most patients with sarcoidosis (Moscovic, 1978). Based upon acid-fast

staining, variable size, and the prevailing occurrence of lipoid analogues of Mutch granules, he suggested that the structures represented CWDF (L forms) of mycobacterial organisms. He concluded that sarcoidosis is caused by a mycobacterial CWDF, and that traditional concepts of mycobacterial infections should be expanded to encompass the L-phase form of mycobacteria. In support, additional investigators have suggested that acid-fast organisms found in skin, lymph nodes and lung tissue from patients with sarcoidosis represent mycobacterial CWDF (Cantwell, 1981; Cantwell, 1982).

5.3.2 Culture of an Acid-Fast Organism

In earlier studies, CWDF were grown from the blood of 53 of 55 and 28 of 29 patients with sarcoidosis (Judge and Mattman, 1976; Judge, 1979; Judge and Mattman, 1982). No organisms were grown from the blood of 146 control subjects. The organisms grew within 24 hours. Morphologically, the micro-colonies resembled L forms of M. tuberculosis and other mycobacteria without distinguishing staining or morphologic properties. The organisms were microaerophilic and grew a few millimeters below the surface in semisolid broth, but were unable to multiply in strictly anaerobic conditions. The organisms did not depend on hypertonicity, and growth within red blood cells was a common characteristic. Findings of variable size, predominantly coccoid forms, larger L forms, and short acid-fast rods, suggested that the organisms were CWDF of mycobacteria. However, unlike CWDF grown from the blood of patients with tuberculosis, which occasionally revert to their wild type (intact cell wall) in vitro, the organisms grown from the blood of patients with sarcoidosis did not revert to a wild type under any culture condition. More recently Almenoff et. al. grew a CWDF from the blood of 19 of 20 subjects with sarcoidosis (Almenoff et al., 1996A). Findings that organisms were acid-fast and stained positively with a monoclonal antibody raised against M. tuberculosis whole cell antigen (H37RV), confirmed that the organisms were of mycobacterial origin.

Graham et al. grew acid-fast CWDF from biopsies of skin lesions from six of nine patients with sarcoidosis (Graham et al., 1988). Bacterial colonies were small, clear, moist and required

from three to 12 months to appear. Also, in a Russian study, filterable forms that passed through a 0.22 Fm filter, and indistinguishable from those of the tubercle bacillus, were grown from bronchial washings of 36 of 47 subjects with sarcoidosis and from blood samples of ten of the patients (Khomenko et al., 1987). Organisms were identified by Ziehl-Nielsen and Morahashi acid-fast stains and by immunofluorescence using an antibody raised in Guinea pigs. Barth et al. grew acid-fast slender rods suggestive of CWDF from the aqueous humor of a patient with sarcoidosis (Barth et al., 1979).

5.3.3 Animal Studies

In a series of studies, Mitchell and Rees demonstrated that homogenates of human sarcoid tissue injected into the foot pads of mice caused the slow development of widely disseminated granulomas in lymph nodes, lung, liver, spleen and muscle (Mitchell and Rees, 1969; Mitchell and Rees, 1972; Mitchell et al., 1976). Granulomatous inflammation was associated with the development of positive Kveim reactions and was passed from mouse to mouse four consecutive times. In contrast, mice inoculated with homogenates originating from human controls, autoclaved sarcoid tissue, sarcoid homogenates which had been stored for one week at -20 degrees, or fresh homogenates which had been exposed to cobalt irradiation, did not develop granulomatous changes or Kveim responses. Further, they concluded that the transmissible agent, which passed through a 0.2 Fm membrane filter, could represent a mycobacterial L form. Support came from finding acid-fast rods in Ziehl-Nielsen stained sections of mouse tissue showing epithelioid cell granulomas after a first passage from one and after a second passage from an additional patient with sarcoidosis. From a pooled homogenate of pulmonary tissue from mice given this second-passage homogenate a mycobacterium was isolated with cultural characteristics of human M. tuberculosis.

Similar studies were performed by Taub et. al. (Taub and Siltzbach, 1972; Taub et al., 1974), who observed that homogenates of lymph node material from patients with sarcoidosis caused granulomas in the foot pads of mice. However, unlike the findings of Mitchell and Rees, granulomatous changes were restricted to the site of injection, and no abnormalities were found in

lymph nodes, liver, spleen, or lung, and there was no response to the Kveim antigen. The foot pad response was passed to a second mouse, and did not occur following freezing and thawing of the material, thereby suggesting that the granulomatous changes were caused by a live organism.

Barth et al. found that mice inoculated with acid-fast micro-colonies isolated by culture from the aqueous humor of a patient with sarcoidosis developed "nonconsolidated nodularity" in the lungs (Barth et al., 1979). Acid-fast micro-colonies were found in smears of liver, lung, spleen, blood and ocular fluid from the mice.

In an extensive study performed by Judge as part of a Ph.D. dissertation (Judge, 1979) acid-fast CWDF grown from the blood of patients with sarcoidosis were concentrated by centrifugation and resuspended to give a turbidity reading intermediate between #4 and #5 on the McFarland scale. The "sarcoidosis organisms" were then injected intraperitoneally into mice. Subsequently, tissue from various organs was obtained at selected intervals for up to 90 days or at the time of death of the animal. Pathologic review of gross and microscopic samples revealed the presence of granulomas in various stages of development as early as 16 days. Organs frequently involved included the lung, liver, spleen, kidney and eye. Infrequently changes were seen in stomach, heart, and lymph nodes. Overall, granulomatous inflammation was found in 11 of 19 mice. In all animals, including those without evidence of granulomatous changes, acid-fast CWDF were found in tissue impressions of lung, spleen, eye and liver and grown from the blood. Extensive use of control animals revealed that granulomatous changes did not result from injection of sterile medium, and that acid-fast organisms found in the injected animals were not endogenous to the animal. In animals given viable organisms, the organisms recovered from blood cultures were always found to be acid-fast and to have growth, morphology, and staining properties similar to those of the inoculated organism. There was no evidence at any time that organisms had reverted back to their wild type.

Because animals developed granulomatous changes slowly during the 90 days of observation, additional animals were injected with cortisone (40 mg) prior to injection of the

"sarcoidosis organisms". These immunosuppressed animals developed extensive granulomatous disease within three weeks with extensive involvement of kidneys, liver, lung, and spleen, and 30% mortality.

In further studies, it was determined that mice injected with acid-fast CWDF isolated from the blood of patients with active pulmonary tuberculosis developed granulomatous disease similar to that found in animals injected with the "sarcoidosis organisms", except that animals injected with tuberculosis organisms developed less eye involvement.

5.3.4 Molecular Biology Studies

In general, recent molecular biology studies have demonstrated a link between mycobacteria and sarcoidosis. Saboor et. al. using a complex-specific insertion sequence IS986/IS6110 to detect DNA from M. tuberculosis complex bacteria and the conserved sequences of the mycobacterial groEL gene to detect DNA from mycobacteria other than M. tuberculosis found M. tuberculosis DNA in 50% of the patients with sarcoidosis and nontuberculosis mycobacterial DNA in a further 20% (Saboor et al., 1992). The false positive polymerase chain reaction (PCR) rate for M. tuberculosis was 9%. In a similar study using the same primers, the authors found M. tuberculosis DNA in granulomatous tissue from 7 of 16 patients with sarcoidosis (Fidler et al., 1993A; Fidler et al., 1993B). By use of liquid-phase DNA/RNA hybridization with a DNA probe specific for the rRNA of the M. tuberculosis complex, Mitchell et. al. found that hybridization with spleen tissue from patients with sarcoidosis was 4.8 times higher than that obtained with normal spleen tissue (Mitchell et al., 1992). In contrast, Bocart et al. using several oligonucleotide primers including the IS6110 insertion element found M. tuberculosis DNA in tissue samples from only 2 of 18 patients with sarcoidosis (Bocart et al, 1992). However, no patients with proven tuberculosis were included as positive controls. By use of paraffin-embedded tissue samples and PCR amplification, Popper et al. found strong signals for mycobacterial DNA in 2 of 15 samples from patients with sarcoidosis (Popper et al., 1994), whereas Ghossein et al. using similar techniques failed to find mycobacterial DNA in samples from ten patients (Ghossein et al., 1994). In a recent detailed article, Mangiapan and

Hance (Mangiapan and Hance, 1995) suggested that the divergent findings of molecular biology studies may, in part, be due to differences in mycobacterial DNA extraction methods, quantity of DNA amplified, choice of target sequences, choice of oligonucleotide primers, reaction conditions, amplification protocol, method for detecting amplified products, and contamination. They concluded that if mycobacterial DNA is present in most sarcoid tissues, it must be present in relatively small amounts. They suggested that even PCR techniques may not be sufficiently sensitive to identify small amounts of mycobacterial DNA (1 intact mycobacterium/105 human cells) in tissue samples from patients with sarcoidosis.

5.3.5 T Lymphocytes

T lymphocytes increase in number in mice immunized with mycobacterial tuberculosis (Janis et al., 1989). Activation of cells occurred in vivo and did not require major histocompatibility complex class II recognition. Additionally, in humans M. tuberculosis organisms, but not 65 KD heat shock protein, activated a large fraction of human peripheral blood T-cells (Kabelitz et al., 1990). Therefore, it is of interest that Balbi et al. found that subjects with sarcoidosis had an elevated number of blood and lung CD3+T-cells (Balbi et al., 1990). In an additional study by the same investigators, subjects with sarcoidosis and tuberculosis were found to have an expansion of the V2+ subset of T-cells, leading the authors to speculate that the sarcoid antigen is related to the mycobacteria family (Balbi et al., 1993).

5.4 PRELIMINARY DATA

5.4.1 Culture Studies

Using culture techniques favorable for the growth of CWDF, acid-fast CWDF were grown from the blood of 19 of 20 subjects with sarcoidosis, and from the blood of 0 of 20 controls (Almenoff et al., 1996A). Organisms stained positively with a monoclonal antibody raised against Mycobacterium tuberculosis whole cell antigen (H37RV). Final determinations of acid fast staining and staining with the monoclonal antibody were made by two of the investigators who did not know

the source of the samples. Additional findings of variable size, predominantly coccoid form, larger L forms, and short acid-fast rods, indicated that the mycobacterial organisms were CWDF.

5.4.2 Molecular Biology Studies

In preliminary studies (unpublished), DNA was extracted from CWDF organisms grown from the blood of patients with active sarcoidosis. Oligonucleotide primers were used that were specifically designed to recognize a conserved region of 16S ribosomal RNA. Bands in gels were visualized using cyber-green staining. To date, 11 of 14 samples from patients with sarcoidosis and one of ten samples from controls have demonstrated positive amplification. Each PCR "run" also included negative controls including distilled water and media, and positive controls including M. tuberculosis and Rhodococcus. Sequence data of an isolated-amplified 150 bp segment revealed DNA homology with an organism in the actinomycetes family. Currently, additional blood culture samples from sarcoidosis and control subjects are being evaluated, and specific primers are being developed that span larger, more variable regions of the 16S ribosomal gene.

5.4.3 Use of the API20E System

The AP120E system (Plainview, NY) uses 23 biochemical reactions to identify and characterize Enterobacteriaceae and other Gram negative bacilli. In an unpublished study, CWDF grown from the blood of 15 patients with sarcoidosis, 15 patients with untreated pulmonary tuberculosis, and 15 healthy controls, identical biochemical reactions occurred with CWDF from patients with sarcoidosis and tuberculosis. These reactions included arginine dihydrolase (ADH), lysine decarboxylase (LDC), ornithine decarboxylase (ODC), and urease (URE). Additionally, this biochemical pattern has never been described with any Gram negative organism. The findings indicate that the organism grown from the blood of patients with sarcoidosis is very similar metabolically to organisms grown from the blood of patients with untreated tuberculosis.

5.4.4 FPEC-GLC Studies

Through use of frequency-pulsed electron-capture gas-liquid chromatography (FPEC-GLC) in collaboration with Dr. John Brooks at the Center for Disease Control, we have evaluated biochemical profiles of serum in patients with acute and chronic sarcoidosis, untreated pulmonary tuberculosis, and healthy controls. In the study, we detected free nonbound tuberculostearic acid (TSA, 10-methyloctadecanoic) in subjects with untreated M. tuberculosis but not in subjects with sarcoidosis or healthy controls (Almenoff et al., 1996B). In unpublished studies, we did not detect TSA in sera from most patients with atypical mycobacteria. These findings suggest that if sarcoidosis is caused by a mycobacterial organism, TSA is not produced or does not gain access to the systemic circulation. In the course of the studies, a peak, designated p11, was found in high amounts in serum of patients with acute sarcoidosis. A different peak, designated p3, was found in significantly reduced amounts in subjects with acute and chronic sarcoidosis, and undetected in subjects with tuberculosis. Peak 11 was tentatively identified as furyl-2-carboxylic trichychloroethyl-4-(1-epoxy-n-pentyl-6-methyl) trichloroethylformate. Peak 3 was tentatively identified as furyl-2-diethylether. In additional studies, a heptafluorobutyric anhydride derivatized alcohol designated peak 7 was detected in the serum of 14 of 16 patients with sarcoidosis and not in the serum of 10 patients with tuberculosis, or in 10 healthy controls. Studies of peak 7 by chemical ionization gas chromatography mass spectrometry indicate peak 7 to be a C15 branched chain alcohol with a derivatized molecular weight of 424. Further studies are needed to determine if quantitation of these peaks aids in the diagnosis of sarcoidosis or contributes further to understanding the etiology of the disorder.

5.5. PROCEDURES, METHODS AND EXPERIMENTAL DESIGN

5.5.1 Patient Selection

Cases with documented or suspected sarcoidosis, and healthy controls submitted by ACCESS (A Case Control Etiologic Study of Sarcoidosis), are enrolled into the study. Cases with sarcoidosis are categorized as per the ACCESS Protocol.

Blood and tissue samples are obtained according to the ACCESS protocol, and processed by methods described below. We anticipate that the acid-fast L form will grow in approximately 50% of cases with sarcoidosis and 5-10% of controls. In this project blood samples from 100 cases with sarcoidosis and from 100 healthy controls are analyzed. A total of 200 subjects (100 cases, 100 controls) and a proportion of positive controls of 0.1, provide a statistical power of greater than 90% to detect an odds ratio of 4.0. This information is based on the power calculations provided by Dr. Bruce Thompson (Clinical Trials and Surveys Corp.).

5.5.2 Handling and Shipping of Samples

All blood samples to be used for culture of CWDF will be collected in vacutainer tubes containing EDTA. Polyvinylpropylene iodine (PVP) must be used to clean the subject's skin and rubber stopper of the vacutainer tube. The samples should contain a minimum of 4 ml of blood and should be shipped by overnight mail at ambient temperature.

5.5.3 Development of a Monoclonal Antibody to the Sarcoid Organism

A blood culture sample containing acid-fast CWDF from a patient with sarcoidosis is prepared in the ACCESS L Forms Core Laboratory as described below and sent to Dr. Alva Johnson at the Department of Microbiology, Eastern Virginia Medical School, Norfolk, Virginia. Dr. Johnson is responsible for the development and production of a monoclonal and a polyclonal antibody against the acid-fast CWDF of sarcoidosis. Dr. Johnson previously developed the mouse monoclonal antibody against M. tuberculosis H37RV whole cell antigen (Johnson et al., 1980) used in a recent study (Almenoff et al., 1996B) and still being used in our laboratory as described below.

The mouse monoclonal antibody was developed against M. tuberculosis H37RV whole cell antigen using the Kohler-Milstein technique (Kohler and Milstein, 1975). One gram of wet cell pellet of bacteria was suspended in 10 ml of sterile distilled water and inactivated by flowing steam (80-88^{c}) in an autoclave for one hour. The concentration of inactivated cells was adjusted to an absorbency of 0.15 in a 10 X 75 mm curette at 450 nm with a Coleman Junior II A Linear Absorbency Spectrophotometer, Model 6/20A (Perkins Elmer Coleman Instruments Division). One

hundred sixty Fl of selected cell suspension were added to microtiter plates with Immunolon Removal Well Strips (Dynatech Laboratories, Inc., Alexandria, VA.). Plates with cell suspensions were centrifuged at 1200 RPM for 10 minutes, the wells aspirated, washed with a tween-80 (0.05%) saline (0.85%) wash solution, and filled with ethylene glycol for five minutes to fix antigen to the plastic wells. Ethylene glycol was aspirated, the wells washed, and the plates were used or stored at 4^0C for enzyme-linked immunosorbent assay (ELISA) procedures. The H37RV monoclonal antibody was added to selected antigen wells, incubated at 37^0C for one hour, aspirated, and washed. This was followed by addition of a goat anti-mouse alkaline phosphatase conjugate (Sigma Chemical company, St. Louis, MO.), incubation, and a wash procedure. Finally, 160 Fl of alkaline phosphatase substrate (cat # A-5153 Sigma Chemical Co.) was added to appropriate wells for incubation at room temperature for thirty minutes before recording color development at 410 nm with a Dynatech ELISA minireader (Alexandria, VA.). As shown in the table below, there was high absorbency with the H37RV, BCG, and H37RA antigens, minimal absorbency with atypical mycobacterial antigens, and no absorbency with either gram positive or gram negative antigens.

Reactivity of Anti-H37RV Hybridoma Antibody With Different Species of Mycobacteria and Non-Acid Fast Bacteria (ELISA)

Heated Antigen	Result
H37RV	>2.5
BCG	>2.5
H37RA	0.81
M. kansasii	0.00
M. Intracellulare	0.10
M. scrofulaceum	0.07
M. chelonae	0.00
M. fortuitum	0.08
M. avium	0.11
Pseudomonas aeruginosa	0.00
Escherichia coli	0.00
Klebsiella pneumoniae	0.00
Staphylococcus aureus	0.00
Streptococcus pyogenes	0.00

Cells were killed with flowing steam (80-88^{o}C) for I hour.
ELISA data is expressed in optical density (OD).

5.5.4 Blood Culture Analysis for L Forms of Mycobacteria

All culture work and handling of samples are performed in a biological safety cabinet. 7.5 g Veal infusion broth is mixed with 300 ml of tap water that has been autoclaved at 15 lbs (121EC) for 15 minutes, then filter sterilized through a 0.22 micron filter. The pH is adjusted to 5.5 with concentrated hydrochloric acid and then 0.15 g of Noble Agar (Difco) is added to make a modified Veal Infusion Medium (VIM). VIM is dispensed in 9 ml aliquots into sterile glass screw cap tubes. A 10% solution of yeast extract (#0127, Difco) is prepared, autoclaved, filtered through a 0.22 micron filter bottle and stored at 4EC. The VIM and yeast extract (YE) are sterilized in an autoclave at 15 lbs. (121^{o}C) for 15 minutes. Just before inoculating the VIM with subjects' blood, 1 ml of the fresh YE is added aseptically to a 9 ml tube of VIM to make VIM + 1% YE (VIM+YE) and vortexed to mix thoroughly.

Blood is collected into specially prepared purple top (EDTA) vacutainer tubes. The stopper is swabbed with iodine, allowed to sit for one minute, then wiped with an alcohol swab, and allowed to air dry. Approximately 0.3 ml of blood is drawn into a three ml syringe with an 18 gauge needle and transferred to a tube containing VIM+YE. The culture tube is capped, placed in a shaker at 200 rpm and incubated at 37EC. After two weeks, approximately 1.7 ml of the culture is sampled from the turbid region for sterility checks and experiments. One drop of culture is applied to a Blood Agar plate to check for gross contamination. Three drops are applied and smeared to each of three slides, one for Gram's stain, and two for Modified Kinyoun staining. The remaining one ml of culture material is used for extraction of material for DNA studies.

Approximately 2 ml of blood (for a 10% innoculum) are drawn into a sterile Pasteur pipette and transferred to a tube containing VIM+YE. The innoculum is mixed and randomly distributed throughout the medium and incubated at 36^{0}C. At 48 hours, 10 ml of growth are transferred to a glass screw cap tube, 0.1 ml of Xylene added, and the mixture is shaken by hand for five minutes, then allowed to stand in a vertical position for ten minutes. The top portion of the Xylene-medium

emulsion is extracted using a Pasteur pipette and transferred to glass slides for Gram stain, Kinyoun stain, and Indirect Fluorescent Antibody (IFA) analysis.

To detect acid-fast organisms, dried smears of growth from the blood cultures are fixed for one minute using methanol. The methanol is decanted, and the smears are allowed to air dry. The primary stain, Kinyoun's carbol fuchsin, is used to flood the slides and stain the smears for five minutes. The primary stain is modified by adding 0.1 ml of 10% sodium bicarbonate to 9.9 ml of primary Kinyoun stain (HarleCo., Gibbston, N.J.), mixing, and filtering the stain just before use. After the primary stain is decanted, the slides are flooded with 3% HCl in 95% ethanol (decolorizer) and rocked on a staining rack for one minute to remove unbound stain. After decolorization, the slides are gently washed two times in cold water and drained. The slides are flooded with the counterstain metanil yellow (0.05% aqueous solution) for one minute, decanted and allowed to air dry without blotting. The stained smears are placed in a slide holder for draining and drying. These procedures are done with cold water from a beaker because forcibly applying water removes the loosely-adherent L form colonies. The smears are then examined with 200-400X magnification to locate acid-fast micro-colonies. Their typical morphology is confirmed by examination under oil immersion.

5.5.5 Molecular Identification of Acid-Fast Cell-Wall Deficient Forms Grown From the Blood of Patients with Sarcoidosis

Only Primary and Secondary cultures up to January 30, 1998 were examined by PCR using 16s rRNA primers. The results of these experiments were inconclusive. Further molecular studies were halted by the ACCESS Steering Committee. The molecular biology studies are conducted primarily at the Pulmonary and Infectious Disease Research Laboratories at the Mount Sinai School of Medicine/Bronx VA Medical Center. Support services for these laboratories are available from the Brookdale Molecular Research Center at Mount Sinai Medical Center and the Mount Sinai School of Medicine/Bronx VA Research Core.

A strength of these studies is the availability of cultured cell-wall-deficient bacteria. It has been proposed that these organisms are mycobacteria based upon morphologic and biochemical

characteristics. This seems to be a reasonable starting point for molecular studies to determine their taxonomy.

A wealth of genera- and species-specific tools are available for the molecular analysis of mycobacteria. These include primers and probes coding for signature sequences of 16s rRNA, the 65 Kd heat-shock (GroEL) protein, a variety of insertion sequences such as the IS6110/986, of the M. tuberculosis complex, as well as IS900, IS901, IS1110, and IS1245 associated with M. avium complex among others (Taub and Siltzbach, 1972; McFadden et al., 1987; Chen et al., 1989; Boddinghaus et al., 1990; Wilson et al.,1990; Weisberg et al., 1991; Bocart et al., 1992; Mitchell et al., 1992; Saboor et al., 1992; Fidler et al., 1993; Popper et al., 1994).

The pattern of analysis of sarcoid employs methods used to identify a number of previously uncharacterized etiologic agents such as M. genevensae and the Whipple's Disease bacillus (Relman et al., 1992). Deoxyribonucleic acid (DNA) is extracted from cultured organisms. Portions are used as template for polymerase chain reaction amplification (PCR) using primers derived from known bacterial genera consensus sequences. Sequential amplifications proceed using primers of increasing species specificity once a positive result is obtained. Other portions of genomic DNA are digested with restriction endonucleases such as PvuII. Southern blots are hybridized with probes suggested by the results of PCR studies (McFadden et al., 1987; McFadden et al., 1990). The restriction fragment length polymorphisms (RFLP) generated helps to establish the relationship of the unknown organisms to each other and to standard cultivable mycobacteria. These data are combined with sequence data from conserved ribosomal and GroEL sequences to establish the taxonomic identity of the organisms. They also provide useful tools in the form of more specific probes and primers for further molecular epidemiologic studies from clinical specimens.

If there is no evidence for sequence identity with mycobacteria, a similar strategy will be employed using primers and probes from sequences common to larger taxonomic groupings of bacteria. This approach can ultimately be extended to include all eubacteria using conserved sequences coding for 16s rRNA. This very broad approach will not be undertaken at the outset because of the risk of spurious results due to contamination.

If positive amplification is achieved, then the products are sequenced to confirm the identity of the sarcoid-derived isolates. If sarcoid-specific signature sequences are found, these are used to design specific primers for sensitive and specific detection of DNA from these organisms.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 6

DEFINING AN ETIOLOGIC ANTIGEN IN KVEIM REAGENT

6.1 SPECIFIC AIMS

The aims of the ACCESS special laboratory study to define an etiologic agent in Kveim reagent are to determine if: bronchoalveolar lavage (BAL) cells from patients with sarcoidosis are stimulated by validated Kveim reagent (Specific Aim #1); Kveim reagent preferentially stimulates blood mononuclear cells of sarcoid patients compared with normal control individuals (Specific Aim #2); and Kveim-reactive T-cell lines can be established from the lung or blood of patients with sarcoidosis and their T-cell phenotype (Specific Aim #3).

6.2 BLOOD AND LUNG MONONUCLEAR CELL PREPARATION

BAL lung cells are washed twice in buffered saline pH 7.4, resuspended in Roswell Park Institute (RPMI) 1640 solution and counted by hemocytometer. Trypan blue exclusion is used to assess the percentage of viable cells. Differential cell counts are determined using cytocentrifugation on an aliquot of lung cells spun and stained with Diff-Quik; 200 cells are counted, noting the percentage distribution of macrophages, lymphocytes, neutrophils and eosinophils. The remaining lung cells are used in studies outlined below.

Blood is obtained by venipuncture with a heparinized syringe and the mononuclear cells (PBMC) are isolated by centrifugation through lymphocyte separation media (LSM, Boehringer Mannheim, Indianapolis, IN). PBMC are isolated by lymphocyte separation media and lymphocyte responsiveness to validated Kveim-Siltzback reagent measured in a lymphocyte proliferation test (LPT) and cytokine production assay. For selected samples standard lymphocyte phenotyping (CD3, CD4, CD8) is performed on the initial blood T-cell population.

6.3 CELL CULTURE

BAL samples with fewer than 50% lymphocytes (estimated by hemocytometer during cell counting procedure) have an adherence step [(30 min., 37^{o}C on tissue culture plates; cells suspended in RPMI 1640 + 10% fetal calf serum (FCS)] to partially purify lung T cells away from

alveolar macrophages. The non-adherent cells are pooled, washed and counted before analysis. Adherent macrophages are recovered by scraping with a rubber policeman; pooled, washed, counted and cryopreserved in liquid nitrogen (10% dimethyl sulfoxide (DMSO) + 90% FCS).

BAL cells and PBMC are cultured at 2 x 10^5 cells in 96-well U bottom culture dishes for lymphocyte proliferation tests (LPT) by standard [^{3}H]thymidine-uptake assay. Experimental conditions include the following: interleukin (IL) 2, IL 12, Kveim reagent (0.1-100 µg/ml), Kveim plus IL 2, Kveim plus IL 12, tetanus toxoid (as a control), anti-CD3 antibodies or phytohemagglutinin (PHA) 1 Fg/ml (Burroughs-Wellcome) as a positive control or no antigen. The optimal concentrations of antigens are determined in pilot studies. For the cytokine production assay, lung or blood T cells are incubated in 24-well or 96-well flat bottom plates (2x10^6 cells/ml) in media with and without antigen or plate-bound anti-CD3, the supernatants collected at 48 hrs. and frozen at -70^{o}C until assay.

T-cell lines are established by incubation with Kveim ± IL 2 or IL12 and re-stimulated with antigen every two to three weeks with thawed, irradiated (5000R) PBMC. Media plus IL 2 or IL12 are replenished every three to four days during the culture. After two through five rounds of stimulation, the T-cell line is tested in an LPT to assess Kveim reactivity.

6.4 PHENOTYPIC ANALYSIS OF BRONCHOALVEOLAR LAVAGE (BAL) AND BLOOD T-LYMPHOCYTES

Immunofluorescence studies of lung and blood cells are carried out using flow cytometry (FACScan, Becton-Dickinson). For single-color immunofluorescence, lung and blood lymphocytes are incubated (20 min., 4^{o}C) in 96-well U-bottom plates with buffered saline pH 7.4 + 10% normal human AB sera [NHS (decomplemented by heating 56^{o}C for 30 min.)] plus 10% mouse serum, washed, incubated (30 min., 4^{o}C) with primary antibody including FITC-labeled anti-CD3,CD4 and CD8 antibodies. After washing, samples are either run fresh thru the flow cytometer within 2-3 hours or are fixed in 1% paraformaldehyde, stored in the dark at 4^{o}C and evaluated at a later time (within one week). FITC-labeled control antibodies to assess non-specific immunofluorescence are included. The proportion of positive-staining lymphocytes are determined by using forward-angle

and 90º light scatter to gate on lymphocytes; the percentage of positive lymphocytes are estimated by subtracting the control sample value from the value using anti-T-cell antibodies.

6.5 LYMPHOCYTE PROLIFERATION ASSAY

To determine the antigen-reactivity of lung or blood T cells, a standard lymphocyte blast transformation assay is performed. Lung or blood T-cell preparations are incubated in triplicate wells for four to seven days and pulsed with 1.0 FCi [^{3}H]thymidine (6Ci/mmol) per well for the final 18 hours, then collected on glass-fiber filters using a PHD™ cell harvester. T-cell lines (maintained in complete media for seven to ten days after their last antigenic stimulation) are harvested, washed twice in buffered saline and plated in complete media at 1x10^5 cells/200 Fl in flat-bottom wells (Flow Laboratories) with 1x10^5 autologous cryopreserved irradiated (5000R) PBMC as feeder cells. T-cell proliferation is assayed by liquid scintillation counting and quantified both as mean total counts minus mean control counts (Dcpm) and stimulation index (SI; mean of triplicate stimulated cultures divided by mean of triplicate control cultures). To evaluate whether the T cells respond to selected antigens in a major histocompatibility (MHC)-restricted manner, anti-MHC class II monoclonal antibodies (mAbs) (L234) and anti-MHC I mAbs (W6/32) are added to proliferation assays of selected T-cell lines.

6.6 MEASUREMENT OF CYTOKINE PROTEIN IN CELL SUPERNATANTS

Interferon ã (IFNg) and IL 2 protein levels are measured in cell supernatants using enzyme linked immunosorbant assay (ELISA) detection kits (Biosource International, Camarillo, CA) according to the manufacturer's recommendations. The sensitivity of these assays is 5 pg/ml. IL12 (p70 or p40) is measured by ELISA (Pharmingen).

6.7 ANALYSES

For specific aim #1, selected samples of lung cells are phenotyped (CD3, CD4, CD8). Lung cells (total 2 x 10^6) are cultured in complete media with and without Kveim reagent (concentrations to be determined by pilot studies), IL 2, IL 12 or Kveim plus IL 2 or IL 12. Lymphocyte responsiveness to validated Kveim-Siltzbach reagent is measured in a standard lymphocyte proliferation test (LPT) and cytokine production assay (IL 2, IFNg) at an appropriate time interval.

To pilot test different co-stimulatory conditions that may maximize Kveim responsiveness, three different culture conditions are tested if sufficient cells are obtained from BAL: co-incubation with GM-CSF, anti-IL10 or anti-TGFb on different individuals.

We plan on testing one set of culture conditions per year on an estimated six cases' BAL samples/year. The comparisons of greatest interest will be the difference between control wells and those containing Kveim reagent as assessed by LPT (recorded as cpm and analyzed as both cpm and stimulation index) and cytokine production (given as concentration). A significant proliferative response (measured as an increase in proliferation or stimulation index greater than three times control -- this may be altered depending on initial control experiments) or increase in cytokine production (greater than two times control -- this may also be altered depending on initial control experiments) in experimental conditions containing Kveim reagent will be taken as evidence of Kveim responsiveness.

For specific aim #2, three separate conditions will be tested, one per year in order to pilot experimental conditions that may maximize Kveim responsiveness.

We plan to test approximately 20 cases and controls. These samples will utilize similar antigenic stimuli as listed above, but other conditions will be tested to maximize responsiveness to Kveim. Evaluations include the comparison of LPT and cytokine production for each experimental condition between groups (using both unpaired and paired analyses) and within each case as in specific aim #1. A significant difference in the response of PBMC to experimental conditions containing Kveim reagent (same criteria as above) is taken as evidence of Kveim responsiveness.

For specific aim #3, lung and blood T cells are isolated and cultured with validated Kveim reagent and co-stimulating factors such as IL 2 and IL 12. Long-term T-cell lines with reactivity to Kveim are established for repeated testing of components of Kveim reagent. Antigen reactivity is measured by [^{3}H]-thymidine uptake (LPT) and cytokine production after various time periods. These T-cell lines are analyzed with respect to T-cell receptor usage for future correlation with in situ T-cell analysis of sarcoid tissue. The successful development of an in vitro assay for Kveim reactivity

leads to fractionation of the Kveim reagent and biochemical analysis of the compound in order to isolate the responsible component.

Selected lymphocyte cultures are expanded for in vitro analysis depending on cells available and proliferative responses of the T-cell lines. The successful establishment of Kveim responsive T-cell lines would lead to the more extensive characterization of Kveim reagent components. Comparisons of experimental conditions with and without Kveim reagent would allow determination of Kveim responsiveness, using similar criteria as in specific aim #1.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 7

BRONCHOALVEOLAR LAVAGE (BAL) CORE LABORATORY PROCEDURES

7.1 INTRODUCTION

The purpose of the Bronchoalveolar lavage (BAL) Core Laboratory is to provide standardized cell counts which may be used to characterize stored, frozen BAL samples as a guide to their selection for individual studies. For example, a specimen with a large percentage of epithelial cells would be inadequate for a cytokine study, but may be acceptable for microbiological studies. The information from the BAL Core Laboratory will be complementary to the information from local laboratories where total cell counts and differential cell counts may be performed.

BAL samples which are sent to the BAL Core Laboratory include the following:

- Two cytocentrifuged prepared slides. One cytocentrifuged slide is stained with a Wright-Giemsa or equivalent stain. The other slide is unstained.
- A copy of the BAL information sheet.

Upon arrival at the laboratory, the patient identification number upon the slides is noted and compared to the information sheet provided. A cross check determines the identification numbers are the same. If there is a discrepancy, the ACCESS Clinical Center which has sent the specimen to the BAL Core Laboratory is notified and asked to clear up any confusion.

Upon arrival, the slides are examined to determine the quality of the specimen with particular attention to the uptake of stain in the individual cells as well as the density of the cell population. Items of interest are characterized according to the following criteria defined in Section 7.2.

7.2 DETERMINING QUALITY OF SPECIMENS

7.2.1 Adequate Stain

To be an acceptable stain, both macrophages and lymphocytes must be stained adequately. The nuclei of the lymphocytes should be a dark blue, while those of the macrophages should be a lighter blue. Granules should be perceivable. Neutrophils, if identified, should have some red

granules to indicate that there was a counterstain. The density of the slide should be such that individual cells can be characterized and there should be no layering of one cell upon another. The cells should not be so sparse that there is not an adequate number of cells to count. At least 200 cells are required for counts. The usual cytocentrifuge sample contains 1,000-10,000 cells.

7.2.2 Technically Inadequate

Samples are identified and reviewed by both the Principal Investigator of the laboratory, Dr. Baughman, and the technician. If both agree that the sample is technically inadequate, the laboratory sending the sample is notified of the problem. For example, if there are $\geq$ 5% smudge cells on cell count, the sample is considered inadequate. Technically inadequate samples may already be known to the ACCESS Clinical Center sending the sample. Discussion is ongoing about how to prepare better samples to avoid technically inadequate samples.

7.3 Differential Cell Counting

Differential cell counts are performed using standardized procedures (Baughman et al, 1986). Individual slides are examined under high dry magnification. Cells are permounted to improve characterization of the cells. Nucleated cells are differentiated using standard morphological characteristics for macrophages, lymphocytes, neutrophils, eosinophils, epithelial cells and other cell types. Differential cell counts are performed on 200 nucleated cells per slide. Individual slides are counted on two separate occasions at least one day apart by the same observer. If there are large discrepancies in the slide counts, the Principal Investigator of the laboratory reviews the slides.

Replicate counts of a 10% sample of the slides are performed by the BAL Core Laboratory Principal Investigator, who is unaware of the technician's readings. Discrepancies between the Principal Investigator and the technician are resolved. Correlations of counts between each technician and the Principal Investigator are continually reviewed. Previous assessments have shown that in the BAL Core Laboratory, two observers usually have correlation coefficients better than 0.90.

The differential count determined by our laboratory are compared to those obtained by the ACCESS Clinical Centers. Correlations between counts for the BAL Core Laboratory and ACCESS Clinical Centers are continually reviewed. For the purpose of ACCESS, the differential cell counts at the BAL Core Laboratory are considered the standard. These readings are entered in the database that is used in conjunction with further analysis of ACCESS BAL specimens.

7.4 Quality Control

In addition to review of slides by the BAL Core Laboratory Principal Investigator, at least one other laboratory has agreed to provide additional quality control for cell counts. This is provided by Dr. Gary Hunninghake of the University of Iowa. A percentage of slides is sent to that laboratory for independent cell counting to determine the agreement between two different laboratories. If there is large disagreement between laboratories, further standardization will be necessary to obtain consistent differential cell counts.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 8

PATHOGENIC T CELLS IN SARCOIDOSIS

8.1 SPECIFIC AIMS

The aims of this ACCESS Special Laboratory Study are to demonstrate CD4 T-cell clonal expansions in bronchoalveolar lavage, to determine if the clonal T-cell expansions in bronchoalveolar lavage (BAL) are also present in involved tissue, to identify the T-cell receptor alpha-chains expressed by particular “disease relevant” CD4 T-cell clones, and to generate T-cell hybridomas expressing the T-cell receptor of these clones. The goal is to screen for reactivity to candidate antigens using these T-cell hybridomas.

These aims are based on the considerable evidence indicating that T cells are predominantly involved in the immunopathogenesis of sarcoidosis. Previous studies suggest that particular CD4 T-cell clones in the BAL from sarcoidosis patients have been selectively activated. We now hypothesize that these expanded CD4 T-cell clones are important in the immunopathogenesis of disease and are responding to the etiologic stimulus. The stimulating antigen could be foreign or self. As a first set of steps toward the achievement of these goals, we will start by focusing on the potential disease relevance of expanded CD4 T-cell clones in BAL and focus primarily on the establishing the experimental systems for determining their antigen specificity, using sarcoidosis-specific T-cell hybridomas.

8.2 BLOOD AND BAL LYMPHOCYTE PROLIFERATION

BAL lung cells and peripheral blood monocytes are prepared as described in Chapter 6 of the ACCESS Procedures Manual Volume IV. The BAL samples are obtained as described in Chapter 6 (Biological Specimens) of the ACCESS Procedures Manual Volume I. Cells are placed in short-term culture in the presence of supplemental interleukin (IL)-2, and T-cell blasts (nearly all CD4 T cells derived from these cultures are analyzed as described below).

8.3. CELL CULTURE

BAL cells and peripheral blood mononuclear cells are cultured between 2 x 10^5 cells/96 well up to 5 x 10^6 cells/96 well of U bottom cultured dishes for stimulation with IL-2. At selected time points following initial stimulation (5 to 10 days after initial culture and in some instance following second stimulation with IL-2), the cells are collected and aliquoted for use in immunofluoresence analysis and sequence analysis discussed in the sections below.

8.4 PHENOTYPICAL ANALYSIS OF BAL AND BLOOD LYMPHOCYTES

Mononuclear cells are studied by two color and/or three color immunofluoresence staining and cytofluorographic analysis. Fluorescein-conjugated reagents include monoclonal antibodies directed to CD4. Phycoerythrin-conjugated reagents are directed to HLA-DR or IL-2 receptor. Biotinylated reagents include monoclonal antibodies directed to Vâ2, Vâ3, Vâ5.1, Vâ5.2, Vâ6.1, Vâ6.7, Vâ8.1, Vâ9, Vâ12, Vâ13.1, Vâ13.2, Vâ14, Vâ17, Vâ18, Vâ20, Vâ22, and Vâ23-expressing T cells. The methods used for immunofluoresence staining are standard and as described in Section 6.4 in this volume of the Procedures Manual.

8.5 SEQUENCE ANALYSIS OF T-CELL RECEPTOR â-CHAIN JUNCTIONAL REGIONS

The methods for PCR amplification are as described above, see Section 4.3.2 in this volume of the Procedures Manual. Detailed methods of cloning and sequencing of amplified T-cell receptor products are as described in detail in previous publications (Paliard et al., 1991; Forester et al., 1993; Forrester et al., 1994; Fitzgerald et al., 1995). The cloned T-cell receptor fragments are sequenced on an automated ABI 377 sequencer. For particular Vâ-expressing populations, at least 50 â-chain junctional sequences are determined after PCR amplification with a Vâ-specific (forward) and Câ (reverse) primer. All reactions include negative controls to ensure the absence of contamination. Oligoclonality is defined as at least three repeated sequences out of 50 and a non-expanded clone is defined as a single sequence.

8.6 GENERATION OF T-CELL HYBRIDOMAS EXPRESSING THE T-CELL RECEPTOR OF MAJOR SARCOIDOSIS CLONES

BAL T cells bearing appropriate â-chain sequences are stained and sorted as above. These cells are cultured at limiting dilution with a polyclonal activator (PHA) and IL-2. The cells can not be grown indefinitely to allow careful studies of specificity. Thus, after identifying the clones expressing the appropriate â-chain junctional sequence, the T-cell receptor á-chain sequence is determined by anchored PCR using a reverse Cá-specific primer. Restriction sites are built into the primer sequence so that the amplified products can be inserted into the appropriate expression vector.

cDNA from the T-cell clones is amplified using primers specific for the Vá leader, and Cá and â-chain sequences are amplified after the method of Choi, et al. (Choi et al., 1991). Amplified products are also cloned and sequenced in the vector pTZ18R. After verification of the correct sequence, a fragment containing the leader-Vá-Já sequence is inserted into the expression vector pBDW-HCB2 between the spleen focused-forming virus (SFFV) LTR and the mouse Cá sequence.

pBDW-HCB2 also carries the simian virus 40 origin (SV40 Ori), mRNA splicing, and poly (A)-addition signals and the neomycin-resistant (NEO) gene to allow selection with G418. The â-chain fragment containing the leader-Vâ-Dâ-Jâ is inserted into the expression vector MK10 (derived from the hBAc-PrNEO) which contains the mouse Câ sequence downstream of a human â-actin promoter. A mouse T-cell hybridoma (58á$^-$â$^-$) modified from the DO11.10 has been generated to carry á- or â-chain genes (and also express human CD4 after transfection of the human CD4 construct). It is co-transfected with T-cell receptor constructs and selected with G418. Transfectants expressing both á- and â-chains (expressing functional T-cell receptor) are screened by staining with the anti-Vâ antibody and are selected for high T-cell receptor expression by cell sorting on the cytofluorograph. Cells with the highest expression levels are utilized for stimulation studies.

8.7 TESTING HYBRIDOMAS FOR REACTIVITY

Hybridomas generated by the above methods are tested for reactivity to preparations possibly containing the etiologic stimulus in sarcoidosis. This is done in the presence of Epstein-Barr viral transformed peripheral B cells from the same individual being used as antigen presenting cells. Potentially antigenic preparation include: (1) bronchoalveolar lavage fluid, (2) involved lung tissue (with areas of granulomatous inflammation), (3) involved lymph node tissue where available (with areas of granulomatous inflammation), (4) bronchoalveolar lavage cells, (5) Kveim reagent, (6) myobacterial preparations, and (7) other candidate antigen preparations as they are discovered through the work in other laboratory projects in ACCESS.

8.8 ANALYSES

We propose to study approximately 10 ACCESS cases for the purposes of generating the selected T-cell clones. A significant response by our sarcoidosis specific T-cell hybridomas will be determined by comparing the maximum stimulatory effect of specific suspected antigens (see list above) compared to unstimulated hybridoma cells in culture.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 9

IMMUNOGENETICS OF SARCOIDOSIS

9.1 OVERVIEW

GM and KM allotypes are hereditary antigenic determinants on Ig polypeptide chains. They are polymorphic within species and can be used as genetic markers. These determinants are inherited as autosomal codominant genes according to Mendelian laws. GM allotypes, the antigenic determinants of IgG heavy chains, are encoded by three very closely linked cistrons on chromosome 14. They are localized on the constant region of ã1, ã2 and ã3 heavy chains. Linkage disequilibrium in the GM system is absolute and the determinants are transmitted as a group (haplotypes). Each major race has a distinct array of GM haplotypes. (Blacks and Whites do not share any GM haplotypes. This may be relevant in sarcoidosis as it is more prevalent in Blacks.) KM allotypes, the antigenic determinants of k-type light chains, are inherited via three alleles–KM*1, KM*1,2 and KM*3 on chromosome 2.

In addition to Ig allotypes, we examine the roles of polymorphic loci which control tumor necrosis factor-a (TNF-á) and interleukin 1-b (IL1-â). Increased secretion of these cytokines has been found to be associated with disease severity in sarcoidosis, and the individuals with different alleles at these loci may have different levels of cytokines. For TNF-á, we examine the two recently described polymorphisms in the promoter region. Both loci involve a G to A transition–one at position -308 and the other at -238. The fact that these genetic variations are within the promoter region of the TNF-á locus make them likely candidates for playing regulatory roles in the production of TNF-á. For the determination of IL-1â alleles, a polymorphic locus in the IL-1â 5' region is investigated. This polymorphism involves a C to T transition at position -511, which results in an Ava I restriction site.

9.2 CASE AND CONTROL POPULATIONS

Identification of cases and controls is performed according to the standard ACCESS Protocol. Coded DNA samples received from the DNA Core Laboratory are typed for the genetic

markers described above. 0.5 microgram of DNA is sufficient for all markers we plan to study. Only after the samples have been typed will the code be broken to determine whether the sample was from a case or control.

9.3 STATISTICAL CONSIDERATIONS

The control frequency of the least common GM phenotype in whites–GM 1,17 21–is 0.026. For this system, the total sample size needed to detect a tripling of the frequency of GM 1,17 21 in the cases, i.e., rate of that phenotype increasing from 0.026 in controls to 0.078 in cases, is 360. This estimate is based on the desired power of 80% to detect the tripling and two-sided alpha level of 0.05.

The frequencies of the least common phenotypes in the other systems to be studied are similar. Thus, we recommend studying 360 cases and an equal number of matched controls (total 720) to ensure the detection of any important difference in the distribution of various phenotypes between cases and controls. Estimates from the ten ACCESS Clinical Centers suggest the following distribution of cases and controls: 43% black, 54% white, and 3% other.

9.4 DETAILED METHODOLOGY

9.4.1 GM b & g Genomic Determination

GM b and g genomic determinations are performed as follows (Balbin et al., 1994).

Primers:

UP	#1155 (PR 131)	5' ACC CAA GGA TAC CCT TAT GAT T 3'
DOWN	#1156 (PR 132)	5' GAG GCT CTT CTG CGT GAA GC 3'

PCR:

PCR reaction using Perkin Elmer Cetus Gene Amp PCR Kit Part No. 801-0055.

Incubate Taq polymerase and Taq Start antibody (Clontech) in water (see below) for ten minutes before adding other reagents.

Taq start	0.05 Fl
Taq polymerase	0.05 Fl
H_2O	0.5 Fl
Sterile H_2O	6.2 Fl
10XPCR buffer with MgCl	1 Fl
Premixed dNTP mix	0.8 Fl
Upstream primer	0.2 Fl
Downstream primer	0.2 Fl
Total volume	9 Fl
Sample DNA	1 Fl

Add 1 Fl sample DNA to 9 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run in Perkin Elmer System 9600 PCR machine.

50 cycles:	95EC	60EC	72EC
Perkin Elmer 9600:	30 sec	30 sec	--

Expected product length: 685 bp

Restriction Digestion: Restriction digest 10 Fl PCR product with two units Msp A1 restriction enzyme (Promega).

Example:

Sample	H_2O	Enzyme	Buffer MCB	Final Volume
10 Fl	1.8 Fl	0.2 Fl	1 Fl	13 Fl

Make master mix of H_2O, enzyme and buffer. Add sample to the mix and incubate at 37EC for three hours. After incubation, add 3 Fl Ficol Loading Dye and run on an 8% TBE polyacrylamide gel in a Bio-Rad mini-gel apparatus for one hour at 10 mA constant current. Stain the gel with ethidium bromide.

Visualize on U.V. light box and take picture.

Analysis:

Expected fragment sizes:

GM g	327 bp, 295 bp, 63 bp
GM b	171 bp, 158 bp, 156 bp, 137 bp, 63 bp
GM b,g	327 bp, 295 bp, 171 bp, 158 bp, 156 bp, 137 bp, 63 bp

9.4.2 GM f & z Genomic Determination

GM f and z genomic determinations are performed as follows (Balbin et al., 1991).

Primers:

UP	#218 (PR1)	5' CCC CTG GCA CCC TCC TCC AA 3'
DOWN	#216 (PR2)	5' GCC CTG GAC TGG GGC TGC AT 3'

Probes:

(PRz-Alk-P)	5' GAC AAG AAA GTT GGT 3' – Amino link + Alk-P
(Prf-Alk-P)	5' GAC AAG AGA GTT GGT 3' – Amino link + Alk-P

PCR:

PCR reaction using Perkin Elmer Cetus Gene Amp PCR Kit Part No. 801-0055.

Sterile H_2O	6.75 Fl
10XPCR buffer with MgCl	1 Fl
Premixed dNTP mix	0.8 Fl
Upstream primer	0.2 Fl
Downstream primer	0.2 Fl
Taq polymerase	0.05 Fl
Total volume	9 Fl
Sample DNA	1 Fl

Add 1 Fl sample DNA to 9 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run in Perkin Elmer System 9600 PCR machine.

35 cycles:	95EC	70EC	72EC
Perkin Elmer 9600:	15 sec	30 sec	–

Expected product length: 364 bp

Hybridization:

Pre-hybridization solution:	7% SDS 0.25 M NaPO4 1 mM EDTA pH 6.5
Hybridizing solutions:	1 Fl probe (PRf or PRz) per 1 ml pre-hyb. sol.
Wash solution:	0.1% SDS 1X SSC in water

Pre-warm hybridization solution and wash solution to 45EC. Dilute samples 1:2 with 20X SSC. Boil diluted samples ten minutes, quick cool in ice bath and spin in Eppendorf (Centrifuge 5402) at 4EC for ten seconds. Transfer 5 Fl of sample to 1 cm^2 area on Photogene Nylon Membrane (one membrane for each probe) and then allow blot to dry. U.V. crosslink DNA to membrane using Fisher Biotech FB-UVYL-1000. Place blots in heat-seal bags with pre-hybridization solution (1 ml per 10 cm^2) and incubate 20 minutes. Replace pre-hybridization solution with pre-heated hybridization solution, for each probe, and reseal bag. Hybridize for 60 minutes at 45EC. Wash blots twice in wash solution at room temperature for five minutes. Wash a third time in pre-heated wash solution at 45EC for ten minutes. Wash a final time in 1X Photogene Final Wash Solution at room temperature for five minutes. Dry blots on filter paper and place in a Photogene development folder with sufficient Photogene detection reagent to cover blot. In a dark room, place Kodak X-ray film over blots inside a Kodak film cassette and expose overnight. Develop X-ray film.

Analysis:

An exposed spot indicates that the sample is positive for the marker (GM f or GM z).

9.4.3 G2M n Genomic Determination

G2M n genomic determinations are performed as follows (Brusco et al., 1995).

Primers:

UP	#821 (PR G2)	5' AAA TGT TGT GTC GAG TGC CC 3'

DOWN #822 (PR 286) 5' GGC TTG CCG GCC GTG GCA C 3'

PCR:

PCR reaction using Perkin Elmer Cetus Gene Amp PCR Kit Part No. 801-0055.

Incubate Taq polymerase and Taq Start antibody (Clontech) in water (see below) for ten minutes before adding other reagents.

Taq start	0.05 Fl
Taq polymerase	0.05 Fl
H_2O	0.5 Fl
Sterile H_2O	6.2 Fl
10XPCR buffer with MgCl	1 Fl
Premixed dNTP mix	0.8 Fl
Upstream primer	0.2 Fl
Downstream primer	0.2 Fl
Total volume	9 Fl
Sample DNA	1 Fl

Add 1 Fl sample DNA to 9 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run in Perkin Elmer System 9600 PCR machine.

Initial DNA separation at 95EC for five minutes.

40 cycles:	95EC	65EC	72EC
Perkin Elmer 9600:	30 sec	30 sec	30 sec

Expected product length: 902 bp

Restriction Digestion: Restriction digest 10 Fl PCR product with two units Nla III restriction enzyme (NEB 125L).

Example:

Sample	H_2O	Enzyme	BSA	Final Volume
10 Fl	2.7 Fl	0.2 Fl	1 Fl	13 Fl

Make master mix of H_2O, enzyme and buffer. Add sample to the mix and incubate at 37EC for three hours. After incubation, add 3 Fl Ficol Loading Dye and run on an 8% TBE polyacrylamide gel in a Bio-Rad mini-gel apparatus for one hour at 10 mA constant current. Stain the gel with ethidium bromide.

Visualize on U.V. light box and take picture.

Analysis:

Codon	n+/n-	Cut
282	ATG/GTG	Nla III
308	GT (C/T)	–
437	AC (A/G)	–

Expected fragment sizes:

GM n+	237bp, 209 bp, 205 bp, 90 bp, 83 bp, 78 bp
GM n	295 bp, 237 bp, 209 bp, 83 bp, 78 bp
GM n+, –	295 bp, 237 bp, 209 bp, 205 bp, 90 bp, 83 bp, 78 bp

9.4.4 KM Genomic Determination

KM genomic determinations are performed as follows (Moxley and Gibbs, 1992).

Primers:

UP	#1146 (CKLC1)	5' ACT GTG GCT GCA CCA TCT GTC T 3'
DOWN	#1147 (CKLC2)	5' TCA GGC TGG AAC TGA GGA GCA G 3'

PCR:

PCR reaction using Perkin Elmer Cetus Gene Amp PCR Kit Part No. 801-0055.

Sterile H_2O	9.18 Fl
10XPCR buffer with MgCl	1.25 Fl
Premixed dNTP mix	1 Fl
Upstream primer	0.25 Fl
Downstream primer	0.25 Fl
Taq polymerase	0.065 Fl
Total volume	12 Fl
Sample DNA	1 Fl

Add 1 Fl sample DNA to 12 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run in Perkin Elmer System 9600 PCR machine.

35 cycles:	95EC	68EC	72EC
Perkin Elmer 9600:	15 sec	30 sec	--

Expected product length: 360 bp

Restriction Digestion: Restriction digest 5Fl-8 Fl PCR product with one unit Acc 1 restriction enzyme (NEB).

Example:

Sample	H_2O	Enzyme	Buffer 4	Final Volume
6 Fl	2.8 Fl	0.2 Fl	1 Fl	10 Fl

Make master mix of H_2O, enzyme and buffer. Add sample to the mix and incubate at 37EC for two hours. After incubation, add 3 Fl Ficol Loading Dye and run on a 6% TBE polyacrylamide gel in a Bio-Rad mini-gel apparatus for one hour at 10 mA constant current. Stain the gel with ethidium bromide.

Visualize on U.V. light box and take picture.

Example:

Sample	H_2O	Enzyme	Buffer H	Final Volume
6 Fl	2.8 Fl	0.2 Fl	1 Fl	10 Fl

Incubate mix at 50EC for two hours and run on gel as above.

Analysis:

ACC I:

Expected fragment size:

KM 1 or (1,2)	360 bp
KM 1/3 or (1,2)/3	360 bp, 247 bp, 113 bp
KM 3	247 bp, 113 bp

9.4.5 Determination of TNFá Alleles

TNFá alleles are determined as follows (Wilson et al., 1992; Wilson et al., 1993; D'Alfonso and Richiardi, 1994).

Primers:

UP	#124 (TNF1)	5' AGG CAA TAG GTT TTG AGG GCC AT 3'

DOWN #702 (TNF3) 5' ACA CTC CCC ATC CTC CCG GCT 3'

PCR:

PCR reaction using Perkin Elmer Cetus Gene Amp PCR Kit Part No. 801-0055.

Sterile H_2O	9.18	Fl
10XPCR buffer with MgCl	1.25	Fl
Premixed dNTP mix	1	Fl
Upstream primer	0.25	Fl
Downstream primer	0.25	Fl
Taq polymerase	0.065	Fl
Total volume	12	Fl
Sample DNA	1	Fl

Add 1 Fl sample DNA to 12 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run in Perkin Elmer System 9600 PCR machine.

35 cycles:	95EC	60EC	72EC
Perkin Elmer 9600:	15 sec	30 sec	–

Expected product length: 117 bp

Restriction Digestion:

TNF 1,2:

Restriction digest 6 Fl PCR product with three units NcoI restriction enzyme (NEB 193 S). Three hours at 37EC.

Example:

Sample	H_2O	Enzyme	Buffer 4	Final Volume
6 Fl	2.7 Fl	0.3 Fl	1 Fl	10 Fl

TNF G,A:

Restriction digest 6 Fl PCR product with two units NIaIV restriction enzyme (NEB 126 S). Three hours at 37EC.

Example:

Sample	H_2O	Enzyme	BSA	Final Volume
6 Fl	3.7 Fl	0.2 Fl	0.1 Fl	10 Fl

Make master mix of H_2O, enzyme and buffer. Add sample to the mix and incubate at 37EC for two hours. After incubation, add 3 Fl Ficol Loading Dye and run on a 10% TBE

polyacrylamide gel in a Bio-Rad mini-gel apparatus for one hour at 10 mA constant current.

Stain the gel with ethidium bromide.

Visualize on U.V. light box and take picture.

Analysis:

Expected fragment size:

<u>TNF1,2</u>:	
TNF1	97 bp and 20 bp
TNF2	117 bp
TNF1,2	117 bp, 97 bp and 20 bp
<u>TNF G,A</u>:	
TNF G	50 bp, 47 bp and 20 bp
TNF A	70 bp and 47 bp
TNF G,A	70 bp, 50 bp, 47 bp and 20 bp

9.4.6 Determination of IL1-â Alleles

IL1-â alleles are determined as follows (di Giovine et al., 1992).

Primers:

UP	#322 (IL1â-3)	5'TGG CAT TGA TCT GGT TCA TC 3'
DOWN	#323 (IL1â-4)	5' GTT TAG GAA TCT TCC CAC TT 3'

PCR:

PCR reaction using Perkin Elmer Cetus Gene Amp PCR Kit Part No. 801-0055.

Sterile H_2O	6.75 Fl
10XPCR buffer with MgCl	1 Fl
Premixed dNTP mix	0.8 Fl
Upstream primer	0.2 Fl
Downstream primer	0.2 Fl
Taq polymerase	0.05 Fl
Total volume	9 Fl

Sample DNA	1	Fl

Add 1 Fl sample DNA to 9 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run in Perkin Elmer System 9600 PCR machine.

35 cycles:	95EC	51.5EC	72EC
Perkin Elmer 9600:	15 sec	30 sec	–

Expected product length: 305 bp

Restriction Digestion: Restriction digest 10 Fl PCR product with two units Ava 1 restriction enzyme (NEB 152S).

Example:

Sample	H_2O	Enzyme	Buffer 4	Final Volume
10 Fl	1.8 Fl	0.2 Fl	1 Fl	13 Fl

Make master mix of H_2O, enzyme and buffer. Add sample to the mix and incubate at 37EC for two hours. After incubation, add 3 Fl Ficol Loading Dye and run on an 8% TBE polyacrylamide gel in a Bio-Rad mini-gel apparatus for one hour at 10 mA constant current. Stain the gel with ethidium bromide.

Visualize on U.V. light box and take picture.

Analysis:

Expected fragment sizes:

IL1â-1	190 bp and 115 bp
IL1â-2	305 bp
IL1â-1,2	305 bp, 190 bp and 115 bp

9.4.7 Determinations of IL1â-3953 Alleles

IL1â-3953 alleles are determined as follows (Kornman et al., 1997).

Primers:

UP	#971851 (IL1â-7)	5' CTCAGGTGTCCTCCAAGAAATCAAA 3'
DOWN	#971818 (IL1â-6)	5' GCTTTTTTGCTGTGAGTCCCG 3'

Stored in primer box -20EC as 10X solution.

[10X] = 150 FM soln. Make 1X for working concentration.

PCR:

PCR reaction using Perkin Elmer Cetus GeneAmp PCR Kit Part No. 801-0055.

Taq start	0.05	Fl	
Taq polymerase	0.05	Fl	
H_20	0.5	Fl	
	20 min.		
Sterile H_20	6.2	Fl	
10XPCR buffer with MgCl	1	Fl	
Premixed dNTP mix	0.8	Fl	
Upstream primer	0.2	Fl	
Downstream primer	0.2	Fl	
Total volume	9	Fl	controls JP (1) Weeks (2) Phil (1,2)
Sample DNA	1	Fl	

Add 1 Fl sample DNA to 9 Fl mix in a Perkin Elmer 0.25 ml PCR tube and run Method 10 (see PCR Methods List) in Perkin Elmer System 9600 PCR machine (protocol below).

35 cycles:	95EC	60EC
Perkin Elmer 9600	15 sec	30 sec
Expended product length:	194 bp	

Restriction digestion:

Restriction digest 10 Fl PCR product with 4 units aTaq1 restriction enzyme (NEB 149S).

Example:

Sample	H_20	Enzyme	BSA	Final Volume
10 Fl	2.7 Fl	0.2 Fl	0.1 Fl	18 Fl

Make master mix of H_20, enzyme, and buffer. Add sample to the mix and incubate at 65EC for two hours. After incubation, add 3 Fl Ficol Loading Dye and run on an 10% TBE polyacrylamide gel in

a Bio-Rad mini-gel apparatus for one hour at 10 mA constant current. Stain the gel with ethidium bromide.

Visualize on U.V. light box and take picture.

Analysis:

Expected fragment sizes:

IL1â-1	108 bp, and 86 bp
IL1â-2	194 bp
IL1â-1,2	194 bp, 108 bp, and 86 bp.

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL
Volume IV

CHAPTER 10

DATA TRANSMISSION FROM CORE LABORATORIES TO CLINICAL COORDINATING CENTER

10.1 INTRODUCTION

The Clinical Center staff are responsible for sending specimens to ACCESS Core Laboratories and the Central Registry as described in Chapter 6 of Volume I of the ACCESS Procedures Manual. An overview of the biological specimen processing is given in Figure 10-1. The details of processing and analyzing these specimens are presented in Chapters 1-9 of this volume of the Procedures Manual. The procedures for data transmission from the Core Laboratories to the Clinical Coordinating Center are presented in this chapter.

Core Laboratory staff provide the Clinical Coordinating Center (CCC) with the following information:

1. Inventory of specimens received during each specified time interval,
2. The conditions of each specimen received in this period,
3. Results of Core Laboratory analyses, and
4. Disposition of each specimen.

These data are used by CCC staff to evaluate the Clinical Centers' adherence to Protocol with respect to shipment of specimens and to maintain a complete inventory of all specimens including the location of each specimen. These data are also used in the data analyses of the Core Laboratory results.

10.2 DNA CORE LABORATORY

10.2.1 Inventory and Quality Control Data

Each month the DNA Core Laboratory staff submits a report on the receipt and processing of specimens received during the prior month. The sample spread sheet for this report is given in Exhibit 10-1. This spread sheet includes the following information; the ACCESS specimen

collection number for each specimen received, the date the specimen was received, the condition of the specimen, and the volume of the blood sample. For each sample processed during the reporting period the total genomic DNA and whether the sample is satisfactory to generate genomic DNA are reported. For the specimens shipped to the Central Repository the total number of aliquots submitted and the date of the shipment are reported.

The DNA Core Laboratory is responsible for preparing frozen cell pellets for the Ribosomal DNA Core Laboratory at the University of Iowa. The report for the cell pellets includes the number of cells obtained, whether the quality of the specimen is acceptable and the date the cell pellets were shipped to the Ribosomal DNA Core Laboratory. Also, the DNA Core Laboratory sends 2 Fg specimens of DNA to the Medical University of South Carolina for use in the Immunogenetics of Sarcoidosis Special Laboratory Study.

10.2.2 Analysis of Specimens

The DNA Core Laboratory does not perform any further analyses of specimens.

10.3 CENTRAL REPOSITORY

10.3.1 Inventory of ACCESS Specimens

The Central Repository provides the Clinical Coordinating Center with its inventory in one database. The database contains an inventory of the material that has been received from the DNA Core Laboratory and an inventory of the BAL fluid and slides submitted by Clinical Centers. This database includes the ACCESS specimen number, the date the specimen was received, the type of specimen, the condition of the specimen on receipt and a code that specifies any restrictions on the availability of each specimen stored in the Central Repository. Each case or control enrolled in ACCESS designates whether his/her specimens may be used for ACCESS only, for ACCESS and other research, or the case or control must be contacted for specific consent prior to use of the specimen for any non-ACCESS research.

Also, the database contains “shipping” information used to record the transfer of specimens to one of the Core Laboratories. The shipping information includes the ACCESS specimen number

and the type of specimen for each specimen, the number of specimens shipped, the date of the shipment and the destination of the shipment. A copy of this database is sent in ASCII files to the CCC on a monthly basis.

A separate database is maintained to link the name, title, department, institution affiliation, address, telephone number and fax number of each Clinical Center and Core Laboratory sending ACCESS specimens to or receiving ACCESS specimens from the Central Repository.

10.4 HLA CLASS II TYPING CORE LABORATORY

An Excel spreadsheet containing the inventory of specimens received and results for those specimens that have been analyzed is transmitted to the CCC on a monthly basis by e-mail. Exhibit 10-3 gives the column headings for the spreadsheet.

10.5 RNA CORE LABORATORY

An Excel spreadsheet containing the inventory of specimens are transmitted to the CCC by e-mail. Exhibit 10-4 gives the column headings for the spreadsheet.

10.6 RIBOSOMAL DNA CORE LABORATORY

Excel spreadsheets containing the results of the analyses of specimens are transmitted to the CCC periodically attached to the routine Clinical Center data transmissions. Exhibit 10-5 gives the column headings for the spreadsheets. A separate spreadsheet is sent for each primer.

10.7 L-FORMS CORE LABORATORY

A diskette with the inventory of specimens and results of analyses is sent to the CCC periodically. Exhibit 10-6 gives the column headings for the Excel spreadsheet on the diskettes.

10.8 ANTIGEN IN KVEIM REAGENT CORE LABORATORY

This study has been conducted only at the Johns Hopkins University School of Medicine, Bayview Campus. The Principal Investigator does not plan to send information to the CCC on the processing and quality of the specimens analyzed. The Core Laboratory staff maintain a log of specimens entered into this Core Laboratory study.

10.8.1 Data Analysis

All data analyses for this project were performed at the Core Laboratory. Copies of the data and analyses are transmitted to the CCC attached to routine Clinical Center data transmissions.

10.9 BRONCHOALVEOLAR LAVAGE (BAL) CORE LABORATORY

An Excel spreadsheet containing the results of cell counts for specimens received is transmitted to the CCC periodically by e-mail. Exhibit 10-7 gives the column headings for the spreadsheet.

10.10 PATHOGENIC T CELLS IN SARCOIDOSIS

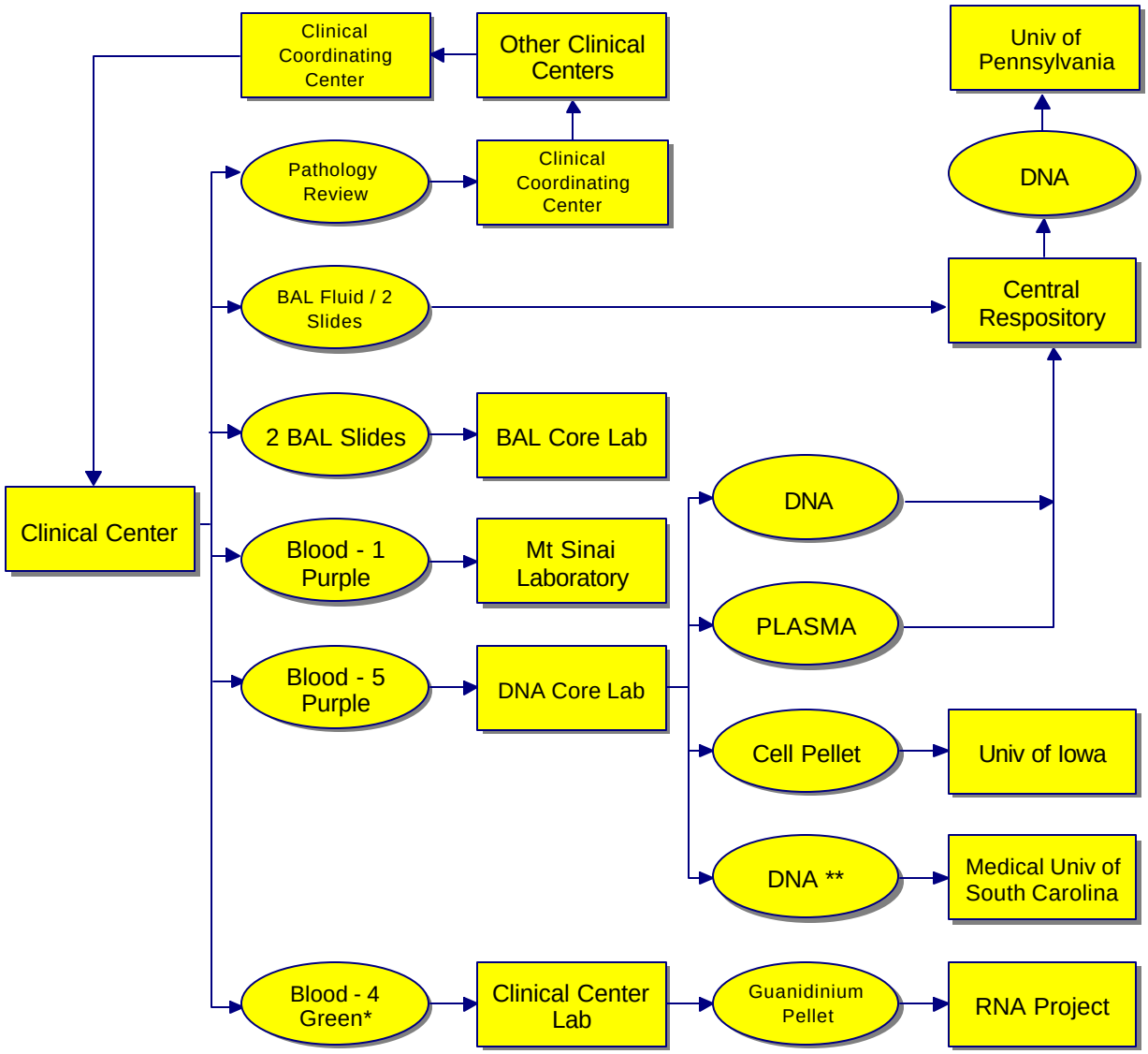
An Excel spreadsheet containing the inventory of specimens is transmitted to the CCC periodically by e-mail. Exhibit 10-8 gives the column headings for the spreadsheet.

10.11 IMMUNOGENETICS OF SARCOIDOSIS

A list of specimens received is transmitted to the CCC in an Excel spreadsheet on a monthly basis by e-mail. The results of analyses are transmitted periodically in an Excel spreadsheet by e-mail. Exhibit 10-9 gives the column headings for the results spreadsheet.

FIGURE 10-1

BIOLOGICAL SPECIMEN PROCESSING



* Heparinized (green top) tubes to be collected in the Beth Israel Hospital, Boston, Massachusetts only (until further notice).

** 2 Micrograms

EXHIBIT 10-1

DNA CORE LAB REPORT

Specimen		Sample	Blood	Sample	Total	DNA Qlty	Aliquots	Shipped	Date	Cells to	Cell No.	Date	Aliquot	Date	
ID	Date	Broken?	Sample	Processed	Genomic	Acceptable	to	Repository	Shipped to	Iowa	Acceptable	Shipped to	to S.	Shipped to	
Number	Received	(Yes/No)	Vol.(ml)	(Yes/No)	DNA (ug)	(Yes/No)	DNA	Plasma	Repository	(x106)	Iowa (Y/N)	Iowa	Carolina	S. Carolina	Comments

EXHIBIT 10-2

CENTRAL REPOSITORY REPORT

SampleID	TYPE	REC_DATE	REC_SITE	COMMENTS	CONDITION	RESTRICT	BIOHAZ	FREEZER	RACK	BOX	COLUMN	ROW	STUDYNUM	SHIPSTAT	SHIPSITE	SHIPNO	SHIPDATE	CELL

EXHIBIT 10-3

HLA Class II Typing Core Lab Report

ACCESS Log Number	CHOP HLA Typing Lab Number	Date Specimen Received	Specimen Condition	DNA Amplified	DRB1	DRB1	DRB3	DRB4	DRB5	DQB1	DQB1	DPB1	DPB1	Case or Control	Case/Control Number

EXHIBIT 10-4

RNA Core Lab Report

Sample	Blood ID#	Date In	Quantity	Total Cells	Total Amt.		Quality	Initial DD	Comments
			(ml)	($x10^6$)	RNA (mg)	RNA gel	of RNA		

EXHIBIT 10-5

Ribosomal DNA Core Lab Report

DATE	ACCESS							
RECD	NUMBER	PCR date	RESULT	PCR date	RESULT	PCR date	RESULT	FINAL

EXHIBIT 10-6

L-Forms Core Lab Report

SAMPLE #	DATE RECEIVED	ACCESS FORM	CENTER #	DATE INOCULATED	DATE EXTRACTED	SECONDARY DATE	QUALITY OF SAMPLE	BAP	GRAM STAIN	MODIFIED KINYOUN

EXHIBIT 10-7

BAL Core Lab Report

Specimen ID	Strained	Air/Dry	Date of Receipt	Condition	Center	Diff Macs	Polys	Lymphs	Eos	Epithel

EXHIBIT 10-8

Pathogenic T Cells in Sarcoidosis Lab Report

Study	Pt. code #	Diagnosis	Protocol #	NJC Pt. ID #	Fluid Rec'd	Date Drawn	Date Rec'd	DOB	SEX	Physician	Phys Phone (303) 398-	Phys. Address	Pt. phone	Race	Inventory	Liq. Nitrogen Storage

EXHIBIT 10-9

Immunogenetics of Sarcoidosis Lab Report

Sample#	TNF a (1,2)	TNF a (G,A)	IL1 B(511)	IL1 B(3953)	GM (f,z)	GM (n)	KM (1,3)

A Case Control Etiologic Study of Sarcoidosis

PROCEDURES MANUAL VOLUME IV

REFERENCES

Aiello, L.P., Robinson, G.S., Lin, Y.W., Nishio, Y., and King, G.L. (1994). Identification of multiple genes in bovine retinal pericytes altered by exposure to elevated levels of glucose by using mRNA differential display. *Proc. Natl. Acad. Sci. USA*. **91.** 6231-6235.

Almenoff, P.L., Johnson, A., Lesser, M., and Mattman, L.H. (1996A). Growth of acid-fast L forms from the blood of patients with sarcoidosis. *Thorax.* **51.** 530-533.

Almenoff, P.L., Brooks, J.B., Johnson A., and Lesser, M. (1996B). Differentiation of sarcoidosis from tuberculosis by use of electron capture gas-liquid chromatography. *Lung.* **174**. 349-358.

Amac, N., Randall, J., Kojima, R., Milford, E.L., and Gullans, S.R. (1994). Identification of a new human (H+)-ATPase proton pump homology differentially expressed in alloactivated lymphocytes. *J. Am. Soc. Nephrol.* **5.** 740.

Ausubel, F.M., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A., and Struhl, K. (Eds) (1991). In *Current Protocols in Molecular Biology*. Volume 2, John Wiley & Sons, New York.

Babbitt, B. P., Allen, P.M., Matsueda, G., Haber, E., and Unanue, E.R. (1985). Binding of immunogenic peptides to Ia histocompatibility molecules. *Nature* **317**: 359-361.

Balbi, B., Moller, D.R., Kirby, M., Holroyd, K.J., and Crystal, R.G. (1990). Increased numbers of T lymphocytes with ((-positive antigen receptors in a subgroup of individuals with pulmonary sarcoidosis. *J. Clin. Invest.* **85.** 1353-1361.

Balbi, B., Valle, M.T., Oddera, S., Giunti, D., Manca, F., Rossi, G.A., and Allegra, L. (1993). T-lymphocytes with ((+ V(2+ antigen receptors are present in increased proportions in a fraction of patients with tuberculosis or with sarcoidosis. *Am. Rev. Respir. Dis.* **148.** 1685-1690.

Balbín, M., Grubb A., Abrahamson M., Grubb R. (1991). Determination of allotypes Glm(f) and Glm(z) at the genomic level by subclass-specific amplification of DNA and use of allele-specific probes. *Experimental and Clinical Immunogenetics*. **8**. 88-95.

Balbín, M., Grubb A., de Lange G.G., Grubb P. (1994). DNA sequences specific for Caucasian G3m(b) and (g) allotypes: allotyping at the genomic level. *Immunogenetics.* **39**. 187-193.

Baro, C. and Butt, C.G. (1969). Hamazaki-Wesenberg bodies in sarcoidosis. *Lab. Med. Bull. Pathol.* **10.** 281.

Barth, C.L., Judge, M.S., Mattman,L.H., and Hessburg, D.C. (1979). Isolation of an acid-fast organism from the aqueous humor in a case of sarcoidosis. *Henry Ford Hosp. Med. J.* **27.** 127-133.

Baughman, R.P., Strohofer, S., and Kim, C.K. (1986). Variation of differential cell counts of bronchoalveolar lavage fluid. *Arch. Path. Lab. Med.* **110.** 341-343.

Bisaccia, E., Scarborough, D. A., and Carr, R.D. (1983). Cutaneous sarcoid granuloma formation in resolving herpes zoster scars. *Arch. Dermatol.* **119.** 788-789.

Bocart, D., Lecossier, D., De Lassence, A., Valeyre, D., Battesti, J.P., and Hance, A.J. (1992). A search for mycobacterial DNA in granulomatous tissues from patients with sarcoidosis using the polymerase chain reaction. *Am. Rev. Respir. Dis.* **145.** 1142-1148.

Boddinghaus, B., Roggal, T., Flohr, T., Blocker, H., and Bottger, E.C. (1990). Detection and identification of mycobacteria by amplification of rRNA. *J. Clin. Microbiol.* **28.** 1751-1759.

Bodmer, J.G., Marsh, S.G., Albert, E.D., Bodmer, W.F., Bontrop, R.E., Charron, D., Dupont, B., Erlich, H.A., Mach, B., and Mayr, W.R. (1995). Nomenclature for factors of the HLA system. *Tissue Antigens*. **46**. 1-18.

Brenner, R.M., Amac, N., Kojima, R., Randall, J., Milford, E.L., and Gullans, S.R. (1994). DDRT-PCR analysis of mRNA expression in human mononuclear cells reveals comparable patterns of expression in genetically diverse individuals. *J. Am. Soc. Nephrol*. **5.** 741.

Britschgi, T.B. and Giovannoni, S.J. (1991). Phylogenetic analysis of natural marine bacterioplankton population by rRNA gene cloning and sequencing. *Appl. Environ. Microbiol.* **57.** 1707-1713.

Brunet, J.F., Shapiro, E., Foster, S.A., Kandel, E.R., and Lino, Y. (1991) Identification of a peptide specific for Aplysia sensory neurons by PCR-based differential screening. *Science.* **252.** 856-859.

Brusco, A., de lange, G.G., Boccazzi, C., Carbonara, A.O. (1995). Molecular characterization of G2m(n+) and G2m(n-) allotypes. *Immunogenetics.* **42**. 414-417.

Bugawan, T.L., Begovich, A.B., and Erlich, H.A. (1990). Rapid HLA-DPB typing using enzymatically amplified DNA and non-radioactive sequence-specific oligonucleotide probes. *Immunogenetics.* **32.** 231-241.

Burke, W.M., Keogh, A., Maloney, P.J., Delprado, W., Bryant, D.H., and Spratt, P. (1990). Transmission of sarcoidosis via cardiac transplantation. [Letter] *Lancet.* **336.** 1579.

Cantwell, A.R. (1981). Variable acid-fast bacteria in a case of systemic sarcoidosis and hypodermitis sclerodermiformis. *Dermatologica*. **163.** 239-248.

Cantwell, A.R. (1982). Histologic observations of variably acid-fast pleomorphic bacteria in systemic sarcoidosis: Report of 3 cases. *Growth.* **46.** 113-125.

Chadarevian, J., Raphael, S.A., and Murphy, G.F. (1992). Histologic, ultrastructural and immunocytochemical features of the granulomas seen in a child with the syndrome of familial granulomatous arthritis, uveitis, and rash. *Arch. Path. Lab. Med.* **117.** 1050-1052.

Chen, K., Neimark, H., Runmore, P., and Steinman C.R. (1989). Broad-range DNA probes for detecting and amplifying eubacterial nucleic acids. *FEMS Microbiol. Lett.* **57.** 19-24.

Cho, C., Linscheer, W.G., Hirschkorn, M.A., and Ashutosh, K., (1984). Sarcoid like granulomas as an early manifestation of Whipple's disease. *Gastroenterology.* **87.** 941-947.

Choi, Y.W., Kotzin, B., Lafferty, J., White, J., Pigeon, M., Kubo, R., Kappler, J., Marrack, P.A. (1991). Method for production of antibodies to human T-cell receptor beta-chain variable regions. *Proc Natl Acad Sci USA*. **88**. 8357-8361.

Chomczynski, P. and Sacchi, N. (1987). Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal. Biochem.* **162.** 156-159.

Christie, J.D. and Callihan, D.R. (1995). The laboratory diagnosis of mycobacterial diseases. *Clin. Lab. Med.* **15.** 279-306.

Chryssanthou, E., Andersson, B., Petrini, B., Lofdahl, S., and Tollemar, J. (1994). Detection of Candida albicans DNA in serum by polymerase chain reaction. *Scand. J. Infect. Dis.* **26.** 479-485.

D' Alfonso, S., Richiardi, P.M. (1994). A polymorphic variation in a putative regulation box of the TNFA promoter region. *Immunogenetics* . **39**. 150-154.

di Giovine, F.S., Takhsh, E., Blakemore, A.I.F., and Duff, G.W. (1992). Single base polymorphism at -511 in the human interleukin-l beta gene (IL1ß). *Human Molecular Genetics.* **1**. 450.

Dyer, P. A., Jawaheer, D., Ollier, B., Pouton,K., Sinnott, P., and Thomson, W. (1993). HLA allele detection using molecular techniques. *Disease Markers* **11**: 145-160.

Ehlers, S., Mielke, M.E., and Hahn, H. (1994). The mRNA-phenotype of granuloma formation in $CD4^{+}$T-cell-associated cytokine gene expression during primary murine listeriosis. *Immunobiol.* **191.** 432-440.

Fidler, H.M., Rook, G.A., Johnson, N. Mcl., and Mcfadden, J. (1993A). *Mycobacterium tuberculosis* DNA in tissue affected by sarcoidosis. *Br. Med. J.* **306.** 546-549.

Fidler, H.M., Rook, G.A., Johnson, N. McI., and Mcfadden, J. (1993B). Search for mycobacterial DNA in granulomatous tissues from patients with sarcoidosis using the polymerase chain reaction. [Letter] *Am. Rev. Respir. Dis.* **147.** 777-778.

Fitzgerald, J.E., Ricalton, N.S., Meyer, A.C., West, S.G., Kaplan, H., Behrendt, C., Kotzin, B.L. (1995). Analysis of clonal CDE8+ T cell expansions in normal individuals and patients with rheumatoid arthritis. *J. Immunol*. **154**. 3538-3547.

Forester, J.M., Newman, L.S., King, T.E., Jr., Kotzin, B.L. (1993) Clonal expansion of lung Vä1 T-cells in a subset of patients with sarcoidosis. *J. Clin. Invest.* **91**. 292-300.

Forrester, J.M., Wang, Y., Ricalton, N., Fitzgerald, J.E., Loveless, J., Newman, L.S., King, T.E., Jr., Kotzin, B.L. (1994). TCR expression of activated T cell clones in the lungs of patients with pulmonary sarcoidosis. *J Immunol*. **153**. 4291-4301.

Gerdes, J., Richter, E., Rusch-Gerdes, S., Greinert, V., Galle, J., Schlaak, M., Flad, H.D., and Magnussen, H. (1992). Mycobacterial nucleic acids in sarcoid lesions. *Lancet.* **339.** 1536-1537.

Ghossein, R.A., Ross, D.G., Salomon, R.N., and Rabson, A.R. (1994). A search of mycobacterial DNA in sarcoidosis using the polymerase chain reaction. *Am. J. Clin. Pathol.* **101.** 733-737.

Goodman, J.I., Bradley, J.F., Ross, A.E., Goellner, P., Lagus, A., Vitale, B., Berger, B.W., Luger, S., and Johnson, R.C. (1995). Bloodstream invasion in early Lyme Disease: results from a prospective, controlled, blinded study using the polymerase chain reaction. *Am. J. Med.* **99.** 6-12.

Graham, D.Y., Markesich, D.C., Kalter, D.C., and Yoshimura, H.H. (1988). Isolation of cell wall-defective acid-fast bacteria from skin lesions of patients with sarcoidosis. Sarcoidosis and other granulomatous disorders, C. Grassi, G. Rizzato,E.Pozzi, eds. Elsevier Science, New York. 161-164.

Graham, D.Y., Markesich, D.C., Kalter, D.C., Moss, M.T., Hermon-Taylor, J., and El-Zaatari, F. A. (1992). Mycobacterial etiology of sarcoidosis. *Lancet*. **340.** 52-53.

Gullans, S.R., Orisio, S., Perico, N., Randall, J., Kojima, R., and Remuzzi, G. (1994). Differential display RT-PCR analysis of mRNA expression in human renal biopsy tissue. *J. Am. Soc. Nephrol.* **5.** 980.

Gustafson, S., Proper, J.A., Bowie, E.J.W., and Sommer, S.S. (1987). Parameters affecting the yield of DNA from human blood. *Anal. Biochem.* **165.** 294-299.

Heyll, A., Meckenstock, G., Aul, C., Sohngen, D., Borchard, F., Hadding, U., Modder, U., Leschke, M., and Schneider, W. (1994). Possible transmission of sarcoidosis via allogenic bone marrow transplantation. *Bone Marrow Transplantation.* **14.** 161-164.

Hills, S.E., Parkes, S.A., and Baker, S. BdeC. (1987). Epidemiology of sarcoidosis in the Isle of Man - 2: Evidence for space - time clustering. *Thorax*. **41.** 427-430.

Hunninghake, G. W., and Crystal, R. G. (1981). Pulmonary sarcoidosis: a disorder mediated by excess helper T lymphocyte activity at sites of disease activity. *N Eng J Med* **305**: 429-432.

Impraim, C.C., Saiki, R.K., Erlich, H.A., and Teplitz, R.L. (1987). Analysis of DNA extracted from formalin-fixed paraffin-embedded tissues by enzymatic amplification and hybridization with sequence-specific oligonucleotides. *Biochem. Biophys. Res. Comm.* **142.** 710-716.

Ishihara, M., Inoko, H., Suzuki, K., Ono, H., Hiraga, Y., Ando, H., Naruse, T., Ishida, T., and Ohno, S. (1996). HLA class II genotyping of sarcoidosis patients in Hokkaido by PCR-RFLP. *Japanese Journal of Ophthalmology* **40**: 540-543.

Janis, E.M., Kaufmann, S.H.E., Schwartz, R.H., and Pardoll, D.M. (1989). Activation of ((T cells in the primary immune response to Mycobacterium tuberculosis. *Science*. **244.** 713-716.

Johnson, A.H., Wright, G.L., Chaparas, S.D., and Mancuso, D.J. (1980). Analytical gradient polyacrylamide gel-crossed line immunoelectrophoresis. A technique for locating species specific Mycobacterium tuberculosis H37RV antigens in polyacrylamide gel columns. *Immunol. Commun.* **9.** 595-609.

Joyce-Brady, M. (1992). "Tastes great less filling". The debate about mycobacteria and sarcoidosis. *Am. Rev. Respir. Dis.* **145.** 986-987.

Judge, M.S. (1979). Evidence implicating a mycobacterium as the causative agent of sarcoidosis, and comparison of this organism with the blood-borne mycobacterium of tuberculosis. Ph.D. dissertation, Wayne State University, Detroit.

Judge, M.S. and Mattman, L.H. (1976). Isolation of an acid-fast organism from the blood of sarcoidosis patients. *Bacteriol. Proc. Am. Soc. Microbiol.* **13**.

Judge, M.S. and Mattman, L.H. (1982). Cell wall deficient mycobacteria in tuberculosis, sarcoidosis, and leprosy. In Cell wall deficient bacteria, Domingue G.J., Ed., Addison-Wesley, Reading, MA, chap 10.

Kabelitz, D., Bender, A., Schondelmaier, S., Schoel,B., and Kaufmann, S.H.E. (1990). A large fraction of human peripheral blood (/(T cells is activated by Mycobacterium tuberculosis but not by its 65-kD heat shock protein. *J. Exp. Med.* **171.** 667-679.

Kazerooni, E.A. and Cascade, P.N. (1995). Recurrent miliary sarcoidosis after lung transplantation. [Letter] *Radiology.* **194.** 913.

Kendall, T., Byerley, D.J., and Dean, R. (1991). Isolation of DNA from blood. *Anal. Biochem.* **195.** 74-76.

Kern, D.G., Neill, M.A., Wrenn, D.S., and Varone, J.C. (1993). Investigation of a unique time-space cluster of sarcoidosis in fire fighters. *Am. Rev. Resp. Dis.* **148.** 974-980.

Khomenko, A.G., Golyshevskaya, V.I., and Elshanskaya, M.P. (1987). Bacteriological study of bronchoalveolar washings and blood plasma in sarcoidosis patients. *Klin. Med.* (Moscow) **65.** 80-84.

Kimura, A., and T. Saszuki (1992.). Eleventh International Histocompatibility Workshop Reference Protocol for the HLA DNA-Typing Technique . New York, Oxford University Press.

Koch, M.L. and Cote, R.A. (1965). Comparison of fluorescence microscopy with Ziehl-Neelsen stain for demonstration of acid-fast bacilli in smear preparations and tissue sections. *Am. Rev. Respir. Dis.* **91.** 283-284.

Kohler, G. and Milstein, C. (1975). Continuous cultures of fused cells secreting antibody of redefined specificity. *Nature.* **256.** 495-497.

Kojima, R., Randall, J., Brenner, B.M., and Gullans, S.R. (1994). Differential display analysis of mRNA expression: targeting internal DNA sequence. *J. Am. Soc. Nephrol.* **5.** 318.

Kornman, K.S., Crane, A., Wang, H.Y., di Giovine, F.S., Neuman, M.G., Pirk, F.W., Wilson, Jr., T.G., Higginbottom, F.L., and Duff, G.W. (1997). The interleukin-1 genotype as a severity factor in adult periodontal disease. *Journal of Clinical Periodontology*. **24**. 72-77.

Langebberg, A., Yen, T.S., and LeBoit, P.E. (1991). Granulomatous vasculitis occurring after cutaneous herpes zoster despite absence of the viral genome. *J. Am. Acad. Derm.* **24.** 429-433.

Liang, P., Averboukh, L., Keyomarsi, K., Sager, R., and Pardee, A.B. (1992). Differential display and cloning of messenger RNAs from human breast cancer versus mammary epithelial cells. *Cancer Res*. **52.** 6966-6968.

Liang, P., Averboukh, L., and Pardee, A.B. (1993). Distribution and cloning cDNAs generated in differential mRNA display: refinements and optimization. *Nucleic Acids Res.* **21.** 3269-3275.

Liang, P. and Pardee, A.B. (1992). Differential display of eukaryotic messenger RNA by means of the polymerase chain reaction. *Science*. **257.** 967-971.

Liesack, W. and Stackebrandt, E. (1992). Occurrence of novel groups of the domain bacteria as revealed by analysis of genetic material isolated from an Australian terrestrial environment. *J. Bacteriol.* **174.** 5072-5078.

Lisby, G., Milman, N., and Jacobsen, G.K. (1993). Search for Mycobacterium paratuberculosis DNA in tissue from patients with sarcoidosis by enzymatic gene amplification. *APMIS*. **101.** 876-878.

Lyons, D.J., Sinclair, A., Smith, H.G., Mitchell, D.N., and Dalgleish, A.G. (1991). Search for a retroviral cause for sarcoidosis: no evidence from peripheral blood studies. *Eur. Respir. J.* **4.** 445-449.

Madisen, L., Hoar, D.I., Holroy, D., Crisp, M., and Hodes, M.E. (1987). DNA banking: The effects of storage of blood and isolated DNA on the integrity of DNA. *Am. J. Med. Genet.* **27.** 379-390.

Mangiapan, G. and Hance, A.J. (1995). Mycobacteria and Sarcoidosis: An overview and summary of recent molecular biological data. *Sarcoidosis.* **12.** 20-37.

Martinetti, M., Tinelli, C., Kolek, V., Cuccia, M., Salvaneschi, L., Pasturenzi, L., Semenzato, G., Cipriani, A., Bartova, A., and Luisetti, M. (1995). The sarcoidosis map: A joint survey of clinical and immunologic finding in two European countries. *Am J Respir Crit Care Med.* **152**: 557-564.

Martinez, F.J., Orens, J.B., Deeb, M., Brunsting, L.A. Flint, A., and Lynch, J.P. (1994). Recurrence of sarcoidosis following bilateral allogenic lung transplantation. *Chest.* **106.** 1597-1599.

McFadden, J.J., Butcher, P.D., Thomson, J., Chiodini, R.J., and Hermon-Taylor, J. (1987). The use of DNA probes identifying restriction-fragment-length polymorphisms to examine the Mycobacterium Avium Complex. *Molecular Microbiology.* ***1.*** 283-291.

McFadden, J.J., Kunze, Z., and Seechurn, P. (1990). DNA probes for detection and identification of mycobacteria. In *Molecular Biology of the Mycobacteria*. J.J. McFadden, ed. Surrey University Press, pp. 139-172.

Mickelson, E., Smith, A., McKinney, S., Anderson, G., and Hansen, J.A. (1993). A comparative study of HLA-DRB1 typing by standard serology and hybridization of non-radioactive sequence-specific oligonucleotide probes to PCR-amplified DNA. *Tissue Antigens*. **41.** 86-93.

Mitchell, D.N. and Rees, R.J.W. (1969). An attempt to demonstrate a transmissable agent from sarcoid tissue. In *Proceedings of Fifth International Conference on Sarcoidosis.* 76-80.

Mitchell, D.N. and Rees, R.J.W. (1972). The production of granulomas in mice by sarcoid tissue suspensions. In *Proceedings of the Sixth International Conference on Sarcoidosis.* 12-19.

Mitchell, D.N., Goswami, K.K.A., and Rees, R.J.W. (1976). Transmissible agents from human sarcoid and Crohn's disease tissues. *Lancet.* **2.** 761-765.

Mitchell, I.C., Turk, J.L., and Mitchell, D.N. (1992). Detection of mycobacterial rRNA in sarcoidosis with liquid phase hybridization. *Lancet.* **339.** 1015-1017.

Moscovic, E.A. (1978). Sarcoidosis and mycobacterial L-forms: A critical reappraisal of pleomorphic chromogenic bodies (Hamazaki corpuscles) in lymph nodes. *Pathol. Annual*. **13.** 69-164.

Moxley, G. and Gibbs, R.S. (1992). Polymerase chain reaction-based genotyping for allotypic markers of immunoglobulin Kappa shows allelic association of KM with Kappa variable segment. *Genomics*. **13**. 104-108.

Murakami, S., Takahashi, Y., Yoshida, S., Fuke, I., Ohmae, K., Mori, C., Takagi, M., Takamizawa, A., and Okayama, H. (1994). High sensitive detection of viral RNA genomes in blood specimens by an optimized reverse transcription-polymerase chain reaction. *J. Med. Virol.* **43.** 75-81.

Nichols, L., Florentine, B., Lewis, W., Sattler, F., Rarick, M.U., and Brynes, R.K. (1991). Bone marrow examination for the diagnosis of mycobacterial and fungal infections in the acquired immunodeficiency syndrome. *Arch. Pathol. Lab. Med.* **115.** 1125-1132.

Nikkels, A.F., Debrus, S., Delvenne, P., Sadzot-Delvaux, C., Piette, J., Rentier, B., and Pierard, G.E. (1994). Viral glycoproteins in herpesviridae granulomas. *Am. Jnl. Dermatopathology.* **16.** 588-592.

Nishio, Y., Aiello, L.P., and King, G.L. (1994). Glucose induced genes in bovine aortic smooth muscle cells identified by mRNA differential display. *FASEB J.* **8.** 103-106.

Obata, F., Ito, K., Kaneko, T., Yang, Y., Onda, K., Ito, I., Yabe, N., Watanabe, K., and Kashiwagi, N. (1991). HLA-DR gene frequencies in the Japanese population obtained by oligonucleotide genotyping. *Tissue Antigens.* **38.** 124-132.

Paliard, X., deVries, J.E., Spits, H. (1991). Comparison of lymphokine secretion and responsiveness of human T cell clones isolated in IL-4 and in IL-2. *Cell Immunol*. **135**. 383-393.

Parkes, S.A., Baker, S. BdeC., Bourdillon, R.E., Murray, C.R., and Rakshit, M. (1987). Epidemiology of sarcoidosis in the Isle of Man - 1: A case controlled study. *Thorax.* **42.** 420-426.

Pasturenzi, L., Martinetti, M., Cuccia, M., Cipriani, A., Semanzato, G., and Luisetti, M. (1993). HLA class I, II and III polymorphism in Italian Patients with sarcoidosis. The Pavia-Padova Sarcoidosis Study Group. *Chest* **104**: 1170-1175.

Patel, R., Smith, T.F., Espy, M., Portela, D., Wiesner, R. H., Krom, R. A., and Paya, C.V. (1995). A prospective comparison of molecular diagnostic techniques for the early detection of Cytomegalovirus in liver transplant recipients. *J. Infect. Dis.* **171.** 1010-1014.

Popper, H.H., Winter, E., and Hofler, G. (1994). DNA of *Mycobacterium* tuberculosis in formalin-fixed, paraffin-embedded tissue in tuberculosis and sarcoidosis detected by polymerase chain reaction. *Am. J. Clin. Pathol.* **101.** 738-741.

Randall, J., Kojima, R., and Gullans, S.R. (1994). Identification of differentially expressed genes during adaptation to hyperosmolar stress. *J Am Soc Nephrol.* **5.** 319.

Relman, D. (1993). The identification of uncultured microbial pathogens. *J. Infectious Diseases.* **168.** 1-8.

Relman, D.A., Schmidt, T. M., MacDermott, R.P., and Falkow, S. (1992). Identification of uncultured bacillus of Whipple's disease. *New Eng. J. Med.* **327.** 293-301.

Richter, J., Bartak, F., and Halova, R. (1969). Detection of mycobacteria by fluorescent microscopy in sarcoidosis. In *Proceedings of the Fifth International Conference on Sarcoidosis.* 83-84.

Ross, K.S., Haites, N.E. and Kelly, K.F. (1990). Repeated freezing and thawing of peripheral blood and DNA in suspension: Effects on DNA yield and integrity. *J Med Genet.* **27.** 569-570.

Rowley, A.H., Wolinsky, S.M., Relman, D.A., Sambol, S.P., Sullivan, J., Terai, M., and Shulman, S.T. (1994). Search for highly conserved viral and bacterial nucleic acid sequences corresponding to an etiologic agent of Kawasaki Disease. *Pediatr. Res.* **36.** 567-571.

Russell, M.E., Utans, U., Wallace, A.F., Liang, P., Arceci, R.J., Karnovsky, M.J., Wyner, L.R., Yamashita, Y., and Tarn, C. (1994). Identification and upregulation of galactose/N-acetylgalactosamine macrophage lectin in rat cardiac allografts with arteriosclerosis. *J Clin Invest.* **94.** 722-730.

Saboor, S.A., Johnson, N. McI., and McFadden, J. (1992). Detection of mycobacterial DNA in sarcoidosis and tuberculosis with polymerase chain reaction. *Lancet.* **339.** 1012-1015.

Saiki, R.K., Gelfand, D.H., Stoffel, S., Scharf, S.J., Higuchi, R., Horn, G.T., Mullis, K.B., and Erlich, H.A. (1988). Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science.* **239.** 487-491.

Sanderson, J.D., Moss, M.T., Tizard, M.L.V., and Herman-Taylor, J. (1992). Mycobacterium paratuberculosis DNA in Crohn's disease tissue. *Gut.* **3.** 890-896.

Schaumann, J. (1941). On the nature of certain peculiar corpuscles present in the tissue of lymphogranulomatoisis benigna. *Acta Med. Scandinav.* **106.** 239-253.

Schluger, N.W., Condox, R., Lewis, S., and Rom, W.N. (1994). Amplification of DNA of mycobacterium tuberculosis from peripheral blood of patients with pulmonary tuberculosis. *Lancet.* **344.** 232-33.

Schmidt, T.M. and Relman, D. A. (1994). Phylogenetic identification of uncultured pathogens using ribosomal RNA sequences. *Meth. Enzymol.* **235.** 205-222.

Schneeberger, C. and Zeillinger, R. (1996). PCR-mediated synthesis of exogenous competitors for quantitative RT-PCR. *Biotechniques.* **20.** 360.

Sharma, O.P. and Kadakia, D. (1986). Etiology of sarcoidosis. *Seminars Resp. Med.* **8.** 95-102.

Southern, J.F., Moscicki, R.A., Magro, C., Dickersin, G.R., Fallon, J.T., and Bloch, K.J.. (1989). Lymphedema, lymphocytic myocarditis, and sarcoid like granulomatosis. Manifestations of Whipple's disease. *JAMA*. **261.** 467-70.

Spapen, H.D., Segers, O., DeWit, N., Goosen, A., Buydens, P., Diercky, R., and Somers, G. (1989). Electron microscopic detection of Whipple's bacillus in sarcoid like periodic acid-Schiff-negative granulomas. *Dig. Dis. Sci.* **34.** 640-3.

Stackebrandt, E. and Woese, C.R. (1991). A definition of the domains archaea, bacteria and eurcarya in terms of small subunit ribosomal RNA characteristics. *System. Appl. Micro.* **14.** 305-310. Gustav Fischer Verlag, Stuttgart/New York.

Su, W.P., Kuechle, M.K., Peters, M.S., and Muller, S.A. (1992). Palisading granulomas caused by infectious diseases. *Am. J. Of Dermatopathology.* **14.** 211-215.

Sunday, M.E. (1995). Differential display RT-PCR for identifying novel gene expression in the lung. *Am. J. Physiology*. **265.** L273-284.

Taub, R.N., Sachar, D., Siltzbach, L.E., and Janowitz, H. (1974). Transmission of ileitis and sarcoid granulomas to mice. *Trans. Assoc. Am. Physicians.* **87.** 219-224.

Taub, R.N. and Siltzbach, L.E. (1972). Induction of granulomas in mice by injection of human sarcoid and ileitis homogenates. In *Proceeding of the Sixth International Conference on Sarcoidosis.* 20-21.

Teodorica, L., Bugawan, A., Begovich, B., and Erlich, H. A. (1990). Rapid HLA-DPB typing using enzymatically amplified DNA and non-radioactive sequence -specific oligonucleotide probes. *Immunogenetics* **32**: 231-241.

Thakker, B., Black, M., and Foulis, A.K. (1992). Mycobacterial nucleic acids in sarcoid lesions. [Letter] *Lancet.* **339.** 1537.

Utans, U., Liang, P., Wyner, R., Karnovsky, M.J., and Russell, M.E. (1994). Chronic cardiac rejection: identification of five unregulated genes in transplanted hearts by differential mRNA display. *Proc. Natl. Acad. Sci.* **91.** 6463-6467.

van Belkum, A. (1994). DNA fingerprinting of medically important micro-organisms by use of PCR. *Clin. Microbiol. Rev.* **7.** 174-184.

van Etta, L.L., Filice, G.A., Ferguson, R.M., and Gerding, D.N. (1983). Corynebacterium egia: a review of 12 cases of human infection. *Rev. Infect. Dis.* **5.** 1012-1017.

Vanek, J. (1968). Acid-fast bacilli of mycobacterial nature in sarcoidosis. *Beitr. Pathol. Anat.* **136.** 303-315.

Vanek, J. and Schwarz, J. (1970). Demonstration of acid-fast rods in sarcoidosis. *Am. Rev. Respir. Dis.* **101.** 395-400.

Vaughan, R.W., Lanchbury, J.S., Marsh, S.G.E., Hall, M.A., Bodmer, J.G., and Welsh, K.I. (1990). The application of oligonucleotide probes to HLA Class II typing of the DRB sub-region. *Tissue Antigens.* **36.** 149-155.

Wang, N., Schraufnagle, D.E., and Sampson, M.G. (1981). The tadpole-shaped structures in human non-necrotizing granulomas. *Am. Rev. Resp. Dis.* **123.** 560-564.

Weisberg, W.G., Barns, S.M., Pelletier, D.A., and Lane, D.J. (1991). 16S ribosomal DNA amplification for phylogenetic study. *J. Bacteriol.* **173.** 697-703.

Williams, W.R. and Davies, B.H. (1986). Pseudo-leptospires in bronchoalveolar lavage fluid and blood cell culture. *J. Exp. Path.* **67.** 167-170.

Wilson, A.G., de Vries, N., Pociot, F., di Giovine, F.S., van der Putte, L.B.A. and Duff, G.W. (1993). An allelic polymorphism within the human tumor necrosis factor a promoter region is strongly associated with HLA A1, B8, and DR3 alleles. *Journal of Experimental Medicine* **177**. 557-560.

Wilson, A.G., di Giovine, F.S., Blakemore, A.I.F. and Duff, G.W. (1992). Single base polymorphism in the human tumor necrosis factor alpha (TNFa) gene detectable by Nco1 restriction of PCR product. *Human Molecular Genetics.* **1**. 353.

Wilson, K.H., Blitchington, R.B., and Greene, R.C. (1990). Amplification of bacterial 16S ribosomal DNA with polymerase chain reaction. *J. Clin. Microbiol.* **28.** 942-1946.

Wright, A.L., Cotton, D.W.K., Winfield, D.A., and Messenger, A.G. (1989). Granuloma formation in herpes zoster scars. *Dermatologica.* **179.** 45-6.

Zhogbi, H.Y., Daiger, S.P., McCall, A., O'Brien, W.E., and Beaudet, A.L. (1989). Extensive DNA polymorphism at the factor XIIIa (F13a) locus and linkage to HLA. *Am J Hum Genet* **44.** 845-853.

Zimmermann, J.W. and Schultz, R.M. (1994). Analysis of gene expression in the preimplantation mouse embryo: use of the mRNA differential display. *Proc. Natl. Acad. Sci. USA* **91.** 5456-5460.