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VA-NIH COOPERATIVE STUDY
OF HEPATITIS PREVENTION

EFFICACY OF HEPATITIS B IMMUNE SERUM GLOBULIN (ANTI-HBAg GAMMA GLOBULIN) FOR THE PREVENTION OR MODIFICATION OF POST-TRANSFUSION HEPATITIS

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A. TITLE OF RESEARCH PROJECT: Efficacy of Hepatitis B Immune Serum Globulin (Anti-HBAg Gamma Globulin) For The Prevention or Modification of Post-Transfusion Hepatitis.

B. NAMES OF INVESTIGATORS and OTHER PARTICIPANTS:

Principals: H. J. Zimmerman, M. D., Washington, D. C.
L. B. Seeff, M. D., Washington, D. C.

Associates:

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Central Pathologist:

K. Ishak, M. D., AFIP, Washington, D. C.

NIH:

June Dunnick, PhD., Health Scientist Administrator, NIH, Bethesda, Maryland
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C. DURATION OF STUDY: 2 - 3 years

D. SUBJECTS FOR STUDY:

All patients, regardless of age or sex, who receive transfusions of either whole blood or packed cells at any of the above eight VA hospitals, are potential candidates, unless specifically excluded (see later). The total number of patients to be admitted to this study will be approximately 1,000.

E. NARRATIVE DESCRIPTION OF STUDY:

a. Purpose - The study will be a controlled, randomized and double blind clinical trial to evaluate the efficacy of Hepatitis B Serum Globulin, in comparison with conventional serum globulin, in the prevention or modification of post-transfusion hepatitis.

b. Background Information - The Veterans Administration is presently concluding a cooperative study conducted in eight hospitals to determine the efficacy of conventional gamma globulin in preventing or modifying post-transfusion hepatitis. Preliminary results indicate that the incidence of hepatitis following transfusion in these hospitals is approximately 9% (1.4% icteric; 7.6% anicteric), and that the gamma globulin has been ineffective in reducing the total incidence of hepatitis when compared to an albumin placebo (8.2% gamma globulin; 10.2% placebo). It has, however, led to a slight, but significant, ($P = < 0.05$) reduction in the incidence of icteric hepatitis (0.7% gamma globulin; 2% placebo). The results also indicate, as have others, that the most important risk factors responsible for this high incidence of hepatitis are: (1) the proportion of blood derived from commercial sources, (2) the number of units transfused and (3) the HBAg status of the donor blood[1].

During the past three decades, ten other major studies have been conducted to evaluate the prophylactic effectiveness of gamma globulin in this setting, of which five have provided positive and five negative results[2-12]. The most recently published study[12], and by far the largest one undertaken to date, indicates that 2.8% of the transfused patients developed symptomatic hepatitis, the same risk factors as in the VA study and a total absence of effect of gamma globulin in preventing or modifying post-transfusion hepatitis. These results reflect the prevailing attitude, that gamma globulin, although effective in modifying viral A hepatitis, appears to be ineffective in reducing the high incidence of hepatitis following transfusion.

The continuing significant incidence of this disease, with its attendant high mortality and morbidity, remains an important problem and clearly requires additional therapeutic maneuvering, in order to reverse the trend. From the foregoing data, it is obvious that the incidence of this disease following transfusion may be reduced by: (1) decreasing the number of units transfused; (2) removing HBAg positive blood from the donor pool; (3) converting entirely to the use of volunteer blood; or (4) employing a more effective prophylactic agent than the conventional gamma globulin.

The first step, and seemingly the easiest, would be to make every effort to reduce the number of units transfused. It has already been urged that the use of one unit transfusions be discontinued, where possible. However, with the increasing number of complicated surgical procedures being performed, particularly cardiac surgery, often requiring large volumes of blood, a reduction in the transfusion rate does not seem to be a feasible solution to the problem at this time.

The removal of HBAg positive donor blood appears to offer more limited hope than had been expected. It has not proven to be of significant value in reducing the incidence of post-transfusion hepatitis in the VA Cooperative Study as of this date. Furthermore, only 25% of patients who received HBAg positive donor blood in this study, developed post-transfusion hepatitis. This observation is in accord with those of Gocke[13], and suggests that, although the testing and removal of HBAg positive blood from the donor pool is, and should be mandatory, a reduction in incidence of only one-fourth is to be expected.

An important and positive step would be to convert the blood banking practice in this country to an entirely voluntary one. With close to 20% of all blood dispensed being derived from non-volunteer sources, however, the probability of this change occurring in the near future would seem to be remote.

In the past year, three important studies have been published indicating that the prophylactic use of hyperimmune serum globulin (gamma globulin rich in antibody against the HBAg) is likely to be effective in preventing post-transfusion hepatitis. Krugman et al[14] indicate that Hepatitis B Immune Serum Globulin appears to be 70% effective in preventing hepatitis in individuals exposed to the Willowbrook MS-2 Strain (Serum Hepatitis) of hepatitis, whereas conventional gamma globulin has proven to be quite ineffective when tested in the same setting. A large study conducted in Korea[15], employing gamma globulin which, in retrospect was discovered to have a high anti-HBAg titer, indicated that this gamma

globulin was effective in reducing both HBAg positive and HBAg negative endemic hepatitis in U.S. soldiers. Finally, Soulier et al[16], have studied the hyperimmune serum globulin in patients who have received transfusions, and concluded that "passive immunization appears to be both effective and innocuous".

These promising results have prompted the initiation of several cooperative studies to test the effectiveness of hyperimmune serum globulin in a number of settings in which the incidence of hepatitis is high. The NHLI is sponsoring large-scale studies to test the effectiveness of this form of gamma globulin in preventing hepatitis in the setting of (1) accidental exposure to HBAg; and (2) chronic dialysis units[17]. The VA, in collaboration with the NIAID, is presently conducting a study to evaluate the effectiveness of hyperimmune serum globulin, derived from a different source, in preventing hepatitis in medical and paramedical individuals accidentally exposed by a needlestick or by ingestion to hepatitis infectious serum[18].

The VA, because of its extensive experience gained in conducting cooperative studies in the field of hepatitis, provides an excellent setting in which to evaluate the effectiveness of the Hepatitis B Immune Serum Globulin in preventing post-transfusion hepatitis. The post-transfusion study, presently in the stage of conclusion, has allowed for the identification of VA hospitals with a high incidence of post-transfusion hepatitis. A study conducted in these hospitals, using the same experienced personnel, to evaluate the new high titer gamma globulin in comparison with the conventional gamma globulin employed in the present study, should provide important and conclusive results.

F. DESIGN OF STUDY, SAMPLE SIZE AND DATA PROCESSING:

All transfused patients will be evaluated for eligibility for the study. Patients will be assigned randomly (randomization will be balanced within each hospital) to one of two groups, provided the criteria for inclusion into the study are met and the initial screening of the patients' blood for HBAg is negative. One group will receive two injections of Hepatitis B Immune Serum Globulin, separated by a 28 day interval, and the other, two injections of conventional gamma globulin. The first injection is to be given no later than five days (120 hours) after receipt of the first transfusion unit. Patients who are otherwise eligible, but are found to have HBAg in their serum at the time of initial screening, will not be randomized, but will receive known conventional gamma globulin. All

patients will then be followed at two week intervals for a period of six months and then at two month intervals for an additional six months. At each visit, the patient will be screened for serum GOT and GPT and for the HBAg. Those suspected of having hepatitis will be studied more closely.

In the first post-transfusion study, patients who received gamma globulin in the six hospitals who will be participating in this study, had a 10% incidence of hepatitis. These same six hospitals randomized 450 patients in one year. Since it is hoped that the study can be completed within two years, it has been decided to choose a reduction of 67% as being meaningful, i.e. an incidence of 3.3% in patients receiving Hepatitis B Immune Serum Globulin. If the Type I risk is chosen to be 1% and the Type II risk is chosen to be 5%, then 484 patients would be needed in each group, or a total sample size of 970. This seems to be a reasonable goal for the study.

All completed forms are to be sent to the Co-Chairman (Dr. Seeff), who will promptly review the forms and then forward them to the Eastern Cooperative Studies Center, where they will be checked by the computer programmer and then key punched. The new data will be added to the existing records at least once a week. The computer will be used to prepare appointment schedules for the routine visits, to edit the data for missing forms, for missing or erroneous information, and to send letters to the hospitals concerning these. It will also be used to prepare special reports for monitoring the progress of the study and for analyzing the results.

G. REQUIREMENTS AND PERSONNEL FOR PARTICIPATING HOSPITALS:

Personnel: All personnel presently conducting the "Needlestick Hepatitis Study will function in the same capacity in this study.

1) Responsible Investigator - Assumes overall supervision. Makes clinical decision.

2) Research Assistant - Assumes all administrative responsibilities.

3) Research Nurse - Screens blood bank. Interviews and draws blood on each patient. Follows patients sequentially.

4) Technician - Performs all laboratory tests.

5) Local and Central Pathologist - Interprets liver biopsy sections.

6) Pharmacist - Stores and dispenses gamma globulin.

7) Blood Bank - Provides daily information on blood usage.

Space:

1) Clinical or other area available for seeing patients and drawing blood at

follow-up visit.

2) Laboratory.

3) Office for Research Assistant and Research Nurse.

Consent and Publicity:

1) Research Committee.

2) Hospital Administrator, Chief of Staff, Chief of Services.

3) Background flier to all members of the House Staff.

H. SELECTION OF PATIENTS:

1. Patients To Be Considered:

a. All patients who receive transfusions of whole blood or packed cells are potential candidates for the study unless specifically excluded (see later). No more than five days (120 hours) may elapse between the first transfusion and the first injection. This 120 hour period will be used to evaluate patient eligibility. The injection however may be given at any time during this 120 hour period provided the criteria for inclusion in the study are met. Once patients have been "randomized" into the study, the subsequent administration of additional blood transfusions, the development of hepatitis, or the superimposition of unanticipated complications will not permit removal of the patient from the study. Such patients will receive the second injection and will be monitored for the entire one year period in the same manner as all other patients.

b. Patients with cirrhosis or a history of alcoholism, will not be excluded from the study. This and other pertinent data will be appropriately recorded and considered in the evaluation of these patients' risk and response to "therapy".

2. Patients To Be Excluded:

a. Patients whose illness permits anticipation of the need for repeated transfusions. This would include those with chronic blood loss, refractory or hemolytic anemia, leukemia or hemophilia.

b. Patients who have had transfusions of blood, blood products or gamma globulin or blood products other than serum albumin within the previous six month period. Transfusions of blood or gamma globulin injection previous to this period will not be a reason for exclusion.

c. Patients with an obvious pre-terminal illness in whom survival is expected to be less than six months.

d. Patients with primary or secondary cancer of the liver.

e. Patients with neuropsychiatric disorders in whom hospitalization is indicated primarily for the neuropsychiatric disease.

f. Patients addicted to injectable narcotic drugs. The need for insulin and other therapeutic parenteral drugs, however, will not exclude a patient from the study.

g. Patients whose reliability for follow-up seems poor.

h. Patients participating currently in any other double blind study.

i. Patients who have previously been admitted to this study and who receive later transfusions, having completed participation in this study.

3. Reliability of Patients To Be Studied:

Each investigator will make an effort to evaluate the reliability and probable cooperation of patients in maintaining contact with the hospital. The criteria will include an evaluation of total personality, as well as such items as permanance of home address and employment; the feasibility of periodic absence from work for follow-up visits; the likelihood of conflict between the patient's travel plans and the need for follow-up visits. Based on these general criteria, a judgment should be made at the time of transfusion regarding the feasibility of inclusion of a patient into the study.

4. Patients To Be Included:

Provided the patient is considered reliable and is not excluded by the factors cited above, he will be considered eligible for the study. The patient will then enter into one of two major groups - the Randomized or the Non-Randomized group. The patient may only be entered into the Randomized group (Hepatitis B Immune Serum Globulin vs conventional gamma globulin) if, on initial screening, he is found to be negative for the HBAg. If, however, on initial blood testing, he is HBAg positive, he may receive only known conventional gamma globulin.

I. DETAILS OF STUDY:

1. Initial Daily Screening:

Every morning the Research Nurse will visit the blood bank and record on a 3 X 5 card the name, social security number, number of units transfused and their dates, and the ward number of all patients who have received blood transfusions in the previous 24 hours. The Research Nurse will evaluate each transfused patient for potential admission to the study according to the criteria stated

above. If the patient is not randomized into the study, the Research Nurse should specify the reason on the 3 X 5 screening card. Each screening card should then be filed in the Research Assistant's file of blood transfusions. These cards should be retained and not submitted to the Co-Chairman. Information from these cards will be used to compile the Monthly Report of Transfusions (Appendix IV) The cards, however, should be retained for later evaluation.

When the Research Nurse identifies a potential candidate for the study, she will make arrangements, through the transfusion service, to obtain a sample of the blood taken from that patient for typing & cross matching (i.e. pre-transfusion blood). This blood is to be tested for SGPT and HBAg. She will also make every effort to obtain a 2-4 ml. sample of blood of all transfusion units that the patient receives until the receipt of the first injection. This sample may be obtained from the pilot tube or from the blood bag at the termination of the transfusion. A sufficient quantity should be obtained to perform HBAg testing by RIA, as well as to store at least 1 ml. (preferably at -70°C) for subsequent tests that might be necessary e.g. subtyping of HBAg. These specimens i.e. the pre-transfusion recipient blood and all the donor transfusion bloods are critical samples.

The Research Nurse will then inform the responsible physician of the name(s) of the potential candidates. The Research Nurse and physician will then:

a. Discuss the issue clearly with the patient, giving him full information as to the nature of the study.

b. Clearly outline the patient's obligation for follow-up clinic visits every two weeks for six months and then every two months for an additional six months. (Any drop-outs or missed visits will seriously delay or destroy the study's goal).

c. Have the patient sign VA Consent Form 10-1086 (available locally).

d. Proceed with a history, physical examination and laboratory studies (see Initial Work-up, Form a). This must be accomplished between the date of first transfusion and date of first injection.

The first specimen of blood following transfusion, for baseline evaluation of the liver function tests (Total and Direct Bilirubin, SGOT, SGPT, Alkaline Phosphatase, Protein and Protein Electrophoresis and the HBAg) must be obtained no later than 96 hours after transfusion. This will allow for the results of HBAg

testing (requiring 24 hours by radioimmunoassay) to be available before 120 hours after transfusion have elapsed (by which time the first injection must have been received). The result of HBAg testing of both the pre-transfusion and first post-transfusion recipient blood samples will determine whether the patient is to be randomized i.e. to receive either the low or the high titer gamma globulin, or to receive only the low titer (conventional) gamma globulin. If the HBAg is negative in both the pre-tranfusion (type and cross match) serum sample and the first post-transfusion serum sample (obtained within 96 hours), and the patient is otherwise eligible for the study, he will be placed in the Randomization group. If, however, either or both the pre-transfusion and first post-transfusion specimen are found to be positive for the HBAg, the patient will be entered into the Non-Randomization group (receipt of known conventional low titer gamma globulin). This is to avoid the remote possibility of producing an immune complex disease by giving anti-HBAg to a patient who already has circulating HBAg.

2. Randomization Procedure:

a. After the patient has signed the consent form, an injection date any time within 120 hours following initial transfusion shall be selected. At the option of the local investigator, patients may sign the consent form prior to the administration of the blood or contemplated surgery.

b. On this injection date and following completion of pages 1-4 of Form "a" (Initial Work-up) as well as the appropriate number of Forms j (Blood Transfusions), the physician or Research Nurse will select the next consecutive injection code number from either the Randomization or Non-Randomization group (see above). The numbers 2201 - ? have been allotted to the Randomization group, and 4201 - ? to the Non-Randomization group.

c. The date of randomization will be established as the date of the first injection (no more than 120 hours following the first transfusion).

3. Steps By Research Assistant After Randomization:

a. She will establish a folder for each patient and keep copies of all the patients forms in this folder.

b. She will compile the Contact Data Form and keep this in the patient folder. This form is to be kept locally and not to be sent forward.

c. She will complete the Initial Work-up Form (Form "a") and the appropriate number of Blood Transfusion Forms (Form j) in duplicate.

d. After it is approved by the physician, the original Initial Work-up Form "a" and the Blood Transfusion Form (Form j) should be promptly submitted to the Co-Chairman (Dr. L. B. Seeff) at the VA Hospital, Washington, D. C., immediately after the form has been completed. Do not wait for the administration of the second injection nor for the patients discharge from the hospital. A copy of Forms "a" and "j" will be kept with her records.

e. She will place the original "Consent Form" (VA Form 10-1086) in the patient's chart and keep a copy with her records.

4. Injections:

1) Depending on whether the patient is entered into the Randomization or Non-Randomization group, he will receive two 10 ml. injections of either Hepatitis B Immune Serum Globulin or conventional low titer immune serum globulin, the choice being dependent upon random selection i.e. the next consecutive injection code number; or only low titer conventional immune serum globulin. The first injection must be given no later than 120 hours after receiving the initial transfusion. There is no need, however, to wait for the full 120 hours to elapse. The injection may be given as soon as the initial blood tests have been performed, the results of the HBAg have been made available, the consent form signed and the physical examination completed. The second injection will be given 28± three days after the first injection. 2) The code number of the injected material will be the next consecutive number from either the Randomization or Non-Randomization group. Each number will be available in duplicate, and will be followed by the letter A or the letter B. The number with the letter A will be used for the first injection and that with the letter B for the second injection for the same patient.

a. First Injection

1) The Research Nurse will prepare a prescription for one 10 ml vial of the appropriate code number for the physician's signature. The prescription should read as follows:

> VA COOPERATIVE STUDY HEPATITIS DRUG NUMBER 2501 A (total of 10 m to be given by a staff nurse as a deep IM gluteal injection, 5 m in each buttock....., naming patient and date to be given.

2) The Research Nurse will bring the prescription to the pharmacist.

3) The pharmacist will dispense one vial of the prescribed coded drug directly to the patients ward.

4) The ward registered nurse shall give the injection as ordered by the physician on the date he specifies.

5) The physician shall later confirm that the injection was received.

6) At this time, the second injection shall be scheduled four weeks (28± three days) after the first injection.

b. Second Injection

The same procedure will be followed as for the first injection, and the B equivalent of the first injection given.

1) If the patient is in the hospital, by order to the ward nurse.

2) If the patient is an out-patient, by order to the Research Nurse.

c. Untoward Reactions to the Injections

1) The physician shall make note of any adverse reaction to the injected material.

2) Mild erythema and minimal swelling are to be expected, as well as a moderate amount of discomfort at the injection site. Unusual swelling, pain, or systemic reaction should be briefly noted on Form "a" for the initial injection, on Form "h" for the second injection, and should be fully reported on Form "g" for either injection.

5. Follow-up:

a. Routine - Every two weeks for a total of six months, and thereafter, every second month for an additional six months, the patient will be seen either in the hospital (if still an in-patient) or in the "Hepatitis Prevention Clinic" (if an out-patient) for biochemical (SGOT, SGPT) and serologic (HBAg) evaluation. At least 30 ml. of whole blood should be obtained in order to perform these tests and to allow for an additional 3-5 ml. to be saved. This additional 3-5 ml. should be stored, if possible, at -70°C, for subsequent studies that might be considered necessary in the future. The individual will then be scheduled for a routine visit

two weeks later, provided the SGPT is less than 40 KU and the HBAg negative. Results of routine follow-up will be recorded on Form "b".

b. Suspicious Cases - If an abnormal value for the SGPT is obtained (greater than 40 KU) or the serum found to be positive for HBAg, the individual will be considered a "suspicious case". On the first occasion on which the above abnormalities are noted, all the liver function tests will be performed (Total and Direct Bilirubin, Alkaline Phosphatase, Protein and Protein Electrophoresis, in addition to the routine SGOT, SGPT and HBAg) and the data recorded on Form "c". (Intensive Weekly Follow-up). Thereafter, the patient will be followed at weekly intervals.

c. Intensive Follow-up - Having been placed on intensive follow-up, weekly evaluation will continue until the abnormalities have resolved themselves as follows. If the suspicious event is an abnormal SGPT (greater than 40 KU), whether or not the HBAg is positive, weekly blood tests should be obtained (even if the patient is not hospitalized or has been discharged from the hospital), until the SGPT returns to normal. If the suspicious event is only a positive HBAg, weekly blood tests should be performed for a period of four weeks after the discovery of this abnormality. At this time, unless the SGPT is noted to be abnormal, and even if the HBAg remains positive, the patient may return to the two weekly schedule. At all times, while the patient is on the weekly evaluation schedule, the complete liver function tests and the HBAg will be performed and the data recorded on Form "c". When the patient returns to the two weekly schedule, only the SGOT, SGPT and HBAg need be done and the data recorded on Form "b". At each blood drawing, an additional 3-5 ml. of serum for storage and subsequent testing, should be obtained.

d. Hospitalization and Liver Biopsy*- If abnormalities, as noted above, are found, the patient may be hospitalized at the discretion of the principal investigator and/or the consulting Gastroenterologist or Hepatologist, for additional diagnostic workup and treatment.

If, in the opinion of the primary physician, a liver biopsy is considered necessary for diagnostic or prognostic reasons, it is requested that ten unstained sections of the biopsy or (preferably) the block, be submitted to the office of the Co-Chairman, together with Form "f" (Biopsy Form for Central Pathologist). These specimens will then be recorded and sent to the central pathologist, Dr. K. Ishak, (AFIP, Washington, D. C.) for blind evaluation. The result

* Liver biopsy if performed, at discretion of patient's physician, is considered a part of patient care, and is not required for the study.

of the interpretation of the liver biopsy by the local hospital pathologist, should be recorded on Form "c".

6. Diagnosis of Hepatitis:

Hepatitis will be diagnosed by the computerized procedure currently employed in the VA Cooperative Post-Transfusion and Needlestick Hepatitis Study (see Appendix I). It is also urged that each participant submit his own diagnosis based on his individual clinical appraisal, and hopefully, uninfluenced by the computer diagnosis. This evaluation should be recorded on the Participant Final Diagnosis (Form "d"). This form should be completed for all patients who develop an abnormal SGPT, at the time that the transaminases return to normal, or as soon as a definite cause for the enzyme abnormality is established. Subsequent evaluation by a non-participating panel of experts will be considered.

7. Duration of Follow-up:

Each patient will be evaluated for a complete year as already described, regardless of the course during this time. Individuals who are on the intensive follow-up schedule at the end of the first six month period, should be maintained on this same schedule until the abnormalities have resolved themselves. At this time the patient may be followed at two monthly intervals until the full year after transfusion has elapsed. Continued evaluation for a period of time yet to be determined will be maintained on individuals who remain abnormal at the end of the full year evaluation.

J. SUBMISSION OF FORMS:

The following forms should be air mailed as soon as complete to the Co-Chairman, in Washington, D. C.:

1) Initial Work-up, Form "a" (4 pages)
2) Routine Weekly Follow-up, Form "b" (1 page)
3) Intensive Weekly Follow-up Examination, Form "c" (2 pages)
4) Participant's Final Diagnosis, Form "d" (1 page)
5) Summary of Serial Values in Suspicious Cases, Form "e" (to be submitted after all values have returned to normal) (1 page)
6) Biopsy Form For Central Pathologist, Form "f" (1 page)
7) Adverse Reaction To Assigned Injection, Form "g" (1 page)
8) Second Injection, Form "h" (1 page)
9) Surgery Since Last Visit, Form "i" (1 page)

10) Blood Transfusion Form, Form "j" (1 or more pages)

11) Australia Antigen Data, Form "k" (original to ECSC, modified copy to Dr. Purcell)

12) Terminal Report by letter if the patient should expire during the course of the study. Every effort should be made to obtain an autopsy and a section of the liver should be sent to the Co-Chairman in the same manner as the liver biopsy.

NOTE: If the patient does not return at the time scheduled, the appropriate form must nevertheless be submitted with a notation that the patient did not return. The missed visit may be indicated by sending either Form "b" or the first page of Form "c", depending upon the schedule which the patient is currently following, with the patient's name, weeks since randomization and the other appropriate baseline information completed. A large cross placed through the rest of the form will be taken to indicate a missed visit.

All forms that are received by the Co-Chairman will be reviewed and then forwarded to Eastern Cooperative Studies Center. If unusual values or missing items are noted, a letter will be submitted to the investigator from Eastern Cooperative Studies Center, in order to ascertain the validity of such values or omissions. For this reason, as well as for technical reliability and prompt detection of suspicious cases, it is imperative that all blood tests be performed as soon as possible after the blood has been drawn and that all forms be completed and sent forward promptly.

K. STORING AND MAILING OF SERUM SAMPLES:

Sufficient blood should be drawn at every visit, including pre- and first post-transfusion specimen, to allow for complete biochemical and serologic evaluation at the VA Hospital, for an additional 3 ml. aliquot of serum to be saved for subsequent mailing to Dr. Purcell for confirmation of HBAg and anti-HBAg status, as well as for 2-4 ml. of serum to be saved and stored for subsequent testing which might be considered necessary. Where possible, the serum should be stored at -70°C. Whenever possible, sufficient donor blood should be obtained for HBAg testing at the VA Hospital, at least 1 ml. to be submitted to Dr. Purcell, and for local storage of the remainder.

Serum for Dr. Purcell should be mailed to him at the end of each month The serum should be stored in Neoprene screw top vials, secured tightly and

taped in position. Just below the neck, each tube should bear a single tape label securely attached with ends slightly overlapping. This tape will bear the code number (see later). Since this is the only identifying mark for the specimens, it is essential that the numbers be correct, clearly legible and indelible. Final labels are best put on the tubes prior to freezing. All shipments should be mailed in insulated containers, with the compartment 1/3 to 1/2 filled with dry ice. Specimens should be placed on top of a fitted corrugated card board separator and "nested" carefully in shredded paper, plastic or sawdust as a filler. Shipping containers, clearly marked "RUSH", "FROZEN MATERIAL" and "UP" should be shipped Air Express early in the week. Each container should have two address labels (on top and on the front side), addressed as follows:

Dr. Robert Purcell
NIAID, Building 7
National Institutes of Health
Bethesda, Maryland 20014

It is strongly urged that separate records on the serum samples destine for Dr. Purcell be kept, in order to maintain accuracy and avoid confusion. All samples that are collected for this purpose will be given a number (local identification numbers). As each new sample is obtained, the next consecutive number will be assigned. These numbers should be recorded in a book together with the individuals name, sequence number and the date on which the specimen was obtained. Since Dr. Purcell is already receiving monthly serum samples from the Needlestick Study, each vial submitted to him from the Post-Transfusion Study, should be clearly and indelibly identified as such, so as to avoid confusion and incorrect reporting of results.

At the time of mailing to Dr. Purcell, the appropriate data will be recorded in duplicate on the Australia Antigen Data Form (Form "k"). One set will accompany the blood specimens submitted to Dr. Purcell and the second set will be sent directly to Mrs. Elizabeth Wright (Eastern Cooperative Studies Center, V.A. Hospital, West Haven, Conn. 06516). In the set for Dr. Purcell, the only items to be completed are: "3-4, Hospital No." and "14-17, Local Ident. No.". The duplicate set for Mrs. Wright, to be mailed at the same time should have in addition to items "3-4", and "14-17", the patient's Sequence No. (items 5-7) and item 18 (Ser. Code) completed.

APPENDIX I

DIAGNOSIS OF HEPATITIS - SCORING PROCEDURE

The following scoring procedure was developed for the first post-transfusion study and will be used in this study. Patients are scored whenever they have one or more consecutive SGPT values over 40 (the period of abnormality is called an event; a patient may have several events). The following variables are used to score each event:

Maximum SGPT during the event.
Ratio SGPT (next SGPT after maximum SGPT that has an SGOT).
Ratio SGOT
Ratio = Ratio SGPT/Ratio SGOT
White Blood Count (Higher of first two WBC's during the event).
Alkaline Phosphatase (Maximum during event).
Number of abnormal SGPT values (No more than one per week).
Week of first abnormal SGPT.
Week of maximum SGPT.
Week of last abnormal SGPT.
Initial SGPT.
Initial SGOT.
Week number of halothane or penthrane if these were used.

The patient will not be scored until the SGPT returns to normal or until he reaches week 26.

The primary score is calculated using the following formulas:

1. If SGOT is missing,
   Score = 0.

2. If SGOT <40,
   Score = 0.1 (M SGPT) + 20 (R SGPT)/50 -(40-SGOT)/5.

3. If 40 ≤ SGOT <50
   Score = 0.1 (M SGPT) + 20 (R SGPT)/50.

4. If SGOT ≥ 50 and (M SGPT) < 175 (Ratio)
   Score = 0.1 (M SGPT) + 20 (Ratio).

5. If SGOT ≥ 50 and (M SGPT)> 175 (Ratio)
   Score = 0.02 (M SGPT) + 34 (Ratio).

The primary score is modified if either the white blood count or the alkaline phosphatase is above specified limits:

If the WBC >12,000,
Score = Score - (WBC - 12,000)(0.003).

If the Alk Phos >15.0,
Score = Score - (Alk Phos - 15.0)(0.6).

Under certain conditions hepatitis was thought to be very unlikely no matter what values of SGPT and ratio occurred. Therefore, in the following cases, the score was set equal to zero:

1) Only one abnormal SGPT (over 40).

2) Initial abnormalities of SGPT or SGOT if the event started week 1 or 2.

3) Halothane given within 2 weeks prior to both the start of the event and the week of maximum SGPT value.

A score of 30 or more is considered necessary for the diagnosis of hepatitis.

APPENDIX II

PLANS FOR ANALYSIS

Main Analysis: This will compare the attack rate of "hepatitis" as defined by a score of 30 or higher in the treated group, with the similar rate in the control group. The benefit of high titer HBAg gamma globulin injections, if any occurs, will be expressed as a percent reduction in incidence of hepatitis, - by taking the difference between the control group rate and the treated group rate and dividing this difference by the control group rate. Confidence limits will be calculated for the difference between the two rates, and from these confidence limits, an estimate will be computed for the range of uncertainty of the calculated benefit.

Icterus: Within the group having a score of 30 or higher, the incidence rate in the treated group of cases with a serum bilirubin (total) of 2.5 mg.% or higher, or with a history of yellow sclerae and bilirubin 1.1 - 2.4 mg.%, will be compared with the rate in the control group. Also the cumulative distributions of the individual values in these groups will be compared.

Development Time: Within the group having a score of 30 or higher, the cumulative distribution of number of weeks from onset of suspicion (first abnormal SGPT), to the peak SGPT full development of the hepatitis, will be compared in the treated versus the controls.

Duration: Within the group having a score of 30 or higher, the cumulative distribution of number of weeks from onset of suspicion to return to normal SGPT and SGOT values, will be compared in the treated versus the controls.

HBAg: The attach rate will also be compared in the following subgroup:

1) patients who receive HBAg positive blood.
2) patients who sero-convert.
3) patients who develop HBAg positive blood.

SGPT: The cumulative distributions of highest SGPT value for each patient will be compared regardless of whether total score is 30 or higher.

Adverse Effects: When appraising the "benefit" of any drug for widespread use, one must always balance its efficacy with its adverse or harmful effects. We shall therefore, compare the treated versus the control

group with respect to the incidence of adverse reactions of each different type, as reported on Form "e". The method of balancing these adverse results against the efficacy results is a matter of medical ethical judgment rather than statistical testing.

The above analyses will be done every six months by the Biostatistician. The trend of such results will be revealed to the Policy Board, who may recommend that the study be continued, modified, or stopped entirely.

APPENDIX III

SCREENING CARD

(FORMAT FOR 3 X 5 RULED INDEX CARD, not a printed form)
(for clinic use only, send no copies)

Top (red) line - Name of patient Soc. Sec. #

1. Date Units Matched Units Transfused
2.
3.
4.
5.
6. Patient accepted for study: Yes ___ No ___
7. Reason for Rejection
8. Date 1st Injection
9. Physician

APPENDIX IV

MONTHLY REPORT OF TRANSFUSIONS

Hospital reporting _____

Month covered _____

Participating investigator _____

Date this report _____

Number of transfusions given _____

Number of patients transfused _____

Number of patients randomized _____

Number of patients rejected _____

Patients Rejected by Reason:	Number
1. received blood within 6 mos.	___
2. refused to enter	___
3. lives too far away	___
4. requires frequent transfusions	___
5. moribund or preterminal	___
6. unreliable	___
7. senile or psychotic	___
8. already in another study	___
9. other reason	___
Total Patients Rejected	___

APPENDIX V

EXPLANATION TO PATIENT OF PLAN OF STUDY

During your hospital stay, and as part of your medical or surgical care, it has been necessary for you to receive a blood transfusion or transfusions. There is unfortunately a small risk of developing Viral Hepatitis, with or without yellow jaundice, following the receipt of such blood transfusions, and many treatment programs have been tried to prevent this complication. We are studying the effect of two forms of gamma globulin, one the conventional form and the other, a form of gamma globulin containing measurable antibodies against Serum Hepatitis. The gamma globulin containing antibodies has been found to be protective against Serum Hepatitis after some exposures, but it is not known if it is protective after blood transfusions, although it is hoped that it will be.

If you consent to treatment, you will receive one or other of these forms of gamma globulin, purely by chance, depending upon random selection. The first injection will be given now and a second injection in approximately one months time. We are not aware of any known adverse effects from these injections, other than occasional transient soreness from the injection and very rarely, transient joint pain or fever.

In order to properly learn if the treatment is of benefit to you and to other patients who need blood transfusions, we will request you to come to a follow-up clinic every two weeks for six months, and then every two months for an additional six months, for blood tests to evaluate your liver functions. If these tests should be abnormal, it will be necessary for you to be seen weekly until the tests return to normal. It is to your immediate benefit that any signs of hepatitis which might occur, be detected early to permit appropriate care or, if necessary, hospitalization. Nevertheless, you are at liberty to withdraw from this study at any time.

In order to use this treatment, we need your understanding and approval as acknowledged by your signature on this, and the VA Consent Form.

_____

Patient's Signature Date

PART I - AUTHORIZATION (BY PATIENT) FOR USE OF DRUGS AND/OR PROCEDURES FOR INVESTIGATIONAL PURPOSES BY OR UNDER THE DIRECTION OF THE VETERANS ADMINISTRATION

(PART II ON REVERSE)

_____ (Date) _____ (VA station)

1. I, _____ (Type or print name of patient or subject), hereby voluntarily consent to participate in the following investigation _____ (Title of study and name of investigational drugs and/or procedures used)

2. The nature and purpose of the drug and/or procedure and the pertinent potential complications have been explained to me by Dr. _____ (Type or print name of physician).

I understand that the investigation has been approved, compares alternative methods of diagnosis and/or treatment, and that I may receive a standard, an investigational, or a supportive drug and/or procedure.

I acknowledge that while no guarantee or assurance has been made as to the results that may be obtained, since investigational results cannot be fully foreseen, nonetheless the VA will take every precaution consistent with the best medical practice, and that my participation in this study may prove of benefit to me and in advancing medical knowledge.

_____ (Physician's signature as responsible investigator) _____ (Patient's (or subject's) signature)

PATIENT'S IDENTIFICATION (For typed or written entries give: Name - last, first, middle; Date; Hospital)	IDENTIFICATION NO.	WARD NO.

AUTHORIZATION
FOR USE OF DRUGS AND/OR PROCEDURES
FOR INVESTIGATIONAL PURPOSES

VA FORM MAY 1967 **10-1086**

SUPERSEDES VA FORM 10-1086, JUN 1964, WHICH WILL NOT BE USED.

449351

APPENDIX VII

FLOW SHEET OUTLINE FOR COOPERATIVE STUDY OF POST-TRANSFUSION HEPATITIS

Daily Blood Bank Visit by Research Nurse

↓

File information on 3x5 index cards(Appendix III)

↓

Patients circumstances and chart reviewed for eligibility to study(Protocol, Sect. H

↓

If considered eligible, obtain patients pre-transfusion type and cross-match blood(for SGPT & HBAg),and sample of all units transfused (for HBAg and storage).

↓

Patient interviewed and recruited(Appendix IV)

↓

Initial Work-Up,LFTs and HBAg, no later than 96 hrs after 1st transfusion(Form "a")

↓

If initial test for HBAg(pre- and post-transfusion specimens)negative, then place in RANDOMIZATION GROUP. If either or both specimens positive for HBAg, then place in NON-RANDOMIZATION GROUP.

↓

First injection - no later than 120 hrs after first transfusion

Schedule second injection for 28±3 days after first injection(Form "h").

↓

First follow-up examination, SGOT,SGPT,HBAg two weeks after first injection(Form "b")

Abnormalities detected(SGPT>40, HBAg positive),do complete battery of tests(Alk.Phos.;T/D Bil.,Prot., Electroph.),report on Form "c",and return one week.

↓

SGPT>40,continue weekly visit,report Form "c" until SGPT<40.Then return to two weekly schedule.

No abnormalities(SGPT<40;HBAg neg report Form "b", and return two wee

Fails to return - send appropriate form crossed with letter of explanation.

SGPT normal,HBAg positive.Unless SG becomes abnormal,even if HBAg remai positive,continue weekly visits X 4. Then return to two weekly schedule.

Hospitalize and liver bx.,if considered necessary by physician(Forms "c","d","e","f")

APPENDIX VIII

Guide For Completing Forms

All forms have been precoded and are numbered sequentially. Each question is followed by a box or a series of boxes, and can be answered by inserting a digit or digits in these boxes. It is essential that every box be completed. If, for any reason, the data requested cannot be obtained, a dash should be placed in the box. If a patient does not keep an appointment, the appropriate form ("B" or "C") should have the baseline information completed (Name, Hospital, Code, Sequence Number, Date of Examination and Weeks Since Randomization), a cross put through the rest of the form and the form submitted to the Office of the Chairman in the usual way. This form should be submitted for every appointment, whether or not it has been kept.

Initial Workup(Form "a")

Page 1:

Item 3-4: Each hospital will be designated a code as follows: East Orange - 05; Hines - 06; Miami - 08; New York - 09; Pittsburgh - 10; San Juan - 13; - 14; - 15.

Items 5-46: Self explanatory.

Page 2:

Items 47-52: Self explanatory.

Item 53: Please give details, next to the word "Specify",of average daily, or if appropriate, weekly alcohol consumption.

Items 54-70: Self explanatory.

Page 3:

Items 14-23; 35-42; 52-61. A copy of the AMA code for "Gaseous and Volatile Agents" is enclosed. In addition, please write in the name of the anesthetic agent employed.

Page 4:

Items 8-11; 18-21: As each specimen of blood (donor or recipient) is received in the laboratory for testing, it should be given a number in the order in which it is received. These four digit numbers will be used as the code for specimens which will be mailed subsequently to Dr. R. Purcell for HBAg and anti-HBAg testing, and recorded on Form "k", hence the designation "Form k number". This number will serve to readily distinguish specimens and vastly simplify their recognition by the computer programmer and statistician.

Items 17 and 65: Anti-HBAg will be, in most cases, answered as "not done". However, it will be tested for Dr. Purcell and subsequently reported to Mrs. Wright at ESCS.

Items 66-67: All transfusions given from the first unit until the receipt of the gamma globulin (no later than four days after the first transfusion) should be recorded here and reported in detail on Form "J".

Routine Weekly Follow-up (Form "b")
Self explanatory.

Intensive Follow-up Examination (Form "c")
Page 1: Self explanatory.

Page 2:
Items 16-75: The boxes under the heading "Began (days)" and "Lasted (days)", require to be completed at all times. If the symptom does not occur, the boxes should be completed with zeros. If a symptom does occur, the number of days that it began prior to the present examination should be recorded under the heading "Began". If it lasted until the present examination, the number appearing in the "Lasted" column, will be the same as that in "Began" column. If it disappeared prior to the present examination, its duration will be recorded in the "Lasted" column.

Participants Final Diagnosis (Form "d')
Self explanatory.

Summary of Serial Values in Suspicious Cases (Form "e")
Self explanatory.

Biopsy Form For Central Pathologist (Form "f")
Only items 1-13 are to be completed. The slides, or preferably the block, should accompany this form when submitted to the Office of the Chairman. From this office it will be sent under a new code to Dr. Ishak and thence to Mrs. Wright (ESCS) on receipt of Dr. Ishak's interpretation.

Adverse Reaction to Assigned Injection (Form "g")
Self explanatory.

Second Injection (Form "h")
Self explanatory.

Surgery Since Last Visit (Form "i")
Self explanatory.

Blood Transfusions (Form "j")
Completion of the form is self explanatory. It is to be emphasized, however, that the form k identity number (14-17) is the number given consecutively to each specimen of blood, whether donor or recipient, as it is obtained in the laboratory for liver function and HBAg testing. The form k number on this form, obviously refers only to donor blood. The same number will appear as appropriate on forms a, b, and c.

Since Dr. Purcell will be receiving specimens of blood from both the Needlestick and PTS II Studies, it is mandatory that the specimens sent him are clearly identified as to their study source.

Australia Antigen Data (Form "k")

This form is to be completed in duplicate, at the end of each month when the specimens are submitted to Dr. Purcell. The copy which accompanies the blood specimen for Dr. Purcell, should only have items "3-4, Hospital Number" and "14-17, Local Ident. Number (Form k number)", completed. The copy to be mailed to Mrs. Wright, ESCS, will have in addition to items "3-4" and "14-17", items "5-7, Sequence Number", "8-13, Date Blood Drawn", and item "18, Ser. Code", completed. PLEASE BE SURE TO CLEARLY IDENTIFY ON THE LABEL ATTACHED TO THE VIAL, THE STUDY SOURCE OF THE SPECIMEN i.e. NEEDLESTICK OR PTS II.

VA Cooperative Study of Hepatitis - PTS 2 RCS 10-127-C22

INITIAL WORKUP (Form a)
(Send to Chairman after first injection)

NAME _____ OCCUPATION _____
(Last) (First) (Middle)

HOME ADDRESS & TEL. NO. _____

1-2 Card No. [0][1] 3-4 Hospital Code [ ][ ] _____ 5-7 Seq. No. [ ][ ][ ]

8-16 Soc. Sec. No. [ ][ ][ ][ ][ ][ ][ ][ ][ ] 17-18 Age [ ][ ]

19 Sex (Male=1; Female=2) [ ] 20 Race (W=1;N=2;Or=3;Ind=4;Other=5) [ ]

21-26 Date of Randomization [ ][ ][ ][ ][ ][ ]

Major Diagnosis _____

Secondary Diagnoses _____

_____

PERTINENT PAST HISTORY

A. TRANSFUSIONS AND GAMMA GLOBULIN

27-28 Number of transfusions prior to 6 months [ ][ ]

Most recent transfusion prior to 6 mos

29-34 Date [ ][ ][ ][ ][ ][ ] 35-36 Amount [ ][ ] Blood or Product _____ Hospital & City _____

Other Prior transfusions

Date	Blood or Product	Amount	Hospital & City

37 Gamma globulin therapy prior to 6 months (No=1 Yes=2) [ ] Date(s) _____

Reason Given _____ Amount _____

B. PAST HISTORY OF LIVER DISEASE

38 Viral hepatitis (No=1;Yes=2) [ ] 39 If yes, number of episodes [ ]

40-45 Date of most recent episode [ ][ ][ ][ ][ ][ ]

46 Type of viral hepatitis (Virus A=1,Virus B=2,Don't know=3) [ ]

Other episodes _____

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FEB 1973

47 Alcoholic Hepatitis (No=1;Yes=2) [ ] Dates _____

48 Cirrhosis (No=1;Yes=2) [ ] Date(s) _____

49 Cholelithiasis (No=1;Yes=2) [ ] Date(s) _____

50 Pancreatitis (No=1;Yes=2) [ ] Date(s) _____

51 Other liver disease (Including drugs and toxins) (No=1;Yes=2) [ ]

Date(s) _____ (Specify _____

52 Jaundice at any time(No=1; Yes=2) [ ] Date(s) _____

Cause _____

C. ALCOHOL

53 Alcohol(None=1;Social=2;Heavy=3) [ ] Specify _____

D. PAST HISTORY OF NON-LIVER DISEASE

54 Any previous disease (No=1;Yes=2) [ ] Date(s) _____

Specify _____

55 Drugs used in past 4 weeks (No=1;Yes=2) [ ]

	Types of Drugs	No=1	Yes=2	List Names of Drugs
56	Anabolic steroids			
57	Anticoagulants			
58	Anti-convulsants			
59	Anti-diabetics			
60	Anti-hypertensives			
61	Anti-microbials			
62	Anti-rheumatics			
63	Analgesics			
64	Diuretics			
65	Hormones			
66	Narcotics			
67	Sedatives			
68	Tranquilizers			
69	Chemicals			
70	Other			

HOSPITAL NO. [ ][ ] Sequence No. [ ][ ][ ]

1-2 Card Number [0 2] 3-4 Hospital [ ] 5-7 Sequence No. [ ]

SURGERY - Report most recent surgery in 8-26, next most recent in 27-45, third most recent in 46-64. Do not report any surgery which dates back more than six months

Most recent surgery 8-13 Date [ ]

Specify _____

Anesthesia, Specify agent (AMA Code) 14-15 [ ] _____

16-17 [ ] _____ 18-19 [ ] _____

20-21 [ ] _____ 22-23 [ ] _____

24-25 Total duration of anesthesia (in half hours) [ ]

26 Reaction to anesthesia (No=1;Yes=2) [ ] Specify _____

Second most recent surgery 27-32 Date [ ]

Specify _____

Anesthesia, Specify agent (AMA Code) 33-34 [ ] _____

35-36 [ ] _____ 37-38 [ ] _____

39-40 [ ] _____ 41-42 [ ] _____

43-44 Total duration of anesthesia (in half hours) [ ]

45 Reaction to anesthesia (No=1;Yes=2) [ ] Specify _____

Third most recent surgery 46-51 Date [ ]

Specify _____

Anesthesia, specify agent (AMA Code) 52-53 [ ] _____

54-55 [ ] _____ 56-57 [ ] _____

58-59 [ ] _____ 60-61 [ ] _____

62-63 Total duration of anesthesia (in half hours) [ ]

64 Reaction to anesthesia (No=1;Yes=2) [ ] Specify _____

PHYSICAL SIGNS NOW

65 Jaundice (No=1;Yes=2) [ ] 66-67 Hepatomegaly, cm below RCM [ ]

68-69 Splenomegaly, cm below RCM [ ] 70 Spider Nevi (No=1;Yes=2) [ ]

71 Collateral venous pattern (No=1;Yes=2) [ ]

72 Other signs (NO=1;Yes=2) [ ] Specify _____

1-2 Card Number 0 3 3-4 Hospital [ ][ ] 5-7 Sequence No. [ ][ ][ ]

PRE-TRANSFUSION BLOOD SAMPLE

8-11 Form k number [ ][ ][ ][ ] 12-15 SGPT [ ][ ][ ][ ]

16 HBAg (Neg=1;Pos=2) [ ] Method _____

17 Anti-HBAg (Neg=1;Pos=2;Not done=3) [ ] Method _____

BASELINE POST-TRANSFUSION LABORATORY DATA (Testing to begin within 96 hours)

18-21 Form k number [ ][ ][ ][ ] 22-26 Total white blood count [ ][ ][ ][ ][ ]

27-28 Neutrophils [ ][ ] % 29-30 Lymphocytes [ ][ ] % 31-32 Eosinophils [ ][ ] %

33-35 Serum bilirubin, total [ ][ ][ ] mg% 36-38 Serum bil.,direct [ ][ ][ ] mg%

39-42 SGPT [ ][ ][ ][ ] 43-46 SGOT [ ][ ][ ][ ]

47-49 Alkaline phosphatase [ ][ ][ ] Bodansky units

50-51 Total protein [ ][ ] gm% 52-53 Albumin [ ][ ] gm%

Electrophoresis: 54-55 Albumin [ ][ ] gm% 56-57 Alpha$_1$ globulin [ ][ ] gm%

58-59 Alpha$_2$ globulin [ ][ ] gm% 60-61 Beta globulin [ ][ ] gm%

62-63 Gamma globulin [ ][ ] gm%

64 HBAg (Neg=1;Pos=2) [ ] Method _____

65 Anti-HBAg (Neg=1;Pos=2,Not done=3) [ ] Method _____

TRANSFUSIONS

66-67 Number of units transfused in 4 day period [ ][ ] Report on form j.

RANDOMIZATION AND INJECTION

68-73 Date [ ][ ][ ][ ][ ][ ] 74-77 Drug Code [ ][ ][ ][ ] A

78 Reaction to injection (No=1;Yes=2) [ ] If yes, report details on form g.

_____ M.D.
(Signature) Date

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ROUTINE FOLLOW-UP EXAMINATION (Form b)

PATIENT'S NAME _____

1-2 Card Number [0][4] 3-4 Hospital [ ][ ] _____ 5-7 Sequence No. [ ][ ][ ]

8-13 Date this exam. [ ][ ]/[ ][ ]/[ ][ ] 14-15 Weeks since randomization [ ][ ]

16 Is patient hospitalized? If so, give reason [ ]
(Not hosp=1, original diagnosis=2, suspected hepatitis=3, other=4)

HISTORY (since last visit)

17 Working (No=1;Yes=2) [ ]

18 Alcohol consumption (None=1;Light=2;Heavy=3) [ ] Specify _____

19 Drugs used (No=1;Yes=2) [ ] Type _____ Reason _____

20 Injection of any kind (No=1;Yes=2) [ ] Type _____ Reason _____

21 Exposure to jaundiced person (No=1;Yes=2) [ ] Specify _____

22 Family illness suggesting hepatitis (No=1;Yes=2) [ ] Type _____

23 Transfusions since last visit (No=1;Yes=2) [ ] Report details on form j

24 Surgery since last visit (No=1;Yes=2) [ ] Report details on form i

LABORATORY STUDIES

31-34 SGOT [ ][ ][ ][ ] 35-38 SGPT [ ][ ][ ][ ]

67 HBAg (Neg=1;Pos=2) [ ] Method _____

68 Anti-HBAg (Neg=1;Pos=2,Not Done=3) [ ] Method _____

69-72 Form k number [ ][ ][ ][ ]

FOLLOW-UP

73 Hospital Admission (No=1;Yes=2) [ ] Date _____

74 Next visit in one week (No=1;Yes=2) [ ]

_____ M.D.
(Signature) Date

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INTENSIVE WEEKLY FOLLOW-UP EXAMINATION (Form c, Page 1)

PATIENT'S NAME _____

1-2 Card Number [0 5] 3-4 Hospital [ ] _____ 5-7 Sequence No. [ ]

8-13 Date this exam. [ ] 14-15 Weeks since randomization [ ]

16 Is patient hospitalized? If so, give reason [ ]
(Not hosp=1;original diagnosis=2;suspected hepatitis=3;other=4)

HISTORY (since last visit)

17 Working (No=1;Yes=2) [ ]

18 Alcohol consumption (None=1;Light=2;Heavy=3) [ ] Specify _____

19 Drugs used (No=1;Yes=2) [ ] Type _____ Reason _____

20 Injection of any kind (No=1;Yes=2) [ ] Type _____ Reason _____

21 Exposure to jaundiced person (No=1;Yes=2) [ ] Specify _____

22 Family illness suggesting hepatitis (No=1;Yes=2) [ ] Type _____

23 Transfusions since last visit (No=1;Yes=2) [ ] Report details on form j.

24 Surgery since last visit (No=1;Yes=2) [ ] Report details on form i.

LABORATORY STUDIES

25-27 Serum bilirubin, total [ ] mg% 28-30 Serum bil. direct [ ] mg%

31-34 SGOT [ ] 35-38 SGPT [ ]

39-41 Alkaline Phosphatase-Bod. Units [ ] 42-46 Total WBC [ ]

47-48 Neutrophils [ ] % 49-50 Lymphocytes [ ] % 51-52 Eosinophils [ ] %

53-54 Total Protein [ ] gm% 55-56 Albumin [ ] gm%

Electrophoresis: 57-58 Albumin [ ] gm% 59-60 $Alpha_1$ Glob. [ ] gm%

61-62 $Alpha_2$ Glob. [ ] gm% 63-64 Beta Glob. [ ] 65-66 Gamma Glob. [ ] gm%

67 HBAg (Neg=1;Pos=2) [ ] Method _____

68 Anti-HBAg (Neg=1;Pos=2;Not Done=3) [ ] Method _____

69-72 Form k number [ ]

FOLLOW-UP

73 Hospital Admission (No=1;Yes=2) [ ] Date _____

74 Next visit in one week (No=1;Yes=2) [ ]

75 Liver biopsy (No=1;Yes=2) [ ] Date performed _____

Interpretation by local pathologist _____

1-2 Card Number [0 6] 3-4 Hospital [ ] _____ 5-7 Sequence No. [ ]

8-13 Date this exam. [ ] 14-15 Weeks since randomization [ ]

SYMPTOMS (since last visit)

		(No=1;Yes=2)	ONSET Began (days)		Lasted (days)	
16	Anorexia	[ ]	17-18	[ ]	19-20	[ ]
21	Fever	[ ]	22-23	[ ]	24-25	[ ]
26	Pruritis	[ ]	27-28	[ ]	29-30	[ ]
31	Dark Urine	[ ]	32-33	[ ]	34-35	[ ]
36	Yellow Sclerac	[ ]	37-38	[ ]	39-40	[ ]
41	Joint Pains	[ ]	42-43	[ ]	44-45	[ ]
46	Nausea	[ ]	47-48	[ ]	49-50	[ ]
51	Malaise	[ ]	52-53	[ ]	54-55	[ ]
56	Loss of taste for cigarettes	[ ]	57-58	[ ]	59-60	[ ]
61	Rash	[ ]	62-63	[ ]	64-65	[ ]
66	Light Stools	[ ]	67-68	[ ]	69-70	[ ]
71	Other (No=1;Yes=2)	[ ]				

Specify _____

PHYSICAL EXAMINATION

72 Jaundice (No=1;Yes=2) [ ]

73 RUQ Tenderness (No=1;Yes=2) [ ]

74-75 Hepatomegaly [ ] cm below RCM 76-77 Splenomegaly [ ] cm below RCM

78 Evidence of chronic liver disease (No=1;Yes=2) [ ] Specify _____

79 Other (No=1;Yes=2) [ ] Specify _____

_____ M.D.

(Signature) Date

513190

PARTICIPANT'S FINAL DIAGNOSIS (Form d)

(To be submitted only when the participant has made his final diagnosis)

PATIENT'S NAME _____ HOSPITAL _____

1-2 Card Number [0][7] 3-4 Hospital [ ][ ]

5-7 Sequence Number [ ][ ][ ] 8-9 Weeks since randomization [ ][ ]

10 Participant's Diagnosis: Hepatitis (No=1; Yes=2) [ ]

If no, what is the diagnosis? _____

_____

Remarks _____

_____

11-13 Peak serum bilirubin (total) level [ ][ ][ ] mg.%

14 History of yellow sclerae (regardless of bilirubin level) (No=1; Yes=2) [ ]

M.D.

_____

Signature date

VA FORM
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VA Cooperative Study of Hepatitis - PTS 2

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SUMMARY OF SERIAL VALUES IN SUSPICIOUS CASES (Form e)
(to be submitted when final diagnosis has been made)

Name _____ Hospital [ ][ ] _____

Sequence No. [ ][ ][ ]

DATES SAMPLES DRAWN							
Hematocrit--%							
White Blood Cells							
Neutrophiles--%							
Lymphocytes--%							
Monocytes--%							
Eosinophiles--%							
Bands--%							
Platelets							
Reticulocytes--%							
Serology							
Glucose--mg.%							
Urea-N--mg.%							
Bilirubin--Total--mg.%							
Direct--mg.%							
Cholesterol--Total-mg.%							
*Prothrombin Time--Seconds							
*Total Protein--gm.%							
*Albumin--gm.%							
*Globulin--gm.%							
Phosphatase,Alkaline--Bod. Units							
BSP--% retention in 45 min.							
SGOT							
SGPT							
LDH							
HBAg							
Anti-HBAg							

VA Cooperative Study of Hepatitis - PTS 2

REC 10-127-C22

BIOPSY FORM FOR CENTRAL PATHOLOGIST (Form f)

PATIENT'S NAME _____ HOSPITAL _____

Social Security No. _____

Local Pathology Dept. Accession No. _____

1-2 Card Number [0][8] 3-4 Hospital [ ][ ] 5-7 Sequence No. [ ][ ][ ]

8-13 Date Biopsy taken [ ][ ][ ][ ][ ][ ] 14-15 Weeks since randomization [ ][ ]

BIOPSY

	16 Primary Diagnosis	17 Secondary Diagnosis
Diagnostic of hepatitis	[ ] 1	[ ] 1
Consistent with hepatitis	[ ] 2	[ ] 2
Nonspecific abnormality	[ ] 3	[ ] 3
Biopsy not readable	[ ] 4	[ ] 4
No diagnostic abnormalities	[ ] 5	[ ] 5
Other liver disease	[ ] 6	[ ] 6

If other liver disease, please specify _____

_____

_____

18-23 Date biopsy read [ ][ ][ ][ ][ ][ ] _____ Signature

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VA FORM 10-1458f(Test)
FEB 1973

ADVERSE REACTION TO ASSIGNED INJECTION (Form g)

PATIENT'S NAME _____ HOSPITAL _____

1-2 Card Number [0][9] 3-4 Hospital [ ][ ] 5-7 Sequence No. [ ][ ][ ]

8-12 Drug Code [ ][ ][ ][ ]-[ ] 13-18 Date Drug Given [ ][ ][ ][ ][ ][ ]

19 Which Injection (First=1;Second=2) [ ]

IMMEDIATE REACTION

20 Severe pain (No=1;Yes=2) [ ]

21 Anaphylaxis (No=1,Yes=2) [ ]

DELAYED REACTION

Type of Reaction		Days after Injection	
22 Swelling (No=1;Yes=2)	[ ]	23-24	[ ][ ]
25 Hematuria (No=1;Yes=2)	[ ]	26-27	[ ][ ]
28 Fever (No=1;Yes=2)	[ ]	29-30	[ ][ ]
31 Rash (No=1;Yes=2)	[ ]	32-33	[ ][ ]
34 Serum sickness (No=1;Yes=2)	[ ]	35-36	[ ][ ]

_____ M.D.

(Signature) Date

VA FORM
FEB 1973 10-1458g(Test)

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VA Cooperative Study of Hepatitis - PTS 2 RCS 10-127-C22

SURGERY SINCE LAST VISIT (Form i)

PATIENT'S NAME _____ HOSPITAL _____

1-2 Card Number [1][1] 3-4 Hospital [ ][ ] 5-7 Sequence No. [ ][ ][ ]

8-13 Date of Surgery [ ][ ][ ][ ][ ][ ] 14-15 Weeks since randomization [ ][ ]

Specify _____

16-17 Anesthesia, Specify agent [ ][ ] (AMA Code) _____

18-19 Anesthesia, Specify agent [ ][ ] (AMA Code) _____

20-21 Anesthesia, Specify agent [ ][ ] (AMA Code) _____

22-23 Anesthesia, Specify agent [ ][ ] (AMA Code) _____

24-25 Anesthesia, Specify agent [ ][ ] (AMA Code) _____

26-27 Total duration of anesthesia (in half hours) [ ][ ]

28 Reaction to anesthesia, (No=1;Yes=2) [ ]

Specify _____

_____ M.D.

Signature Date

VA FORM 10-1458i(Test)
FEB 1973

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VA Cooperative Study of Hepatitis - PTS 2 RCS 10-127-C22

BLOOD TRANSFUSIONS (Form j)
(Submit a form for each day on which transfusion(s) are given)

PATIENT'S NAME _____ HOSPITAL _____

1-2 Card Number [1][2] 3-4 Hospital [ ][ ] 5-7 Sequence No. [ ][ ][ ]

8-13 Date of transfusion(s) [ ][ ][ ][ ][ ][ ]

For each unit complete the following:
Local Ident. No. (Same number as used on form k)
Type of transfusion (Whole blood=1;Packed Cells=2;Plasma=3;Other=4)
Source of transfusion (ARC=1, Hospital volunteer donor=2, known paid donor=3, Unknown paid donor=4). If paid, give contractor and city where blood was drawn.
HBAg (Neg=1;Pos=2) Method _____
Anti HBAg (Neg=1;Pos=2, Not done=3) Method _____
SGPT (If there is enough blood)
Local Blood Bank Number

Form k Local Ident. No.				Type	Source	HBAg	Anti-HBAg	SGPT	Blood Bank Ident. No.	If Paid Donor Contractor City
14	15	16	17	18	19	20	21	22-25		

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VA FORM
FEB 1973 10-1458j(Test)

_____ M.D.
(Signature)

Date

VA Cooperative Study of Hepatitis - PTS 2 RCS 10-127-C22

AUSTRALIA ANTIGEN DATA (Form k)

1-2 Card Number [1][3] 3-4 Hospital Number [ ][ ]

Sequence No.			Date Blood Drawn Mo		Day		Year		Form k Local Ident. No.				Ser. Code	Date Blood Tested Mo		Day		Year		Results Ag	Ab
5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26

Serum Code (Donor=1; Patient=2)

Shipped by:

M.D.

Date

Tested by:

M.D.

VA Form 10-1458k(Test) - Feb 1973

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