THE TREATMENT OF ACUTE INFECTIOUS HEPATITIS. CONTROLLED STUDIES OF THE EFFECTS OF DIET, REST, AND PHYSICAL RECONDITIONING ON THE ACUTE COURSE OF THE DISEASE AND ON THE INCIDENCE OF RELAPSES AND RESIDUAL ABNORMALITIES [1]

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PART ONE

INTRODUCTION

1.1 *General remarks*

The usual patient with "catarrhal jaundice" was treated symptomatically and rather casually in the years prior to 1940. Emphasis was laid on strictly enforced rest in bed as a result of studies of the many military personnel who acquired acute infectious hepatitis during World War II. It was advocated by some that bed rest should be continued not only until all symptoms and signs had disappeared, but even until the major liver function tests returned to normal (1, 2). Later studies by others (3, 4) suggested that the period of bed rest need not be that prolonged. It remained to be clearly demonstrated that the enforcement of strict bed rest was necessary at any time during the acute phase of the illness.

The role of diet in hepatitis has aroused considerable speculation. Some investigators (5–7) advocated the forcing of a high-protein, high-calorie diet, with or without supplementary vitamins and amino acids. Others (8–10) were unable to demonstrate the effectiveness of one or more of these measures. Because of these divergent conclusions, a re-investigation of the effects of various dietary factors seemed indicated.

The incidence and importance of recurrent and chronic viral hepatitis have been the subject of many reports in the last few years (11–14). There have as yet been no well controlled studies in which attempts have been made to associate recurrent and residual abnormalities with the type of treatment administered during the acute illness.

These several pertinent problems relating to the proper treatment of patients with acute infectious hepatitis were still unsolved at the start of an epidemic of hepatitis among American military personnel in the Korean war.

The United States Army Hospital in Kyoto, Japan, was designated the "Hepatitis Center" for the Far East Theater of Operations in September of 1950. Since that time more than 4000 American military patients with hepatitis have been treated there. During the early phase of the Korean war over 1000 patients with well-established acute hepatitis were hospitalized at this Center at one time.

The 460 patients reported in these studies were all treated at the Hepatitis Center. They were then observed during their convalescence at the near-by Physical Reconditioning Center at Nara. Many of these patients were subsequently seen in a follow-up study either just before leaving the Far East Theater at Sasebo, Japan, or shortly after returning to the United States at their next duty station or their homes.

The "Hepatitis Study Team" which conducted these studies was organized in the spring of 1951. This team consisted of four civilian physicians (T. C. C., R. D. E., W. E. R., C. S. D.) and four

specially assigned Army doctors (J. G. C., N. D., R. W. R., C. W. S.). This group of investigators was accompanied to Japan by a chief technician (M. A. M.) and three research trained dietitians (M. B., M. N., A. S.). The final full-time member of the team coordinated the many administrative tasks (A. O'B.).

The main outline of the projected investigation was determined during the summer of 1951. The Hepatitis Study Team arrived in Japan in September of 1951 and remained there a full year. During the first three months the group critically analyzed the records of patients previously treated at the Hepatitis Center, set up a research laboratory, tested several diets, and trained 28 Japanese personnel to become dietetic and laboratory assistants. The investigations detailed in this report were completed over the next 10 months. The follow-up studies consumed approximately 9 months' additional time, or until July of 1953. In all, approximately two years were expended in these studies, exclusive of the time spent in the analysis and interpretation of the data.

It would not have been possible to accomplish these studies without the many contributions and full-scale cooperation of a large number of interested persons. Only those who by virtue of their command positions were responsible for the help contributed by their staffs, or who worked closely with the authors throughout the study, are mentioned below. In addition, specific contributions are acknowledged in footnotes to the text.

Grateful thanks are due Colin M. MacLeod, M.D., President, Armed Forces Epidemiological Board; Cecil J. Watson, M.D., Chairman, Commission on Liver Disease; William S. Stone, Colonel, M.C., Commandant, Army Medical Service Graduate School; Frank L. Bauer, Lieutenant Colonel, M.C., Director, Medical Division, Army Medical Service Graduate School; Victor Sborov, M. D., Director, Hepatic and Metabolic Division, Army Medical Service Graduate School; F. J. Knoblauch, Colonel, M.C., and A. J. Rapalski, Colonel, M. C., Administrators, Armed Forces Epidemiological Board; William E. Shambora, Major General, M. C., Chief Surgeon, Far East Command; James P. Cooney, Brigadier General, M.C., Surgeon, Japan Logistical Command; Charles L. Leedham, Colonel, M.C., and Francis W. Pruitt, Colonel, M.C., Consultants in Internal Medicine, Far East Command; Sterrett E. Dietrich, Colonel, M.C., Commanding Officer, and Robert S. Jordan, Lieutenant Colonel, M.C., Chief of Medicine, U. S. Army Hospital, Kyoto, Japan; Arthur E. White, Col. M.C., Commanding Officer, U. S. Army Hospital, Nara, Japan; and Herschel O. Griffin, Lieutenant Colonel, M.C., Commanding Officer, U. S. Army Hospital, Sasebo, Japan.

Finally, the authors would like to extend their thanks to those who contributed to the analysis of the data and preparation of the manuscript, namely: Dolores Dalo, Katherine Hendrie, Hazel Hitson, Tomoko Ikkai, Sheilla MacCrellish, Rita Nickerson, Joan Palmer, and Francis Y. Halsey.

1.2 *Preliminary epidemiological and clinical observations*

A report by Havens (15) of the hepatitis epidemic occurring among American troops in the Far East was available before the start of the study. The attack rate had risen steadily after the start of the Korean war, reaching a peak of 34 per thousand per year in Korea in February, 1951. Following this it fell slowly to a level around 8 per thousand per year, where it remained throughout tne study. In contrast to the epidemic in postwar Germany (3), the onset of the illness was sudden in the large majority of patients and more closely resembled that of acute infectious hepatitis than homologous serum jaundice. Few wounded men who might have received plasma or blood were sent to the Hepatitis Center in Kyoto. Since most of the hepatitis patients had received immunizations or injections of antibiotics during the five months preceding admission, it was possible that some of them may have had homologous serum jaundice.

The treatment prescribed at the Hepatitis Center prior to the start of the studies followed closely the principles outlined by Capps and Barker (5). The patients were served a nutritious diet with Multivitamin and choline supplements, and were required to remain in bed until there were no residual symptoms or signs of hepatitis and until the bilirubin and bromsulphalein dye tests were normal. Then progressive ambulation was started cautiously, and if all went well, the patient was at full ambulation in about 2 weeks.

To gain an idea of the type of illness that had been treated prior to the start of the present stud-

ies, the data[9] on 2448 admissions to the Hepatitis Center during the previous year were reviewed. The average duration of hospitalization was 63 days. Four patients (0.2 per cent) died and 17 (0.7 per cent) were evacuated to the United States for "chronic hepatitis." Of 39 patients readmitted because of a suspected recurrence during this period, the diagnosis of hepatitis was established on the second admission in only seven. The disease was apparently continuous in five of the seven, so that only two patients had bonafide relapses or reinfections during the period of observation. Since all hepatitis patients in Southwestern Japan and Korea were by military directive to be transferred to Kyoto, it is unlikely that many patients with definite relapses had been treated elsewhere.

It was important to determine whether any measurable factors other than treatment influenced the course of the disease sufficiently to warrant a subdivision of the patients in the controlled studies before assignment to treatment groups. For this purpose a representative sample of 500 records were examined in greater detail. There was no evidence for an association between the duration of disease in the hospital and the patients' age (officers removed), race, place of onset, type of duty, history of previous hepatitis, coexistent intestinal parasites, duration of symptoms, dark urine or jaundice before admission; or whether the patient was withdrawn from duty before, at the time of, or after the discovery of jaundice. There was no relationship between previous alcohol consumption and duration of disease.

Among 80 patients with symptoms of less than 3 weeks' duration before admission, the duration of illness in the hospital varied directly with the level of the initial total serum bilirubin (correlation coefficient + 0.6). This relationship, in combination with estimates of the variability to be expected in duration of illness, was used to predict the number of patients required in the controlled studies in order to detect a treatment effect large enough to be of clinical interest.

1.3 *Outline of studies and summary of results*

Four studies were completed during the course of these investigations. The first three were controlled studies of the effects of diet, rest, and physical reconditioning on the course of acute infectious hepatitis. The fourth or follow-up study evaluated the incidence of relapses and residual abnormalities.

The first study was designed to determine: 1) Is strictly enforced bed rest required during the active stage of infectious hepatitis, or can patients be allowed up and about the ward as they feel fit? 2) Is the enforced feeding of a diet high in calories and protein and supplemented with choline and vitamins essential, or can patients eat only as much as they desire of a normally nutritious diet? Results of this study demonstrated: 1) Patients acutely ill with infectious hepatitis improved as rapidly when allowed to be up and about the ward at will as did patients kept at strictly enforced bed rest. 2) Patients forced to eat a diet supplying an abundance of calories, protein, and vitamins throughout hospitalization improved more rapidly than did those patients eating only what they chose of a normal diet.

The second study was planned to answer the following questions: How much and what kinds of food must patients with hepatitis, forced to eat throughout their hospitalization, consume in order to achieve maximum improvement during the acute phase of their illness? It was desired to ascertain whether an abundance of calories, protein, or supplements had any advantage over the required ingestion of an adequate or "normal" amount of each. The results demonstrated a small difference in favor of patients eating a high-protein diet.

The third study investigated this problem: How early can patients with infectious hepatitis, allowed reasonable activity on the ward during the active phase of their illness, safely undergo an active physical reconditioning program prior to discharge to duty? It was found that strenuous activity could be undertaken safely as soon as the total serum bilirubin was under 1.5 mg. per 100 ml. and the bromsulphalein retention was 5 per cent or less in 45 minutes.

In the fourth (follow-up) study patients were examined approximately one year after their initial treatment. No differences were discernible between patients allowed up and about at will and those kept at strictly enforced bed rest, or between patients who underwent early physical

[9] Kindly supplied by Capt. B. P. Summers, Registrar, and Lt. Col. R. S. Jordan, Chief of Medicine.

reconditioning and those whose return to full duty was gradual. Although there were no differences among the first study patients enforced to eat a nutritious diet and those who ate only as much as they desired, second study patients who received the high-protein and high-calorie diet showed a slightly higher incidence of mild residual abnormalities.

PART TWO

MATERIALS AND METHODS

2.1 *Selection of patients and allocation into treatment groups*

Patients from Korea and Southwestern Japan were transferred to the Hepatitis Center as soon as the diagnosis of hepatitis was made. The following criteria for acceptance were set up:

1) The patient had to be a male member of the Armed Forces of the United States below the grade of warrant officer.

2) The patient was required to have clinical jaundice or persistent dark urine, along with the probable diagnosis of infectious hepatitis as determined by one of the study's doctors from examination of the field medical record, brief history, and physical examination.

3) The duration of symptoms before admission had to be less than 22 days.

4) There could be no evidence on admission of the following diseases: acute malaria, dysentery, pneumonitis, infectious mononucleosis, or any condition requiring surgical treatment.

5) The accepted patients could not have received intravenous plasma or blood within six months of admission.

6) The patients could not have had infectious hepatitis within the last year.

All patients were seen immediately after arrival at the hospital by the study medical officer on duty and an admission card was filled out. After eligibility for the study had been determined by the above criteria and consecutive "study numbers" had been assigned to each patient accepted, envelopes containing a study number on the outside and a randomly assigned treatment group on the inside were opened and the patients were sent to the designated ward. Thus the physician *had no knowledge of the treatment the patient was destined to receive when eligibility for admission to the study was determined.*

2.2 *Details of patient care*

From the standpoint of statistical validity, it would have been desirable to have had each of the different treatments represented on the same ward. Only in this way could any unknown therapeutic effect of the patient's ward or doctor have been controlled. However,

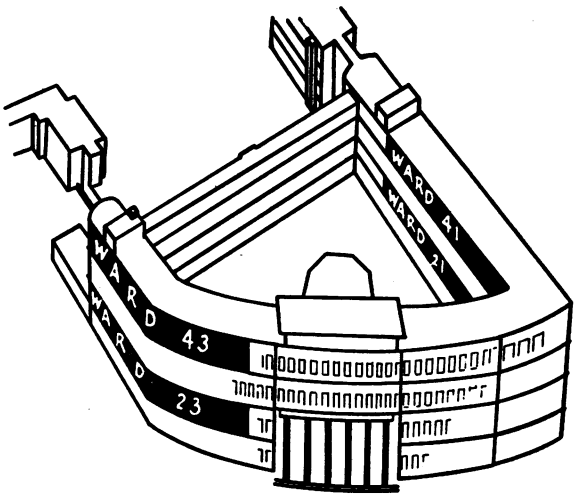

FIGURE 1

since it was reasoned that a patient's adherence to the prescribed regimen would depend for the most part on his confidence in his ward doctor's ability to provide the best available treatment for his speedy recovery and future health, the patients receiving different treatments had to be separated from each other as widely as possible. Therefore the four most widely separated of the eight wards in the hospital were chosen for the studies (Figure 1). Although the patients may have known that different methods of treatment were being used in the hospital, this was explained, when the question arose, with the statement that there were differing views as to the best treatment of hepatitis and that in such a situation it was important that the patient adhere to the regimen prescribed by his own doctor. For this reason it was impossible to rotate the doctors among wards or treatment groups in any one study.

2.3 *Dietary procedures and validation of dietary calculations*

Working in collaboration with the Food Service Division of the Hospital, the research dietitians planned in detail the diets for each of the two treatment groups. Dietary sheets for each patient, showing the amount of each food item to be served, were mimeographed daily. On these the dietetic aides recorded the amounts originally served, refused, and the second servings. Standard servings were weighed on Hanson scales before each meal and meat portions and high-calorie foods such as desserts were weighed individually. Second helpings and uneaten portions were all weighed. If a patient vomited within 6 hours of a meal, half the value of the meal was subtracted from his intake. Sample intake sheets are reproduced in Tables II and III, Appendix II.

Total intakes[10] for each patient were calculated daily on abacuses by the dietetic aides. Each patient's diet sheet was checked by the dietitians after each meal, and as a double check, the values were calculated a second time before they were recorded.

To evaluate the accuracy of measuring, recording, and calculating the diets a tray from each of the three meals during a day was occasionally removed for checking without the aides' knowledge. After weighing each item and independently calculating the results, the dietitians mixed the sample day's diet and sent it to the Chemistry Laboratory of the 406th Medical General Laboratory in Tokyo for analysis.[11]

The results of checks performed on eight daily diets in the first study and six in the second are presented in Table IV, Appendix II. The results for each treatment group were averaged for presentation in the table. A statistical analysis of all the individual checks revealed good correlation of the protein and fat estimates by the three methods. The difference between the calculated and weighed protein contents was small, but on chemical analysis the protein averaged 13.6 grams more than the calculated content. The calculated fat content averaged 4 grams more than the weighed and 28.4 grams more than the chemically analyzed. If one assumes that the chemical analyses represent the "true" approximations, then roughly 9 per cent should be added to the protein content of each diet and 19 per cent subtracted from the fat content. It is possible, however, that as a result of incomplete ether extraction of the fat, the chemical analyses may have yielded low values.

2.4 *Methods for collection of data*

A. *Recording of admission history and physical examination.* When the study was set up it was hoped that by careful recording of historical data it might be possible to determine whether factors other than treatment had some effect on the striking variability in duration. Consequently many details of the patient's past history and present illness, which might conceivably have an influence on the duration of his hepatitis, were recorded in a standardized manner on an 8- by 11-inch punch card. (As in the preliminary observations no one of these variables was found to be significantly associated with the duration of illness as defined in this study.) For the back of the punch card, a semi-graphic recording of the present illness was devised. Employing a numerical grade of intensity, the daily occurrence of malaise, chills and fever, nausea and vomiting, diarrhea, upper abdominal pain, dark urine, light stools, and icterus was recorded. Also charted were the number of meals eaten each day after the onset of symptoms, the patient's activity on each day of his illness prior to admission to the study, the dates of his dispensary and hospital visits, the evacuation procedure, and the methods of treatment during hospitalization prior to transfer to the Hepatitis Center.

A complete physical examination was performed on admission and special attention was paid to the usual stigmata of hepatitis such as jaundice, hepatic size and tenderness, splenomegaly, and spider angiomata.

B. *Clinical observations in the hospital.* Each of the four ward doctors made daily rounds on his own ward and recorded clinical data daily during the patient's first week in the hospital, and twice a week thereafter. In order to insure standardization of clinical observations, group rounds were made once a week on successive wards. The following observations were recorded: degree of anorexia, nausea, upper abdominal pain, and malaise; number of episodes of vomiting and diarrhea each day; liver size and tenderness, palpability of spleen and presence of spiders; temperature, pulse, and weight; and the number of times the patient was out of bed.

C. *Laboratory procedures.* Liver function studies were performed at 3- or 4-day intervals throughout the period of observation. Besides the usual routine admission laboratory studies, each patient had two stool examinations for ova and parasites during the first week of hospitalization, and a heterophile agglutinin titer was performed three weeks after the onset of symptoms. All blood chemistry determinations were performed on blood samples taken between 7 and 8 a.m., with the patient fasting.

The work of the laboratory was supervised by one of the four ward physicians and the civilian chief technician. Ten Japanese chemists[12] were trained to perform the various tests. Although difficulties resulting from the different languages, training, and customs had to be overcome before the study could start, the laboratory work was performed efficiently throughout. At one time more than 2000 individual liver function tests were performed each week.

[10] Food values were taken for the most part from: Composition of Foods—Raw, Processed and Prepared, U. S. Dept. of Agriculture, Handbook No. 8, Washington, D. C., June, 1950.

[11] For the performance of the chemical analyses we wish to thank Col. R. L. Hullinghorst, Director of the 406th Medical General Laboratory, and his successor, Col. R. P. Mason, and Maj. Edward C. Knoblock, Chief of the Chemistry Laboratory. The following methods of analysis were used:

1. "Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists," 1945.
   a. Moisture—par. 27.7 and 28.2.
   b. Ash—par. 28.4 and 34.10.
   c. Fat—par. 28.6 and 27.25.
   d. Protein—par. 28.8 and 2.25.
2. "Analysis of Foods," A. L. Winton and K. B. Winton, 1945.
   a. Fiber — Henneberg Acid-Alkali Gravimetric Method—page 64.
   b. Carbohydrate by difference—page 63.

[12] The authors wish to thank especially Noriaki Wakizaka, M. D., and Koji Hamada, M.D., for their contributions to the laboratory work.

The routine liver function tests included the total and prompt direct (1-minute) serum bilirubin (17), cephalin flocculation (18), thymol turbidity and thymol flocculation (19), the zinc sulfate turbidity (20), and the serum cholinesterase activity (21). The bromsulphalein excretion test (22) was performed at weekly intervals after the total serum bilirubin had decreased to approximately 1.5 mg. per 100 ml. All liver function tests were performed in duplicate and final values represented averages of paired aliquots. When duplicates did not check within 5 per cent the test was repeated the following morning and all four values were averaged. All remaining serum was stored in a deep freeze until the termination of the study.

For the thymol turbidity test a reagent buffered at pH 7.8 as originally described by Maclagan (23) was employed. Although Mateer and co-workers (24) and Neefe, Gambescia, Gardner, and Knowlton (25) have indicated that thymol barbiturate reagent which is buffered at pH 7.55 probably provides a more sensitive procedure for detecting hepatic abnormality, the less sensitive technique was chosen to eliminate abnormal values of doubtful significance. All results of the thymol turbidity tests were reported in terms of Shank-Hoagland units (twice the Maclagan units).

For the bromsulphalein excretion test a dose of 5 mg. per kg. was employed. The body weight used in the calculation of bromsulphalein dosage was the average of the maximum weight at any time and the weight on admission. A maximum dose of 8 ml. was administered. Bromsulphalein dosage was kept constant despite changes in body weight occurring during the period of hospitalization or convalescence. This calculation of BSP dosage was adopted because of the variable weight loss before, and weight gain after admission, the latter depending on the treatment. Later it was found that varying the dosage by 0.5 to 1.0 ml. (equivalent to an error in weight of 11 to 22 pounds) in eight individuals did not significantly alter the per cent retention in 45 minutes.

2.5 *Normal values of liver function tests*

In order to determine the range of normal values of liver function tests among American Military personnel stationed in the Far East, fasting blood samples were collected from 279 enlisted men stationed at Camp Otsu, Japan,[13] and analyzed for prompt reacting (1-minute) serum bilirubin, total serum bilirubin, cephalin flocculation, thymol turbidity, thymol flocculation, zinc sulfate turbidity, and serum cholinesterase activity. All sub-

[13] The authors wish to thank Col. Dwight K. Foster, Commanding Officer, Camp Otsu, for his cooperation in making available the normal subjects.

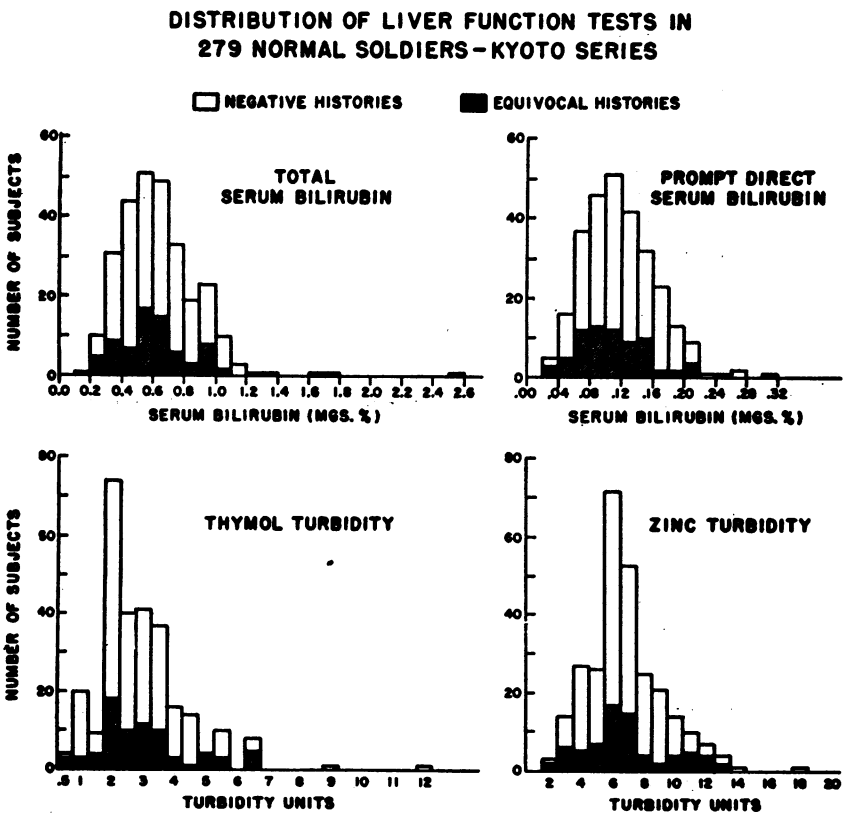

FIGURE 2

TABLE I

Liver function tests in 279 "normal" soldiers (Kyoto series)

	Mean	S.D.	S.E.	Normal limits 95%	Normal limits 99%
Total serum bilirubin—*mg./100 ml.*	0.64	0.26	0.016	1.04	1.62*
Prompt direct serum bilirubin—*mg./100 ml.*	0.12	0.05	0.003	0.20	0.26
Thymol turbidity—Shank-Hoagland units	3.5	1.6	0.095	5.5	6.5
Thymol flocculation				1+	2+
Cephalin flocculation—24 hours				1+	2+
Zinc turbidity—Kunkel units	7	2.4	0.14	11	13
Cholinesterase Δ pH per hour	0.90	0.16	0.01	0.60	0.44

* This value was not available for use in the definition of normal serum bilirubin for the first and second studies. Instead the value 1.50 mg. per 100 ml. described by Zieve and his associates (27) as the 99 per cent upper limit of normality was used.

jects were questioned for a past history of jaundice, hepatitis, infectious mononucleosis, exposure to hepatotoxins, blood or plasma transfusions, amebiasis, Weil's disease, malaria, and a family history of jaundice or anemia. Inquiry relating to present health was directed particularly to the discovery of symptoms associated with hepatitis, such as anorexia, vomiting, diarrhea, dark urine, and abdominal pain.

In analyses of the results of the tests, the individuals were separated into two groups. One group comprised all those without a past or present history of any factor which might be responsible for an abnormal liver function test. The other group was composed of those with positive histories.

These groups are referred to in Figure 2 and Table I, Appendix II, as the normal and equivocal groups. Since a review of the distribution of values of the various liver function tests obtained in the normal and questionably normal groups failed to disclose significant differences, the groups were combined to form a total sample from which the values presented in Table I were derived.

Throughout this study the 99 per cent criterion of normality is employed. Thus, an abnormal test is that found to fall above the value below which 99 per cent of the normals occurred. In only two of the 279 "normal" soldiers, values for liver function studies exceeded the 99 per cent level on more than one test. Both total and prompt direct serum bilirubin were greater than the 99 per cent values in one individual, but repeat determinations 2 days later disclosed values for both tests well within the normal range. The second person had abnormal thymol turbidity and thymol flocculation tests. He had no abnormal symptoms or physical signs. On the basis of these observations, if six liver function tests are performed on a group of presumably normal individuals, the probability that two or more of the tests on the same person will yield values above the 99 per cent level of normality is very small. Approximately 6 per cent of such "normal" individuals, however, may be expected to have one or another of the six tests abnormal.

Because the bromsulphalein retention of the "normal" soldiers was not determined, the conventional 5 per cent retention in 45 minutes was accepted as the upper limit of normal for this study. Since completion of the study, data have been made available to the authors indicating that the 99 per cent level lies between 10 and 14 per cent, depending on the weight of the individual (26). It is possible, therefore, that occasional patients diagnosed as having a prolonged acute course or a relapse on the basis of the bromsulphalein test, were in reality variants of the normal.

2.6 *Criteria for measurement of treatment effects*

In order that the duration of illness might be reliably determined in spite of fluctuations in laboratory observations occurring around the time of ambulation, it was necessary to establish arbitrary rules for the rigid definition of duration of illness. Therefore, in order to start progressive ambulation, the bed rest patient was required to have one normal bromsulphalein test (5 per cent or under) and, for two out of three semi-weekly observation periods, a total serum bilirubin less than 1.5 mg. per 100 ml. The start of ambulation was delayed for 2 weeks if the total serum bilirubin alone persisted elevated, and for 4 weeks if the bromsulphalein alone continued abnormal. The period of time from admission to the start of progressive ambulation for the bed rest patients, and the equivalent period for the patients who had been on *ad lib.* rest throughout, designated arbitrarily as the duration of illness, was the basic measurement of treatment effect on which most of the statistical analyses below are based. The reappearance of abnormalities in the total serum bilirubin or bromsulphalein constituted a laboratory "relapse."[14] A "relapse" was called partial if an abnormality was found on only one observation and was said to be complete if the same abnormality was found in two out of three consecutive periods, or if two or more abnormalities appeared at the same time. If the patient during the course of pro-

[14] The word "relapse" is placed between quotes to signify that the abnormalities classified as a "relapse" for statistical purposes did not necessarily constitute a clinical return of the acute disease.

gressive ambulation developed a partial "relapse," he was held at that level of activity until the next scheduled semi-weekly observation. If he developed a complete "relapse," he was transferred from his own ward, or from the Physical Reconditioning Center, to a fifth ward of the hospital on which all patients were treated alike and clinical and laboratory observations performed as during the acute study. The treatment of relapsed patients consisted of bed rest and the forcing of a moderately high-protein diet. When the original criteria for ambulation had again been attained, the "relapse" was designated as ended and the patient started back on progressive ambulation.

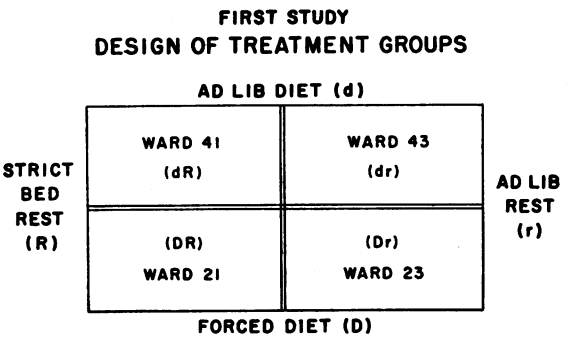

FIGURE 3

PART THREE

FIRST STUDY: THE RELATIVE EFFECTS OF DIET AND REST

3.1 *Design*

In this initial study the course of patients kept at strict bed rest throughout their acute disease was compared with the course of those allowed to be up and around on their hospital ward at will. Thus, the most conservative rest regimen was compared with the least conservative regimen which, since the patient could remain in bed if he wished, still might not be harmful. It was reasoned that if the strict bed rest patients improved faster, the degree of strictness and the necessary duration of the regimen might be suggested by a retrospective analysis of the data, and then further defined in a second study. If *ad lib.* rest proved adequate, two advantages would accrue. First, there would be a distinct saving in personnel necessary to care for the patients, and second, the duration of hospitalization would be shortened appreciably by elimination of the period of physical disability which usually follows prolonged rest in bed.

With respect to diet, the first study was designed as a screening one in which the effects of a nutritious hospital diet offered to the patients *ad lib.* were compared with the effectiveness of a diet in which all nutrients were included in abundant amounts and the patients forced to eat a minimum per day, regardless of anorexia. Thus the forced diet contained a minimum of 3,000 calories, 20 per cent or 150 grams in the form of protein, and was supplemented with choline and a Multivitamin preparation. It was reasoned that if merely providing a nutritious diet to patients was adequate, no further investigation of the dietary aspects would be necessary, and only if the forced diet proved superior would a second study be desirable to determine whether the course was shortened by the forced calories, the high protein content, the supplements, or all three.

The two therapeutic trials summarized above were combined in a single study as outlined in Figure 3. Half the patients were on an *ad lib.* diet and half on a forced diet; similarly half, were on a program of *ad lib.* rest and half were kept in bed. This plan provided the means to determine whether the effect of one treatment factor, diet or rest, was influenced by the response to the other factor. For example, the effect of a diet might vary with the amount of rest, and if this were the case, it would be misleading to refer to an average effect of diet if the amount of rest were unspecified. If there were no such "interaction" between diet and rest, then the average effect of each factor could be determined with only half the number of patients as would be necessary if each were studied alone.

Two-hundred and sixty eligible patients were entered into the study in "blocks" of four. Each patient in a given block was assigned at random to a different one of the four treatment groups. The order of these assignments was determined before the start of the study from a table of random numbers. The patients were admitted in blocks of four for three reasons: 1) to maintain the same number of patients in all treatment groups; 2) to allow the number of patients to be increased if preliminary estimates of the variability of the duration of illness were too small; 3) to provide a means for controlling in the analyses of data the variability introduced by the unknown effects of differences in place and time of infection and fac-

tors in evacuation common to the patients in a given shipment, but expected to vary from one shipment to another.

3.2 *Rest regimens*

A. *Strict bed rest. On admission to the hospital the importance of strict bed rest in the treatment of hepatitis was emphasized to each patient.* This regimen required the patient to observe the following program: 1) Remain in bed at all times except for one trip daily to the latrine and a shower twice a week; 2) eat all meals in bed; 3) utilize all auxiliary services, including post exchange and library carts, at the bedside. Good doctor-patient relationships and constant vigilance on the part of the ward staff resulted in only rare infractions of the bed rest regimen.

Verification of adherence to the schedule was provided by inspection of the ward four to six times daily at irregular intervals. Results of these bed checks were recorded on a mimeographed sheet. If a patient was found out of bed at any other time by any of the ward personnel, this fact was also recorded on the bed check record. In addition, any patient found out of bed was reported to the ward doctor, who repeated the lecture on the importance of strict bed rest and requested complete compliance with the prescribed regimen.

Analysis of the data indicates that the criteria for strict bed rest were met by the great majority of patients (Figure 4). A small percentage failed to meet these criteria and were judged at a level of activity equivalent to or less than that entailed in free bathroom privileges or the eating of meals at the bedside.

B. *Ad lib. rest. No effort was made to control the level of activity of these patients except to prohibit boisterousness as a matter of ward discipline.* They were confined to their wards but permitted out of their rooms as much as they desired except for a one-hour rest period after each meal. Although allowed to be active, these patients were not required to perform tasks about the ward usually assigned to ambulatory military patients. Frequent inspections by the ward doctors were made to evaluate the patients' activity.

The levels of activity of the patients on the two regimens of rest were distinctly different (see Figure 4). From the first day of hospitalization, 45 per cent of the *ad lib.* group were out of bed more than the time involved in visits to the latrine and sitting up for meals. By the seventh day, 55 per cent of the patients, most of whom were still clinically jaundiced, were out of bed more than one-half of the day while only 7 per cent of the patients remained in bed except for latrine visits and meals. This marked difference in activity be-

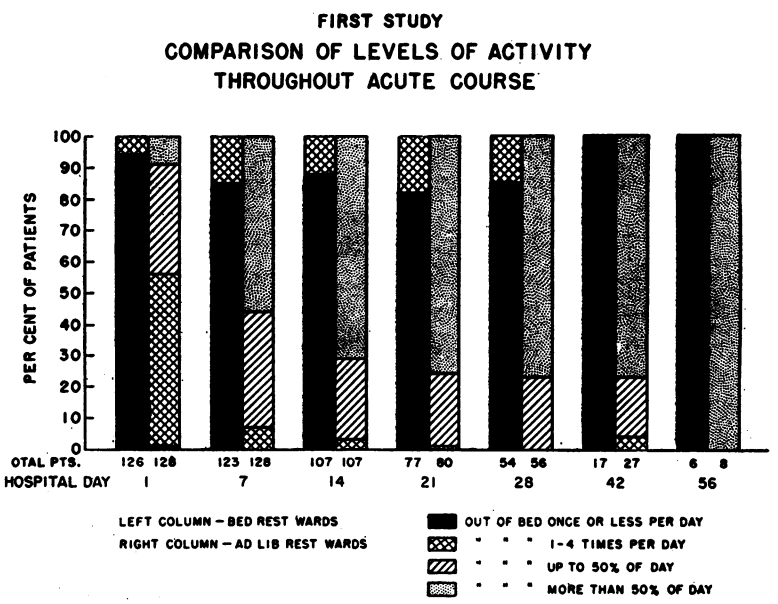

FIGURE 4

tween the strict and *ad lib.* rest wards was maintained throughout hospitalization and was immediately apparent to visitors to the wards.

3.3 *Dietary regimens*

A. *Forced high-protein diet. The potential importance of a forced intake of food in "curing" the disease was repeatedly emphasized to the patients.* They were required to eat a minimum of 3000 calories and 150 grams of protein each day, thus insuring a caloric protein proportion of at least 20 per cent. Fat and carbohydrate contents were allowed to seek their own level in each patient's diet depending upon his selection of food. The diet offered the patient on the menu was greater than this minimum value—at least 4000 calories and 200 grams of protein. Second helpings of all except high-calorie, low-protein foods were available. A high-protein milk drink was served between meals and at bed time. The patients also received choline dihydrogen citrate, 3.9 grams daily, and 2 Multivitamin tablets[15] three times a day. Candy and ice cream sundaes between meals were not allowed.

Patients who were unable to reach the established minimum were tube-fed. The doctors on

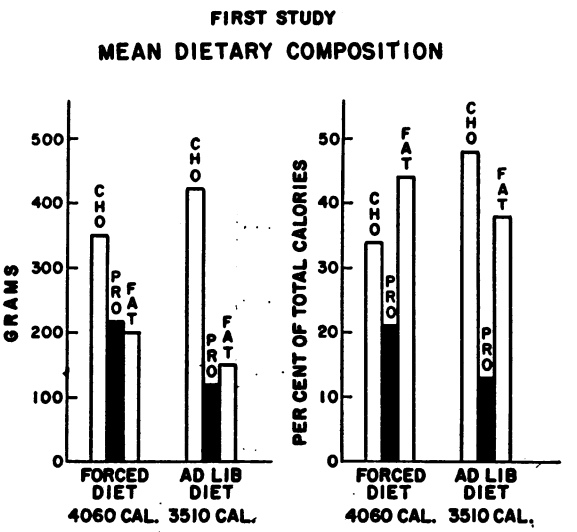

FIGURE 5

the two forced-feeding wards met with the dietitians daily at 1 p.m. to decide if any patients required intubation, the amount of tube feeding necessary, and revision of the tube formula to conform with the food already eaten by the patient on that day. Glucose and saline solutions were occasionally given parenterally. Intravenous protein hydrolysate solutions were not used.

Six patients required tube feedings, two for 1 day only, two for 2 days, one for 3 days, and one for 4 days. It was found that the threat of intubation, or its use in one patient on a ward, was usu-

[15] Total daily dose supplied 15,000 U.S.P. units of vitamin A, 1200 U.S.P. units of vitamin D, 6 mg. of thiamin, 9 mg. of riboflavin, 225 mg. of vitamin C, and 60 mg. of nicotinamide.

TABLE II

Mean dietary intakes for treatment regimens—257 patients

	Diet				Rest			
	Forced		*Ad lib.*		Strict		*Ad lib.*	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Calories	4,060	402	3,510	621	3,730	535	3,840	638
S.E. of diff.		65				73		
P		<.001				.1		
Protein								
Grams	217	21	118	17	167	54	169	52
S.E. of diff.		2				7		
P		<.001				.7		
Per cent of calories	21		13		18		18	
Fat								
Grams	200		150					
Per cent of calories	44		38					
Carbohydrate								
Grams	348		422					
Per cent of calories	35		49					

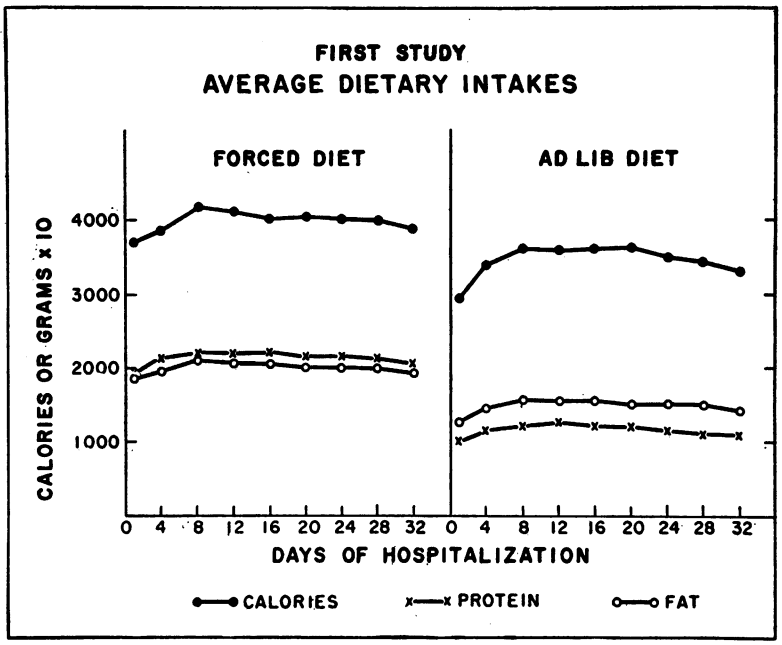

FIGURE 6

ally sufficient to persuade the rest of the anorectic patients to eat the required amount.

B. *Ad lib. diet. The possible benefits of food in the treatment of hepatitis were never mentioned to these patients.* They were served the standard Army hospital diet and no attempt was made to maintain any caloric or food consumption level. Patients were offered between-meal nourishments of fruit juices only. They could order sundaes, ice cream, and candy bars *ad lib.*, through the dietetic aides. Patients admitted with nausea and vomiting received fluids parenterally as necessary for purposes of maintaining hydration and electrolyte balance.

C. *Analysis of dietary intakes.* In Figure 5 are presented the mean intakes for each of the dietary groups in grams and per cent of total calories, from the time of admission to the start of convalescence. The protein differences were striking and the caloric differences small but significant (Table II). The fat content of the forced diet was appreciably higher than that of the *ad lib.* diet, the carbohydrate content lower.

The average intakes at the two dietary levels from admission to the start of convalescence are presented in Figure 6. Both rose somewhat in the first week, but the rise was greater in the *ad lib.* group. Both fell slowly after the first 8 to 12 days.

Since the intakes were *ad lib.* except for the required minimum in the forced group, the individual ranges were great. Figures 7 and 8 present

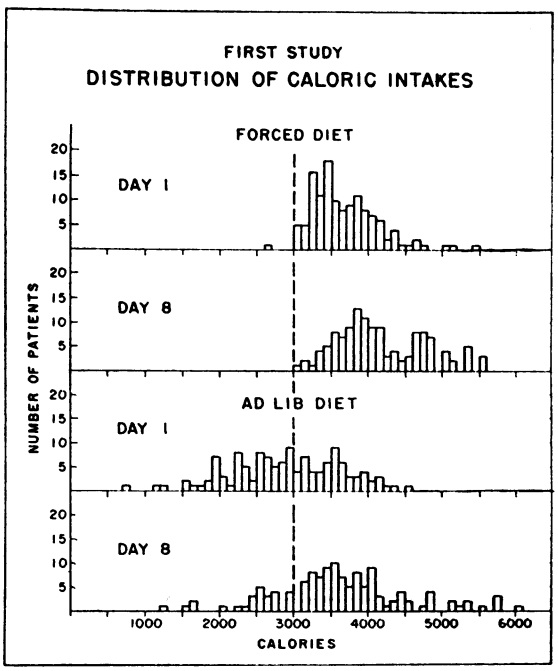

FIGURE 7

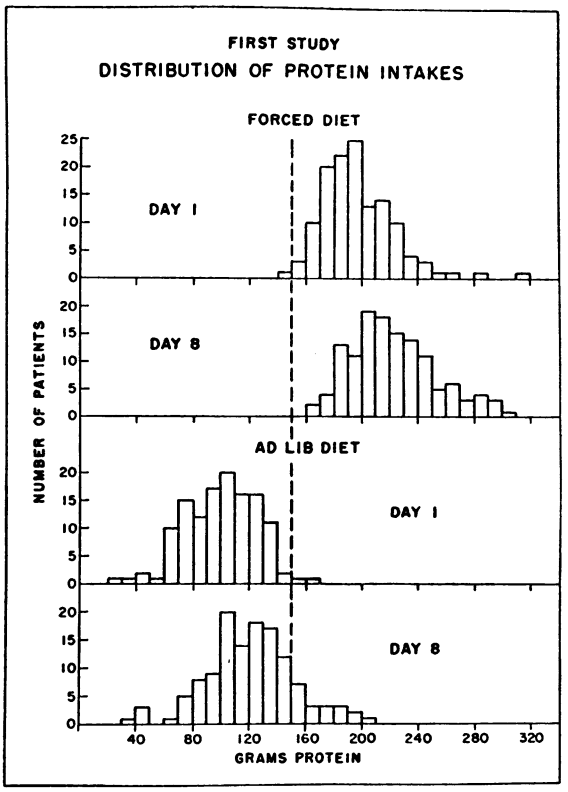

FIGURE 8

the distributions of intakes of calories and protein on the first and eighth hospital days. The range on the eighth day was representative of the intakes from that time on. On the forced-fed wards on day 1 only two patients fell below the prescribed minimum of 3000 calories and 150 grams protein. On the *ad lib.* wards, on the other hand, the range on day 1 was from 700 to 4500 calories, and from 20 to 160 grams of protein; on day 8 from 1200 to 6000 calories and from 30 to 200 grams of protein.

3.4 *Effectiveness of the randomization*

It was necessary to establish whether or not the four treatment groups were comparable with respect to the many variables which might influence the duration of illness, other than the treatments *per se*. A few of these variables were controlled by the criteria used in the selection of patients for the study. The distributions of all of the others, both known and unknown, were left to the play of chance by the use of random numbers for the assignment of eligible patients to the treatment groups.

Thirty-four variables were examined. They included information from the following categories: 1) Medical history; 2) physical findings on admission; and 3) liver function tests on admission. The results of the chi square tests and "analyses of variance" listed in Table V, Appendix II indicated that *the randomization was effective.*

Many of the variables tested were purely objective measurements, such as the level of the serum bilirubin on admission. Others, such as the estimation of liver size and tenderness, reflected the subjective interpretations of each of the four ward doctors. Although every attempt was made to achieve uniformity and objectivity, it was apparent early in the course of the analyses that certain significant differences could be attributed to systematic variations in the interpretation of historical facts and clinical signs and symptoms by the individual ward doctors.

The 34 variables were classified, without prior knowledge of the results of significance tests, into two groups—those in which a "doctor effect" seemed likely to appear, and those in which such effects seemed most improbable. For those 12 variables in which a "doctor effect" was considered improbable, there were no significant differences between the treatment groups. However, there were significant differences for 10 of the 22 variables that were amenable to subjective interpretation. Although these results did not affect the validity of the randomization, they did emphasize the inadequacies of clinical studies in which reliance for the measurement of treatment effects is placed primarily on symptoms and signs.

3.5 *Elimination of patients from the study*

The data on 7 of the 260 patients admitted to the study were removed from the principal analyses (Table VII, Appendix II). Three patients admitted to the study were subsequently found not to have infectious hepatitis. Their final diagnoses were, respectively, infectious mononucleosis, lymphogranuloma venereum, and psychoneurosis. Data on these three patients were removed from all but one of the analyses.

In the case of four other patients, the duration of illness was in doubt. Two of these patients left

the hospital before convalescence, one for an emergency leave and one for special treatment of an acute psychosis. The laboratory findings on the other two patients did not permit a distinction between a short initial illness with a long relapse and a long initial illness without relapse. The data for these four patients were excluded from all but one of those analyses which utilized the durations of illness.

In order to simplify certain analyses it was necessary to have the same number of patients in each of the four treatment groups. To accomplish this, each block of four patients which included any of the above seven patients was removed from the data, leaving 232 patients for these analyses.

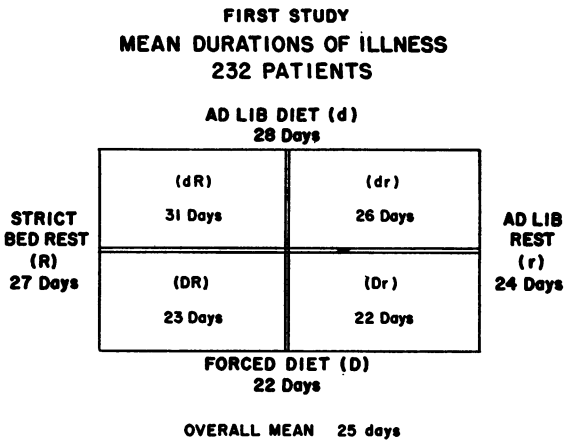

FIGURE 9

3.6 *The effects of treatment on duration of illness*

For both clinical and statistical reasons (see Appendix I, Sec. 3), basic results of the first study are presented as percentage reductions in duration of illness, although the absolute reductions in days of illness (geometric means) are also tabulated. To obtain these results the individual values for durations of illness were converted to logarithms in the basic analyses.

In Figure 9 are shown the average durations of illness (geometric means) for each of the four

TABLE III

First study: Responses to treatment: Percentage reduction in duration of illness—232 patients

Factor		Average response	Response with: Diet: Forced	Diet: *Ad lib.*	Rest: Strict	Rest: *Ad lib.*
Diet	Treatment comparison	(D) − (d)			(DR) − (dR)	(Dr) − (dr)
	% reduction (Absolute difference)*	−22% (−6 days)			−29% (−8 days)	−17% (−4 days)
	95% confidence limits	−14% to −30%				
Rest	Treatment comparison	(R) − (r)	(DR) − (Dr)	(dR) − (dr)		
	% reduction (Absolute difference)*	−10% (+3 days)	−4% (+1 day)	−16% (+5 days)		
	95% confidence limits	−0.1% to −19%				

Treatment levels: D—forced diet; d—*ad lib.* diet; R—strict bed rest; r—*ad lib.* rest.

* The sign of each absolute difference indicates the favorable treatment.

TABLE IV

First study: Responses to treatment: Logarithms of ratios of geometric mean durations—232 patients

Factor		Average response	Response with: Diet: Forced	Diet: *Ad lib.*	Rest: Strict	Rest: *Ad lib.*
Diet	Treatment comparison	(D)/(d)			(DR)/(dR)	(Dr)/(dr)
	Logarithm of ratio	−0.1085			−0.1370	−0.0801
Rest	Treatment comparison	(R)/(r)	(DR)/(Dr)	(dR)/(dr)		
	Logarithm of ratio	+0.0461	+0.0746	+0.0177		
Standard error of response		±0.0232		±0.0328		

TABLE V

First study: Responses to treatment: Influence of various definitions of the duration of illness—232 patients

Treatment group	Mean duration of illness from admission to: Convalescence (days)	Convalescence (weeks)	First normal TSB (days)	Last abnormal* TSB or BSP (days)
Forced diet, strict bed rest (DR)	26	3.1	22	30
Forced diet, *ad lib.* rest (Dr)	25	3.0	21	28
Ad lib. diet, strict bed rest (dR)	34	4.3	25	41
Ad lib. diet, *ad lib.* rest (dr)	30	3.7	25	35
Overall mean	29	3.5	23	34
Average response to:				
Diet (D) − (d)	−7	−1.0	−3	−9
Rest (R) − (r)	+2	+0.3	0	+4
Standard error of response	±1.6	±0.2	±1.2	±2.7

* Includes all "relapses" during convalescence in the hospital and at the Physical Reconditioning Center.

treatment groups; for the four combinations of two groups each of which represents the two levels of rest and two levels of diet; and for the entire study. The effects of diet and rest on the duration of illness are presented in Tables III and IV as comparisons among these geometric means, derived from the logarithmic data presented in Table IV.

The average response to diet was a 22 per cent or 6 days' reduction in duration of illness achieved by the forced diet relative to the ad lib. diet. This reduction is statistically significant at the 0.01 per cent level. The 95 per cent confidence limits indicate that the "true" effect of diet might be anything from a 14 per cent to a 30 per cent reduction in duration of illness in favor of the forced diet. This dietary effect was similar for patients both on strict bed rest and on the *ad lib.* rest regimen. Thus there was no significant interaction between rest and diet.

The average response to rest was a 10 per cent or 3-day reduction in duration of illness in favor of the ad lib. rest program. This result is statistically significant at the 5 per cent level, but the confidence limits show that the "true" reduction is probably not greater than 19 per cent and may well be as small as 0.1 per cent.

Since the definition of duration of illness chosen in the design of this study was necessarily arbitrary, it was important to examine the data retrospectively to determine the influence of different definitions upon the results. These results are

TABLE VI

First study: Treatment groups compared according to various methods for handling "eliminated patients": mean duration of illness from admission to convalescence in days

Treatment group	Blocks containing "eliminated patients" removed	"Eliminated patients" removed	All patients included
Number of patients	232	253	260
Forced diet, strict bed rest (DR)	26	26	26
Forced diet, *ad lib.* rest (Dr)	25	25	25
Ad lib. diet, strict bed rest (dR)	34	35	35
Ad lib. diet, *ad lib.* rest (dr)	30	30	30
Average response to:			
Diet (D) − (d)	−7	−7	−7
Rest (R) − (r)	+2	+3	+3
Standard error of response	±1.6	±1.6	±1.6

TABLE VII

First study: Occurrence of complete bromsulphalein "relapses"—253 patients

Place and time of occurrence	Number of "relapses"	Mean duration of "relapses" *days*
Hospital, first week of convalescence	6	28
Hospital, 2nd week or later in convalescence	9	40
Physical Reconditioning Center	2	21
Total "relapses"	17	33

tabulated in Table V [16] for the following definitions of "duration of illness"; 1) days from admission to convalescence; 2) weeks [17] from admission to convalescence; 3) days from admission to the first two "normal" total serum bilirubins (1.5 mg. per 100 ml.); and 4) days from admission to the last abnormal total serum bilirubin or bromsulphalein retention. Comparisons of the average responses to diet and rest with their standard error indicate that the statistically significant reduction in duration of illness produced by the forced diet is not appreciably influenced by these changes in definition of duration of illness. However, in none of these subsidiary analyses does the small response in favor of *ad lib.* rest reach the 5 per cent level of significance.

To determine whether the removal of patients from the basic data had influenced the results, the effects of diet and rest were obtained from three different analyses as follows (Table VI [16]): 1) with the 7 blocks (4 patients each or 28 patients) containing the "eliminated patients" removed; 2) with only the 7 "eliminated patients" removed; and 3) with the 7 patients left in and their durations of illness estimated when necessary. It is apparent that the results were not influenced by the manner in which the problem of "eliminated patients" was handled.

3.7 *Laboratory relapses before return to duty*

In 17 of the 253 patients (7 per cent), equally distributed among the treatment groups, the bromsulphalein test returned to a persistently abnormal level (for an average of 33 days) after the start of convalescence. In 30 other patients only one bromsulphalein test was abnormal during convalescence and in eight patients the total serum bilirubin was abnormal for one determination (partial "relapse").

There were thus 17 complete laboratory "relapses," all established by bromsulphalein elevations and occurring predominantly in the first few weeks of convalescence (Table VII). Two of the 17 patients complained of transient mild malaise. Only 1 of the 17 had concomitant reappearance of hepatomegaly and in 1 the liver became transiently tender. The total serum bilirubin rose transiently in 2 of these 17 patients (by 0.51 and 1.02 mg. per 100 ml., respectively), but only one determination in each of the 2 patients was above normal. In only 5 of the 17 was the bromsulphalein retention above 10 per cent during the "relapse." In these 5 and in 2 of the remaining 12 there were distinct rises in the zinc and thymol turbidity tests.

The distribution of "relapses" among treatment

[16] For purposes of technical simplicity the data summarized in Tables V and VI were not converted to logarithms before analysis, and the results are expressed as arithmetic means. They are slightly larger than the corresponding geometric means.

[17] Since the bromsulphalein test was performed once a week only, it was thought wise to check the results after the individual durations of illness had been converted from days to weeks.

TABLE VIII

First study: Effects of treatment on occurrence of "relapses"

	Diet				Rest			
	Forced		*Ad lib.*		Strict		*Ad lib.*	
Patients	No.	%	No.	%	No.	%	No.	%
Number of patients	128		125		126		127	
Without "relapse"	106	83	92	74	97	77	101	80
With partial "relapse"	15	12	23	18	19	15	19	15
With complete "relapse"	7	6	10	8	10	8	7	6
	P = .20				P = .75			

groups is presented in Table VIII. There is no evidence of any treatment effect.

3.8 *Other effects of treatment on laboratory tests*

There was a significantly more rapid fall of the mean serum bilirubin in the forced-diet groups than in the ad lib. diet groups. There was a tendency for the flocculation and turbidity tests to be more abnormal at the end of the acute illness in the forced-diet group. No effects of rest on these measurements were apparent.

A. *Mean serum bilirubin trends.* Since laboratory tests were performed at twice-weekly intervals it was possible to construct curves of the means over the first two hospital weeks. A longer period could not be examined in this manner because an increasing number of patients recovered from their illness after 2 weeks. The time intervals chosen for the curves were the following: 1 to 2, 3 to 6, 7 to 10, and 11 to 14 days after admission. When there were two determinations in any one period they were averaged. In each treatment group from one to three patients without at least one determination in each period were omitted from the analyses.

The curves presented in Figure 10 show a more rapid fall in both total and prompt direct serum bilirubins among the forced-diet patients and no difference between the rest groups. The sharper fall in the forced-diet patients is apparent within the first 3 to 6 days after admission. The falls between the admission and 7 to 10-day values are presented in Table IX, and the difference in fall of the total serum bilirubin is significant in the diet comparison.

In addition, it was found that significantly more patients on the *ad lib.* diet had rising total and prompt direct serum bilirubins after admission to the hospital (14 per cent *vs.* 4 per cent and 12 per cent *vs.* 4 per cent, respectively). Detailed data

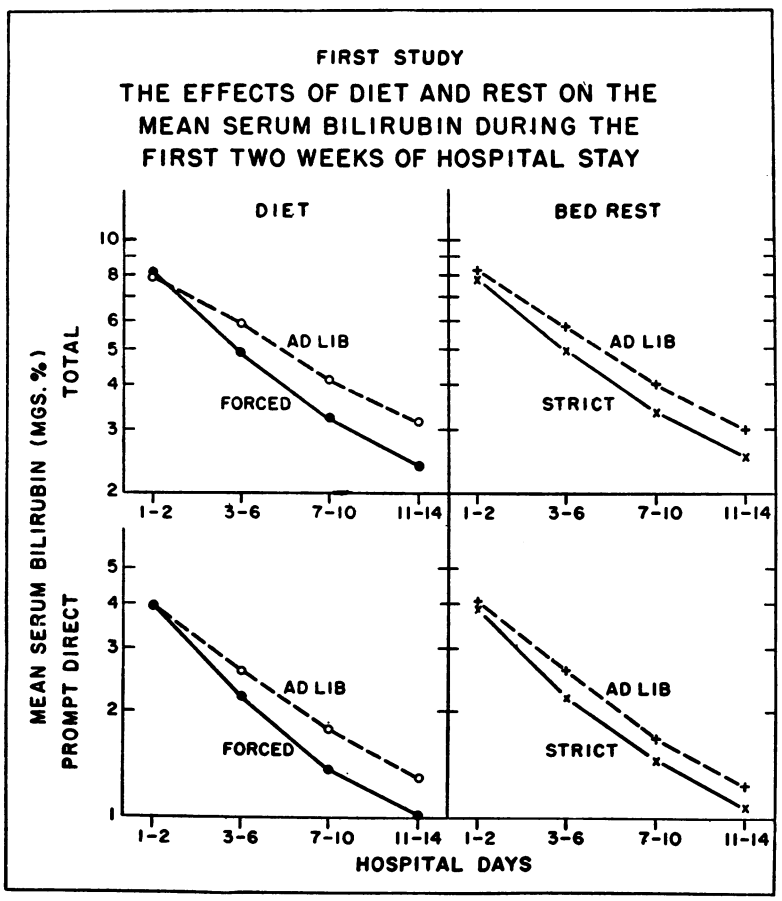

FIGURE 10

TABLE IX

First study: Mean fall in serum bilirubin during the first 7 to 10 days of each treatment regimen

	Diet			Rest		
	Forced	*Ad lib.*	P	Strict	*Ad lib.*	P
Number of patients	127	123		126	124	
Total serum bilirubin (Mg. per 100 ml.)						
Admission value	8.20	7.98		7.88	8.30	
Mean fall	4.91	3.82	.04	4.42	4.33	0.9
S.D.	3.93	4.37		4.06	4.32	
Prompt direct bilirubin (Mg. per 100 ml.)						
Admission value	4.02	3.91		3.92	4.01	
Mean fall	2.59	2.14	0.1	2.40	2.35	0.9
S.D.	2.09	2.31		2.17	2.26	

are presented in Table VIII, Appendix II. It should be noted that in the 23 patients with rises of 1 mg. per 100 ml. or more in total serum bilirubin and in the 21 with rises of 0.5 mg. per 100 ml. or more in the prompt direct serum bilirubins, the rises appeared from 2 to 10 days after admission, with a mean of 4 days. This fact plus the early divergence of the bilirubin curves suggests that the diet effect began within the first week of treatment.

B. *Thymol turbidity, zinc turbidity, cephalin flocculation, and thymol flocculation.* Although not employed in defining the duration of the acute illness or convalescent period, the cephalin flocculation, thymol flocculation, thymol turbidity, and zinc turbidity tests were performed at intervals on all patients. The curves of the mean thymol and zinc turbidity values during the first 2 weeks are presented for comparison of the treatments in Figure 11. The only difference was a more rapid fall of the zinc turbidities in the patients on the *ad lib.* diets. It was found that in significantly more patients on the forced diet the zinc turbidity rose in the first two hospital weeks above the admission value by 2 or more units (47 per cent *vs.* 30 per cent). While more patients on the forced diet also exhibited rising thymol turbidity tests by 1 or more units (34 per cent *vs.* 26 per cent), this difference was not significant.

The different responses in the thymol and zinc turbidity tests to dietary treatment are apparent in Table IX, Appendix II where the means on admission, start of convalescence, and discharge are presented. Similar at the time of admission and discharge, the means of both tests were significantly higher at the start of convalescence in the forced-diet group.

The percentages of patients in the first study with values above the 99 per cent upper limit of normality for turbidity and flocculation tests at the time of admission, at the start of convalescence and on discharge to duty are presented in Tables X and XI, Appendix II. A comparison of the two dietary regimens revealed an approximately equal distribution of the percentage of abnormal tests on admission, but in all tests a greater percentage of abnormal tests were noted in the forced-diet group at the time of convalescence (only the difference in zinc turbidities was significant).

C. *Eosinophils.* Eosinophil counts were performed, in duplicate, on 108 consecutive patients in the first study. In 80 of these patients, eosinophil counts were done regularly during the first 2 weeks of hospitalization and these data are presented in Table XII, Appendix II. No striking differences are observed in the diet or rest comparisons.

D. *Biopsies.* Liver biopsies were not planned as an integral part of the study because it was feared that their performance might often interfere with a patient's adherence to his prescribed treatment. However, they were done for purposes of clinical evaluation on the 43 patients whose bilirubin or bromsulphalein tests had not reached normal by the start of the sixth hospital week. In all of the biopsies there was some residual evidence of hepatitis; in half there was some evidence of "post-necrotic collapse," and in 37 per

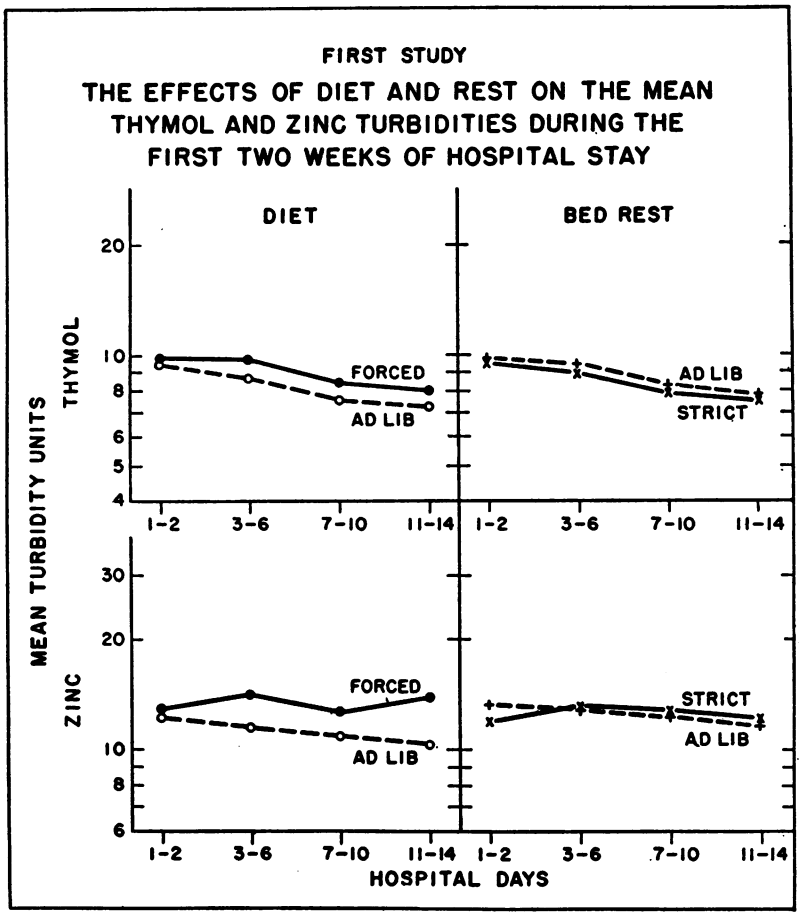

FIGURE 11

cent there was mild fatty metamorphosis. There was no association between the incidence of these abnormalities and either the treatment group or the reason for the biopsy (prolonged elevation of the bilirubin or bromsulphalein tests).

3.9 *Effects of treatment on symptoms and signs*

Since each treatment regimen was on a different ward with a different doctor, subjectively collected information such as symptoms and signs were given little or no weight as criteria for the evaluation of treatment effects. It was hoped, however, that such information might, if collected in a standard manner, add something to the analyses of the responses to treatment. *Differences were noted in the disappearance rate of various symptoms and signs in most of the comparisons made. Although tending to favor the forced-diet and ad lib. rest groups the differences may well have been associated more with "doctor effects" than with the treatment employed.*

A. *Symptoms.* The data are summarized in Table XIII, Appendix II. Because of the possible "doctor effects" (see also Section 3.4) no significance tests have been applied to the results. Figures 12–15 are included in the text to illustrate the general trend of symptoms and the fact that there were no striking differences between the treatment groups. The data suggest that the forced-diet and *ad lib.* rest patients lost their symptoms slightly more rapidly than the *ad lib.* diet and forced-rest patients.

B. *Liver size and tenderness.* The occurrence of liver enlargement and tenderness during the first three hospital weeks is illustrated in Figures 16 and 17 and in Table XIV, Appendix II. *Ad lib.* rest had no demonstrable effects upon the size and tenderness of the patients' livers. Liver en-

largement seemed to diminish more rapidly in the forced-diet group.

C. *Splenomegaly and spider angiomata.* Although the incidence of splenomegaly and spider angiomata might be considerably influenced by "doctor effects," their occurrence on admission was so rare that the importance of "doctor effects" could not be evaluated. The distributions of these abnormalities by treatment groups are presented in Table XIV, Appendix II. The only suggestive difference is a higher incidence of spider angiomata in the forced-diet and *ad lib.* rest groups. Since the doctors on the two wards responsible for these differences in the first study also found, in the second study, more spider angiomata than the other two doctors, this difference may represent a "doctor effect."

D. *Body weight.* The mean weight gains for each treatment group (Table XIV, Appendix II) demonstrate a more rapid gain in weight, in the first 2 weeks only, in the forced-diet group. The data were not compiled after the third hospital week because the curves would have been distorted by the unequal numbers of patients recovering in each treatment group.

3.10 *The effects of ambulation, the "pack" physical fitness test and physical reconditioning on symptoms, signs, and liver function tests*

Recurrent abnormalities in symptoms, signs and liver function tests have frequently been attributed to the mobilization of a patient who has been at strict bed rest, or to exercise begun too early in the convalescent period (1, 12). The first study

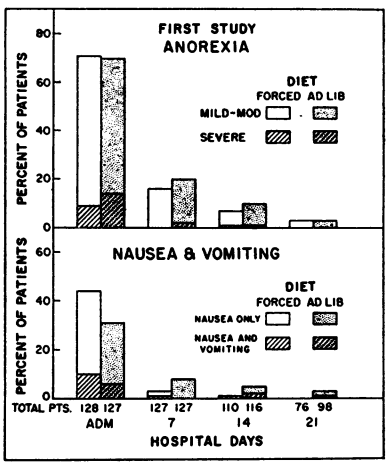

FIG 12. THE EFFECTS OF DIETARY TREATMENT ON THE OCCURRENCE OF ANOREXIA, NAUSEA, AND VOMITING

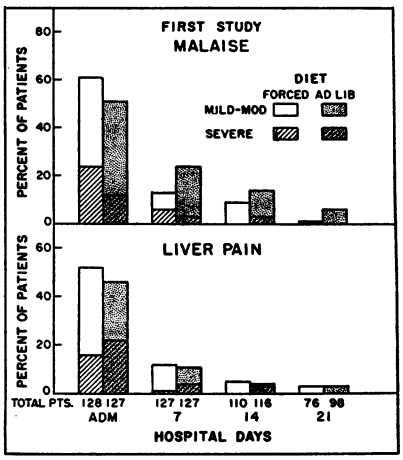

FIG. 14. THE EFFECTS OF DIETARY TREATMENT ON THE OCCURRENCE OF MALAISE AND RIGHT UPPER QUADRANT PAIN

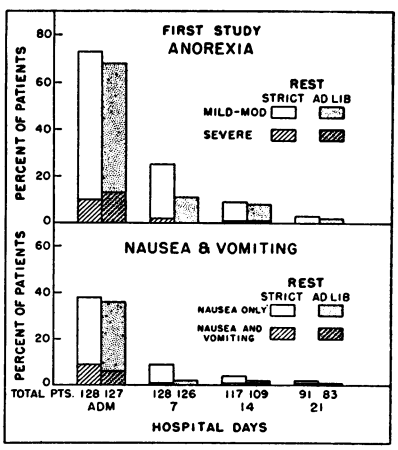

FIG. 13. THE EFFECTS OF REST ON THE OCCURRENCE OF ANOREXIA, NAUSEA, AND VOMITING

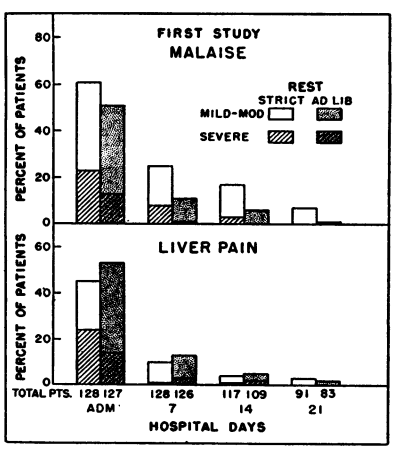

FIG. 15. THE EFFECTS OF REST ON THE OCCURRENCE OF MALAISE AND RIGHT UPPER QUADRANT PAIN

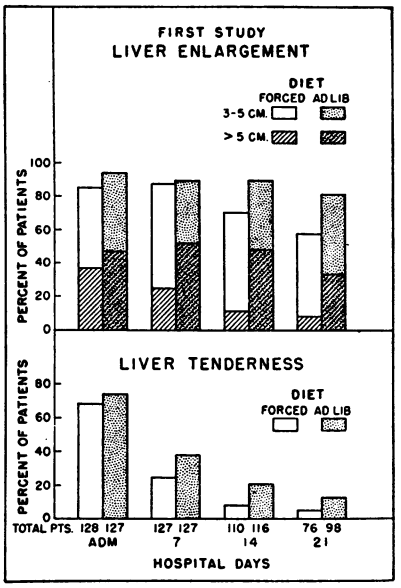

FIG. 16. THE EFFECTS OF DIETARY TREATMENT ON THE OCCURRENCE OF ENLARGEMENT AND TENDERNESS OF THE LIVER

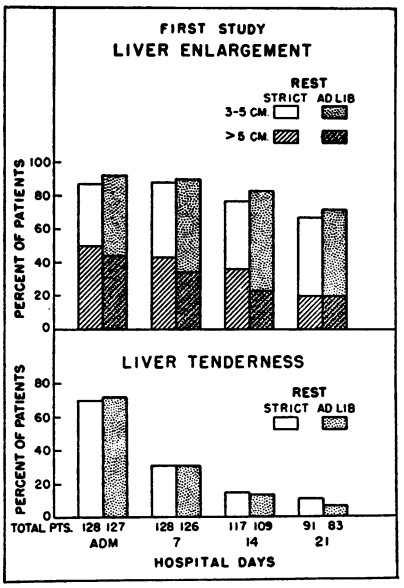

FIG. 17. THE EFFECTS OF REST ON THE OCCURRENCE OF ENLARGEMENT AND TENDERNESS OF THE LIVER

FIGS. 12–17. THE EFFECTS OF THE TREATMENT REGIMENS ON THE OCCURRENCE OF ANOREXIA, NAUSEA, VOMITING, MALAISE, RIGHT UPPER QUADRANT PAIN, ENLARGEMENT AND TENDERNESS OF THE LIVER

offered an opportunity to re-examine these concepts in a controlled manner while at the same time gathering information about the relative ability of patients at strict and *ad lib.* rest to perform exercise during the convalescent period. *In summary, no changes following ambulation could be demonstrated; the ad lib. rest patients were better able to perform physical exertion during the convalescent period, and strenuous exercise resulted in no apparent deleterious effects.*

A. *The effects of ambulation.* For each of the 126 patients on the bed rest wards, the symptoms, liver size and tenderness, and the serum bilirubin and bromsulphalein levels at the start of convalescence and at the end of the first and second weeks of progressive ambulation were recorded. The same data during the equivalent period were tabulated for the 127 patients who were ambulatory *ad lib.* throughout their illness.

Many of the patients still had abnormalities considered by some (3, 5, 28) to be distinct indications for continuation of bed rest. Ambulation was begun as soon as the total serum bilirubin reached 1.5 mg. per 100 ml. instead of the usual 1.0 mg. per 100 ml. (3, 28). The mean serum bilirubins and bromsulphalein retentions at the time of ambulation are presented in Table XV, Appendix II. Forty-eight per cent of the bed rest patients had total serum bilirubins above 1.0 mg. per 100 ml. In 72 per cent the prompt direct bilirubin was above 0.25 mg. per 100 ml., in 6 per cent the bromsulphalein retention in 45 minutes was over 5 per cent.[18] The cephalin flocculation was abnormal in 18 per cent, the thymol flocculation in 40 per cent, the thymol turbidity in 42 per cent and the zinc turbidity in 18 per cent. Fifty-six per cent still had enlarged livers and in 4 per cent tenderness of the liver was still present.

In the strict bed rest group, fluctuations in the incidence of each of these abnormalities occurred after the start of ambulation. These might have been attributed to the change in treatment if they had not occurred with equal frequency in the *ad lib.* rest group whose ambulatory status was unchanged throughout this period. Data illustrating this fact are presented in Table XV, Appendix II.

No patient developed recurrent jaundice during this period. Laboratory "relapses" occurred during the 2 weeks after the start of convalescence

[18] In patients with persistently abnormal bromsulphalein retention, convalescence began, by definition, 4 weeks after their total serum bilirubins were normal.

more often in the bed rest group (5.6 per cent *vs.* 2.4 per cent) but this difference is not significant. A rise in the serum bilirubin or bromsulphalein tests, an increase in liver size, or a return of tenderness or symptoms, occurred jointly in the same patient no more often than might have been expected by chance. Thus there was no evidence that the mobilization of bed rest patients resulted in any important clinical or laboratory abnormalities.

B. *Results of the pack test of physical fitness.* To determine whether the *ad lib.* rest patients were better able to perform strenuous physical exertion early in convalescence, and whether such exertion might have a deleterious effect on either group of patients, the pack test as described by Johnson, Brouha, and Darling (29) was applied to 125 of the patients during the second week of convalescence. The test consisted of stepping onto a bench 20 inches in height every 2 seconds for 5 minutes. Because of the early fear that relapses might be precipitated by such exercise, the test was performed on the first day without a pack, 2 days later with one-half the required pack, and 2 days after that with the full pack (weighing one-third the subject's weight). The third test was scored by the method described by Johnson, Brouha, and Darling (29), taking into account the length of time the patient could continue the test, and the pulse rate on its completion.

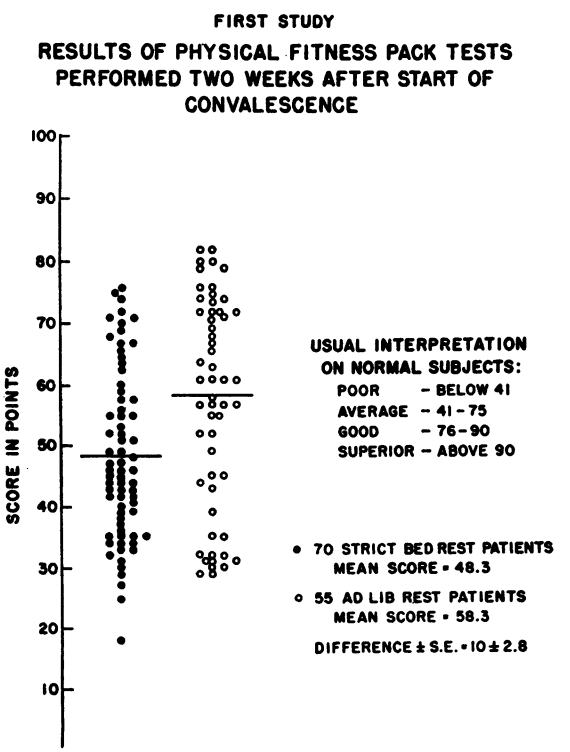

FIGURE 18

A comparison of the scores attained by the 70 strict bed rest and 55 *ad lib.* rest patients who were subjected to the third test is presented in Figure 18. There is considerable overlap between the two groups, but the mean score of the *ad lib.* group is significantly higher ($P = 0.001$) than that of the strict bed rest group. The fact that the tests were performed almost 2 weeks after the start of convalescence makes the difference between the two groups more impressive than it appears on the chart. On the other hand, this was a subsidiary study for which patients were selected according to their availability at a given time rather than at random, and the results, while of interest, may not be as reproducible as implied by the significance test.

A compilation of the results of serum bilirubin and bromsulphalein tests and physical examination performed on the day after the third test revealed no difference between the two groups of patients.

C. *The effects of strenuous physical reconditioning.* Two hundred and two patients were transferred to the Physical Reconditioning Center at Nara (subsequently referred to as the P.R.C.) before their return to active duty. The remaining patients, for various administrative reasons, were sent directly to duty on discharge from the hospital. The patients were discharged from the hospital to the P.R.C. from the 12th to the 79th day after convalescence, the average being 26 days. The means and ranges of total and prompt direct serum bilirubin values on discharge to the P.R.C. are presented in Table XVI, Appendix II. A physical and laboratory check-up was usually performed once during the 10 to 14 days the patients were at the P.R.C. Only two patients had asymptomatic bromsulphalein relapses commencing during physical reconditioning. Although the system of following patients at the P.R.C. in the first study was not well organized and there were no control groups of patients, there was no evidence that strenuous exercise during this stage of convalescence had any deleterious effects.

3.11 *Summary of the results of the first study*

1. Verification of adherence to the regimens of rest and diet revealed the treatment groups to be distinctly dissimilar.

2. Numerous checks on the method of randomization revealed it to have been effective.

3. The removal from the basic data of 7 of the original 260 patients did not change the results.

4. Several analyses of the effects of diet and rest on the duration of the acute illness revealed the following:

a) The patients allowed out of bed *ad lib.* but confined to their hospital ward had a slightly shorter duration of illness than those kept at strict bed rest.

b) The patients forced to eat a diet containing a minimum of 3000 calories and 150 grams of protein supplemented with choline and Multivitamin capsules, had an illness 22 per cent or 6 days shorter in duration than those who were allowed to eat the regular hospital diet *ad lib.* This difference was highly significant.

c) There was no interaction between the effects of diet and rest.

5. Asymptomatic bromsulphalein relapses occurred in 7 per cent of the patients during the observation period and were equally distributed among the treatment groups.

6. There was a significantly more rapid fall of the mean serum bilirubins in the forced-diet group than in the *ad lib.* group. There was a tendency for the flocculation and turbidity tests to be more abnormal at the end of the acute illness in the forced-diet group, but these tests were the same in both groups at the time of discharge.

7. The various treatments had no striking effects on the patients' symptoms and signs.

8. Ambulation of the strict bed rest patients while they still had some abnormalities in physical signs or liver function tests was not followed by demonstrable deleterious effects.

PART FOUR

SECOND STUDY: THE EFFECTS OF VARIOUS DIETARY COMPONENTS

4.1 *Design*

The purpose of the second study was to determine which of the dietary factors—total calories, protein content, or choline and vitamin supplements—were responsible for the reduction in duration of illness achieved by the forced diet in the first study. The design is diagrammed in Figure 23. On the second floor of the hospital, the patients were forced to eat within a range of ± 10 per cent of 4000 calories and on the 4th floor ± 10 per cent of 3000 calories. On the wards at one end of the hospital the diet was composed of 19 per cent protein calories (140 and 190 gm. ± 10 per cent) and at the other end 11 per cent protein calories (80 and 110 gm. ± 10 per cent). Half of the patients on each ward were given 3.9 grams of choline dihydrogen citrate and 6 Multivitamin capsules daily, and the other half received placebos.[19] All patients were allowed to be up and about their wards *ad lib.*

The primary purpose of this treatment plan was to determine if an abundance of each dietary factor had any advantage over an adequate or "normal" amount. Although there was some retrospective evidence from the first study suggesting that lower than "normal" intakes in the acute phase of the disease were usually followed by a prolonged illness, it was considered unwise to investigate this effect in the second study because definite restriction of intake below "normal" in one group of patients would have been required. Since such restriction might well have been harmful, and certainly difficult to achieve, it was decided to accept the results of the first study as indicating that forcing to a "normal" level of intake is advantageous in the anorectic phase of the disease, and attempt to determine in the second study whether high levels of calories, protein, or choline and vitamins have any advantage over "normal" amounts.

The criteria for admission were the same as in the first study, and patients were assigned to treatments in blocks. Although there were eight treatment groups, it seemed desirable to restrict the size of each block to four patients in hopes that such a small block would be more homogeneous on admission than would a block of eight. Each complete set of eight treatments was therefore composed of two kinds of blocks, as follows:

[19] For supplying the choline dihydrogen citrate tablets and their placebos the authors wish to thank Dr. George R. Hazel, Abbott Laboratories, North Chicago, Ill.

Type A

High calories, high protein, supplements (CPS)
"Normal" calories, high protein, placebos (cPs)
High calories, "normal" protein, placebos (Cps)
"Normal" calories, "normal" protein, supplements (cpS)

Type B

High calories, high protein, placebos (CPs)
"Normal" calories, high protein, supplements (cPS)
High calories, "normal" protein, supplements (CpS)
"Normal" calories, "normal" protein, placebos (cps)

It was necessary to randomize the chronological order in which the two kinds of blocks were filled as well as the order of assigning four consecutive patients to the treatments in each block. These assignments were made with the use of a table of random numbers before the study began. *Two hundred patients were admitted to the study* in 50 blocks, 25 of each type.

The same four wards were used in the second study as in the first. An opportunity was afforded to control partially the unknown effects of the physician on the course of his patients' hepatitis by assigning the doctors to different wards. Those who cared for the second floor, forced-fed patients in the first study moved to the fourth floor where the diets contained fewer calories and less protein than the corresponding second floor diets, and vice versa.

4.2 *Rest regimen*

All patients in this study were allowed to be out of bed ad lib. except for a 1 hour rest period after each meal. They were confined to their hospital wards until the start of convalescence. Recording of the amount of time each patient spent in bed was performed as on the *ad lib.* rest wards in the first study, and the results were similar.

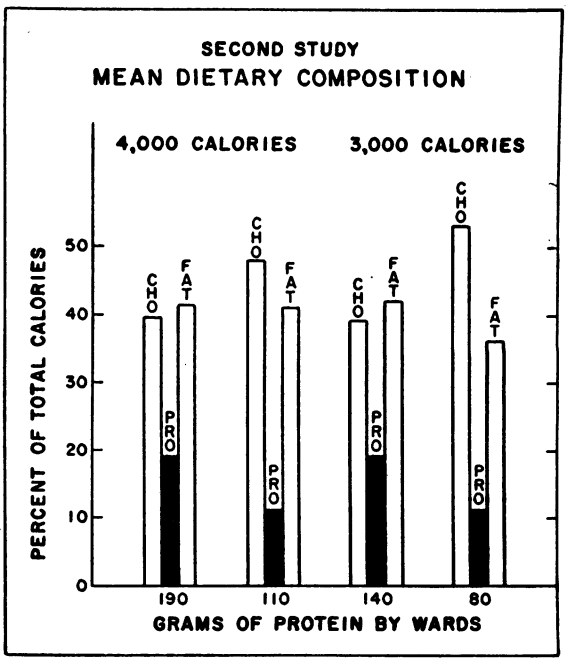

FIGURE 19

4.3 *Dietary regimens*

The content of each of the four basic diets is presented in Table X and Figure 19. It is apparent that as percentage of protein was decreased each caloric level was maintained by adding carbohydrate, and that at a constant percentage of protein calories the total calories were decreased by reducing the amounts of all three dietary substances. In terms of protein content in grams there were four different diets; in terms of per-

TABLE X

Second study: Contents of a typical day's diet on each of the four wards *

	Calories	CHO gm.	Pro gm.	Fat gm.	Choline base† gm.	Methionine gm.	Vit. A I.U.	Thiamin mg.	Riboflavin mg.	Niacin mg.	Vit. C mg.
Ward 23 (CP)	3,992	357	191	200	1.73	4.7	15,000	2.5	5.4	28.8	105
Ward 43 (cP)	2,986	296	140	138	0.88	3.4	13,000	2.1	4.0	24.2	112
Ward 21 (Cp)	4,010	446	111	198	0.70	2.5	14,000	1.9	3.6	19.5	115
Ward 41 (cp)	3,002	406	79	118	0.38	1.8	12,000	1.8	2.1	20.3	201

* Supplements were administered to half the patients on each ward as follows:

Vitamin A	15,000 USP units	Riboflavin	9 mg.
Vitamin D	1,200 USP units	Vitamin C	225 mg.
Thiamin	6 mg.	Nicotinamide	60 mg.
		Choline base†	1.6 gm.

† To convert to choline chloride multiply by 1.3 and to choline dihydrogen citrate by 2.4.

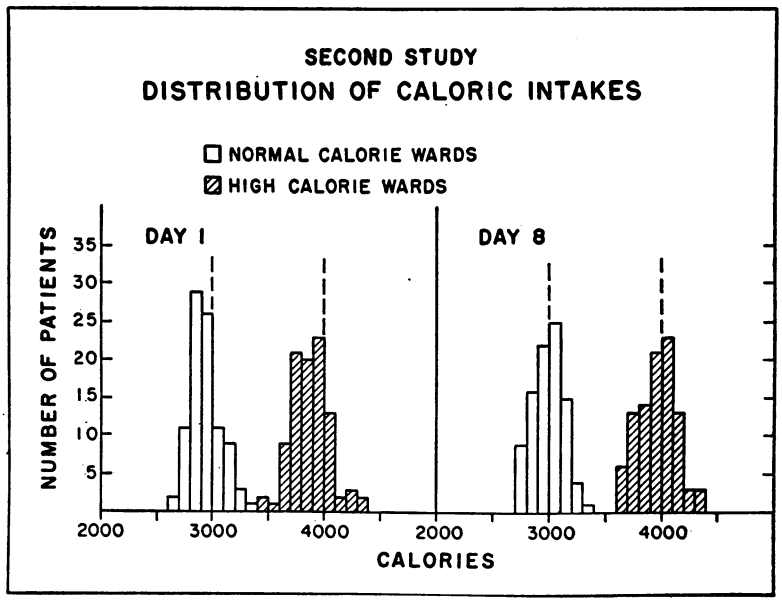

FIGURE 20

centage of protein there were two levels. The fat content varied with the calories but when averaged over calories was essentially the same at the two percentages of protein levels. In the second study all food portions were weighed individually and the smaller number of patients on the wards allowed for closer supervision of each patient's intake.

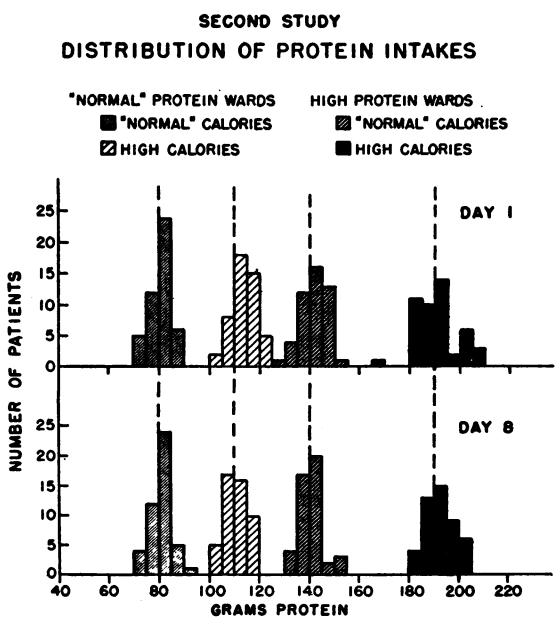

FIGURE 21

The narrow distribution of caloric and protein intakes on the first and eighth hospital days are illustrated in Figures 20 and 21. This is in contrast to the wide range of intakes in both the forced and *ad lib.* dietary groups of the first study (see Figures 6 and 7, Section 3.3). Also different from the first study are the dietary trends presented in Figure 22. Except for a small rise between days 1 and 4 the mean dietary intakes in this study are constant throughout. Here again it can be seen that the fat content of the high and "normal" protein diets is the same.

To maintain the dietary intakes within the prescribed limits, 22 patients had to be tube-fed in the second study—15 for 1 day only, 5 for 2 days, 1 for 3 days, and 1 for 4 days. Seventeen of the tube-fed patients were on the 4000-calorie ward and 5 on the 3000-calorie ward.

4.4 *Effectiveness of the randomization*

Analysis of numerous variables revealed the randomization to have been effective. Tests for the effectiveness were carried out in a manner similar to that used in the first study (Section 3.4). Because of the smaller number of patients assigned to each group, a single "chi-square" test could not be used to test for differences in the percentage distribution of a qualitative variable over the eight treatment groups. Therefore, two

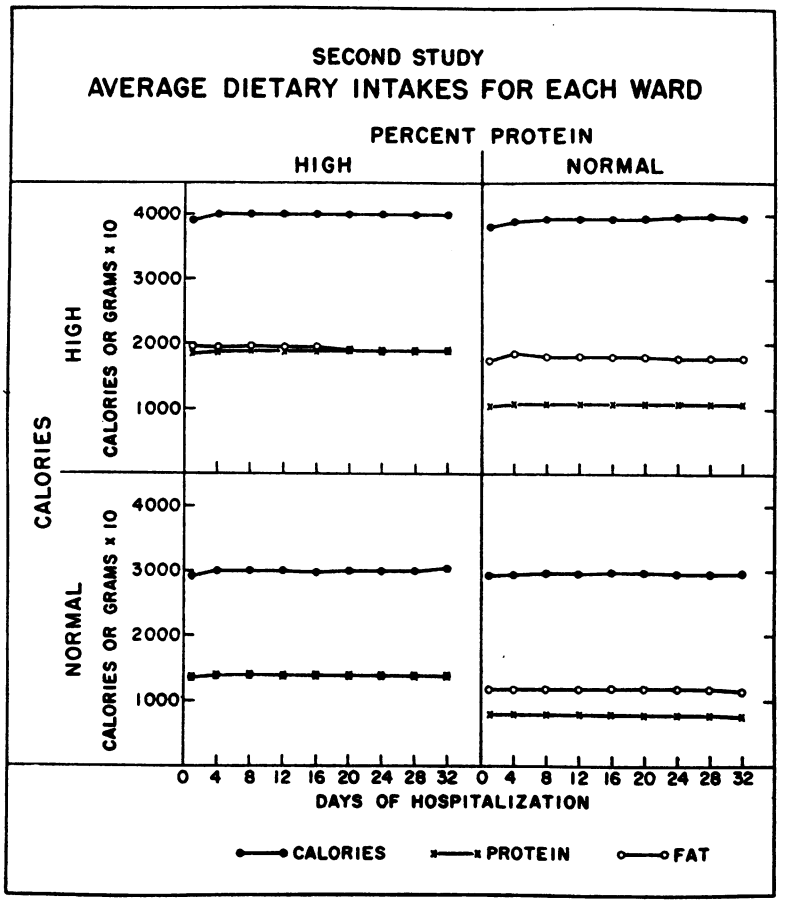

FIGURE 22

"chi-square" tests were used for each of 21 qualitative items—one for a comparison of differences among the four wards and the other for within-ward comparison of the group of patients given supplements (S) with those given placebos (s). Differences among the means of the eight treatment groups were tested for significance in an "analysis of variance" for each of 15 quantitative variables. In the case of those variables which showed significant differences, a separate "within-ward" comparison was also made between the means of the "supplement" and "placebo" groups.

Details of the significance tests applied to 36 variables are presented in Table VI, Appendix II. Among the 14 variables thought unlikely to be influenced by "doctor effects," only one, race, showed significant differences among the treatment groups. On the other hand, among the variables thought to be subject to "doctor effects," 13 out of 22 showed significant "between-ward" differences, while in no instance was the "within-ward" difference significant.

4.5 *Elimination of patients from the study*

The data on 11 of the 200 patients were removed from the basic analyses for the following reasons: Three patients were misdiagnosed, of whom two probably had amebic hepatitis and one was thought to have chronic hemolytic jaundice. Observations on the last eight patients admitted to the study were interrupted in order to hasten completion of the study. A description of each patient is presented in Table VII, Appendix II.

4.6 *The effects of treatment on duration of illness*

As in the first study (Section 3.6) logarithms of the durations of illness were used in the basic analyses of the second study. The geometric means of the durations of illness (from admission

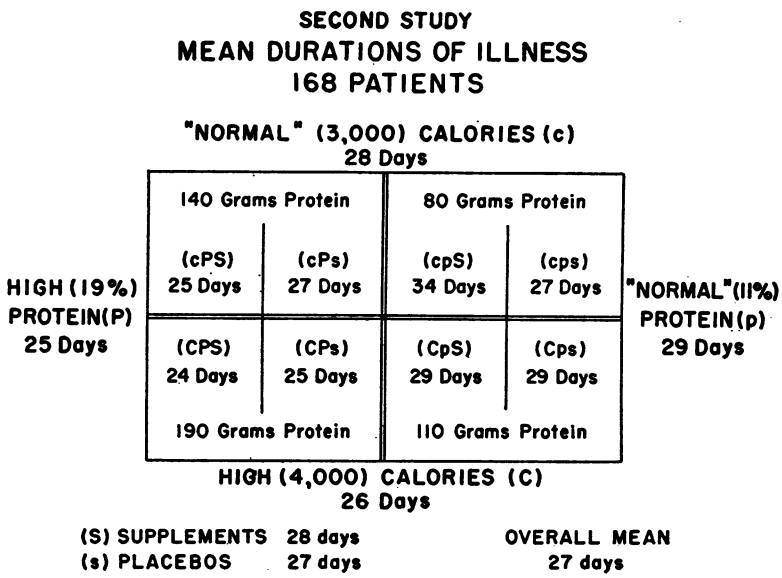

FIGURE 23

Since basic calculations were performed in logarithms, the means in this figure are geometric.

TABLE XI

Second study: Responses to treatment: Percentage reduction in duration of illness—168 patients

Factor		Average response	Response with: Protein High	Protein "Normal"	Calories High	Calories "Normal"	Supplements Added	Supplements Placebos
Protein	Treatment comparison	(P)–(p)			(CP)–(Cp)	(cP)–(cp)	(PS)–(pS)	(Ps)–(ps)
	% reduction	−14%			−13%	−14%	−21%	−6%
	(Absolute difference)*	(−4 days)			(−4 days)	(−4 days)	(−7 days)	(−2 days)
	95% confidence limits	−2% to −24%						
Calories	Treatment comparison	(C)–(c)	(CP)–(cP)	(Cp)–(cp)			(CS)–(cS)	(Cs)–(cs)
	% reduction	−6%	−5%	−6%			−9%	−2%
	(Absolute difference)*	(−2 days)	(−1 day)	(−2 days)			(−3 days)	(−0.5 day)
	95% confidence limits	+8% to −17%						
Supplements	Treatment comparison	(S)–(s)	(PS)–(Ps)	(pS)–(ps)	(CS)–(Cs)	(cS)–(cs)		
	% reduction	−2%	−7%	−10%	−2%	−6%		
	(Absolute difference)*	(+0.5 day)	(−2 days)	(+3 days)	(−0.5 day)	(+2 days)		
	95% confidence limits	+10% to −14%						

Treatment levels: C—high calories; c—"normal" calories; P—high protein; p—"normal" protein; S—supplements; s—placebos.

* The sign of each absolute difference indicates the favorable treatment.

to the start of convalescence) for the eight treatment groups and the major treatment combinations are presented in Figure 23. The effects of caloric intake, protein composition, and dietary supplements on the duration of illness are shown in Table XI as comparisons among the means of Figure 23.

The average response to "calories" was a 6 per cent reduction in duration of illness in favor of the high-calorie diet. That this small difference is not statistically significant at the 5 per cent level is demonstrated by the 95 per cent confidence limits of + 8 per cent to − 17 per cent. The "true" effect of the high-calorie diet might be anything from an 8 per cent increase to a 17 per cent decrease in duration of illness relative to the duration produced by the "normal"-calorie diet.

The average response to the protein content of the diet was a 14 per cent reduction in duration of illness achieved by the high-protein diet with 95 per cent confidence limits of − 2 per cent to − 24 per cent. This result is significant at the 5 per cent level although the "true" effect may lie anywhere on the rather wide confidence interval.

The average response to supplements was negligible, a 2 per cent reduction favoring the placebos with 95 per cent confidence limits of + 10 per cent to − 14 per cent. The differential responses to each treatment factor at the two levels of each of the other factors are also shown in Table XI. Although there is a qualitative suggestion of interactions between protein and supplements and between calories and supplements, neither of the interaction terms is significant at the 5 per cent level.

The logarithmic data in Table XII correspond to the percentage results in Table XI. Standard errors are given for the average responses and the differential responses. Since each of the differential responses is a comparison among only four of the eight treatment groups, the standard error of these responses is greater than that for the average responses. Because of this loss of precision in testing the differential responses, only one of the four protein comparisons is significant at the 5 per cent level. However, the average response to proteins, based on a comparison among all eight treatment groups, just exceeds two standard errors, *i.e.*, is significant at the 5 per cent level. None of the differential responses to calories or supplements approach significance.

Several subsidiary analyses were also done, comparable to those used in the first study. The results are shown in Tables XIII and XIV. The mean values in these tables are arithmetic means. The results are similar to those of the basic analyses, irrespective of the definition of treatment effect or the manner of handling the problem of "eliminated patients." Note, however, that in the analyses based on the first normal bromsulphalein retention the average response to protein is not significant at the 5 per cent level.

TABLE XII

Second study: Responses to treatment: Logarithms of ratios of geometric mean durations—168 patients

Factor		Average response	Response with: Protein High	Protein "Normal"	Calories High	Calories "Normal"	Supplements Added	Supplements Placebos
Protein	Treatment comparison	(P)/(p)			(CP)/(Cp)	(cP)/(cp)	(PS)/(pS)	(Ps)/(ps)
	Logarithm of ratio	−0.0647			−0.0625	−0.0669	−0.1042	−0.0252
Calories	Treatment comparison	(C)/(c)	(CP)/(cP)	(Cp)/(cp)			(CS)/(cS)	(Cs)/(cs)
	Logarithm of ratio	−0.0247	−0.0225	−0.0269			−0.0420	−0.0074
Supplements	Treatment comparison	(S)/(s)	(PS)/(Ps)	(pS)/(ps)	(CS)/(Cs)	(cS)/(cs)		
	Logarithm of ratio	+0.0088	−0.0307	+0.0483	−0.0085	+0.0261		
Standard error of response		±0.0293			±0.0414			

TABLE XIII

Second study: Responses to treatment: Influence of various definitions of the duration of illness—168 patients

Treatment group		Mean duration of illness from admission to: Convalescence* days	Convalescence* weeks	First normal TSB days	First normal BSP days	Last abnormal† TSB or BSP days
High calories, high protein, supplements	(CPS)	27	3.3	20	29	32
High calories, high protein, placebos	(CPs)	28	3.4	22	28	29
"Normal" calories, high protein, supplements	(cPS)	27	3.3	21	30	36
"Normal" calories, high protein, placebos	(cPs)	32	4.0	24	32	39
High calories, "normal" protein, supplements	(CpS)	32	4.0	25	35	38
High calories, "normal" protein, placebos	(Cps)	34	4.3	26	36	41
"Normal" calories, "normal" protein, supplements	(cpS)	37	4.7	26	37	40
"Normal" calories, "normal" protein, placebos	(cps)	33	4.1	27	33	40
Overall mean		31	3.9	24	33	37
Average response to:						
Protein	(P)–(p)	−6	−0.8	−4	−5	−6
Calories	(C)–(c)	−2	−0.2	−1	−1	−3
Supplements	(S)–(s)	−1	−0.1	−2	+1	−1
Standard error of response		±2.2	±0.3	±1.5	±3.0	±2.9

* By prior definition the acute illness ended and convalescence started as soon as the total serum bilirubin had been 1.5 mg./100 ml. or less twice and the bromsulphalein retention 5% or under once, and could be prolonged by a persistently elevated bromsulphalein test by no more than 4 weeks after 2 normal serum bilirubins.

† Includes all "relapses" during convalescence in hospital and at Physical Reconditioning Center.

TABLE XIV

Second study: Treatment groups compared according to various methods of handling "eliminated patients": Mean duration of illness from admission to convalescence in days

Treatment group		Replicates containing "eliminated patients" removed	"Eliminated patients" only removed	All patients included
High calories, high protein, supplements	(CPS)	27	27	28
High calories, high protein, placebos	(CPs)	28	28	28
"Normal" calories, high protein, supplements	(cPS)	27	29	29
"Normal" calories, high protein, placebos	(cPs)	32	31	32
High calories, "normal" protein, supplements	(CpS)	32	32	33
High calories, "normal" protein, placebos	(Cps)	34	36	36
"Normal" calories, "normal" protein, supplements	(cpS)	37	37	39
"Normal" calories, "normal" protein, placebos	(cps)	33	34	33
Average response to:				
Protein	(P)–(p)	−6	−6	−6
Calories	(C)–(c)	−2	−2	−2
Supplements	(S)–(s)	−1	−1	0
Standard error of response		±2.2	±2.0	±2.0
Number of patients		168	189	192

4.7 *Laboratory "relapses"*

The distribution of "relapses" among dietary regimens is presented in Table XV. None of the differences are significant. As in the first study, recurrent jaundice was never observed during convalescence.

4.8 *Other effects of treatment on laboratory tests*

The mean serum bilirubins and bromsulphalein retentions fell more promptly in the high-protein group. No dietary effects on the other laboratory tests were demonstrated.

A. *Trends of mean serum bilirubin and brom-*

TABLE XV

Second study: Occurrence of "relapses" by treatment regimen

	Number of patients	Partial "relapse" TSB* No.	Partial "relapse" BSP† No.	Partial "relapse" Total No.	Partial "relapse" Total %	Partial "relapse" P	Complete "relapse" TSB* No.	Complete "relapse" BSP† No.	Complete "relapse" Total No.	Complete "relapse" Total %	Complete "relapse" P
High protein	94	9	6	15	16		0	4	4	4	
"Normal" protein	95	8	13	21	22	.3	1	3	4	4	—
High calorie	95	11	5	16	17		1	4	5	5	
"Normal" calorie	94	6	14	20	21	.4	0	3	3	3	.5
Supplements	95	9	9	18	19		0	1	1	1	
Placebos	94	8	10	18	19	—	1	6	7	7	.06

* Total serum bilirubin only abnormality.
† Bromsulphalein retention only abnormality.

sulphalein retention. As in the first study, there were distinct differences among the dietary regimens in the curves of the mean prompt direct and total serum bilirubins during the first 2 hospital weeks (see Figure 24). In the protein comparison the difference was striking in favor of the high-protein diets and was confirmed statistically by comparing the mean changes between admission and the 11 to 14-day period (Table XVI). In addition, a significantly greater percentage of patients on the "normal"-protein diets had rises in serum bilirubin after admission (Table VIII, Appendix II). There were no differences between the high- and "normal"-calorie groups by these three criteria. Those receiving choline and vitamin supplements had slightly more rapid falls than the patients receiving placebos. This was not confirmed by significant differences between the mean falls from admission to the 11 to 14-day period, but significantly more patients receiving placebos did have rises in both total and prompt direct serum bilirubins.

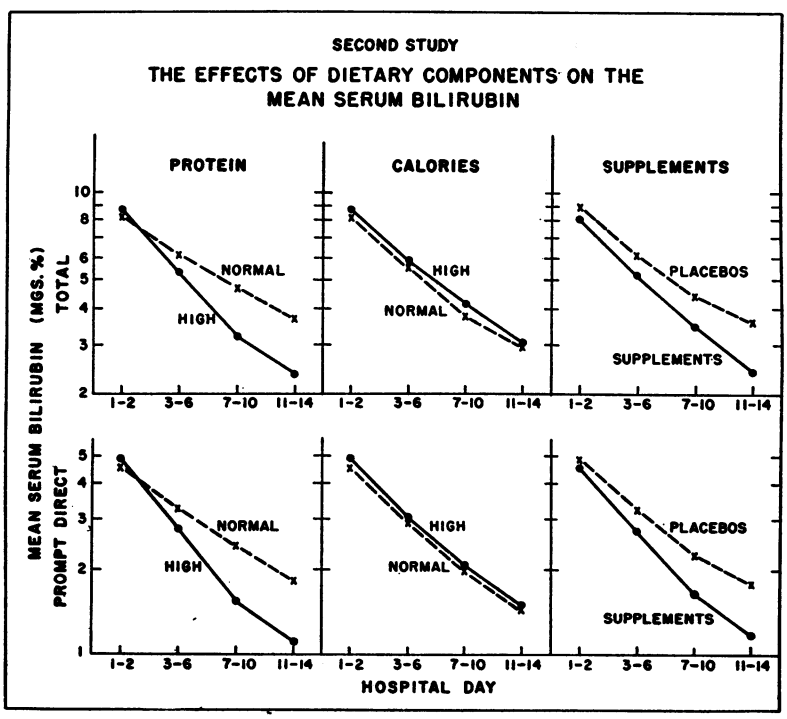

FIGURE 24

TABLE XVI

Second study: Mean fall in serum bilirubin during the first 11 to 14 days of each treatment regimen

	Protein			Calories			Supplements		
	High	"Normal"	P	High	"Normal"	P	Added	Placebos	P
Number of patients	93	92		92	93		94	91	
Total serum bilirubin									
Admission value	8.56	8.08		8.60	8.05		8.19	8.44	
Mean fall	6.37	4.63	.01	5.76	5.25	.5	5.80	5.20	.4
S.D.	4.68	4.54		4.20	5.16		4.83	4.44	
Prompt direct serum bilirubin									
Admission value	4.58	4.78		4.90	4.46		4.55	4.81	
Mean fall	3.78	2.80	.02	3.50	3.08	.3	3.43	3.14	.5
S.D.	2.87	2.64		2.56	3.00		2.80	2.80	

In the second study the bromsulphalein test was performed on admission and at weekly intervals after the total serum bilirubin reached 1.5 mg. per 100 ml. or less. The data in Table XVII show that bromsulphalein excretion also tended to improve more rapidly on the high-protein diet.

B. *Thymol turbidity, zinc turbidity, cephalin flocculation, and thymol flocculation.* Trends of the mean thymol and zinc turbidity values during the first 2 weeks did not show any differences among the dietary regimens. Comparisons of the number of patients in whom tests rose in the first 2 weeks likewise showed no difference. There were also no differences among the treatment groups in the mean values for the thymol and zinc turbidity tests on admission, at convalescence, and on discharge to duty (Table IX, Appendix II).

The percentages of patients with values above the 99 per cent upper limit of normality at the time of admission, at any time during the hospital course, at convalescence and on discharge to duty are presented in Table X, Appendix II. With the exception of a higher percentage of abnormal cephalin flocculations at the time of convalescence in the "normal"-protein group when compared to the high-protein group ($P = 0.05$), there were no differences. This one significant difference was the only one encountered out of 75 significance tests performed in this group of analyses and therefore is probably a chance occurrence.

C. *Serum cholinesterase.* Serum cholinesterase values were abnormally low on admission. The mean for all patients in the second study was 0.64 pH per hr., which is significantly different from 0.80, the mean for the 279 "normal" soldiers (S.E. of the difference = 0.02). During the hospital course the serum cholinesterase values showed a general trend to higher levels which were comparable in the several calorie and protein groups (Table XII, Appendix II).

TABLE XVII

Second study: Mean bromsulphalein retention (per cent in 45 minutes) on admission and during the two weeks after total serum bilirubin became normal

	Protein			Calories			Supplements		
	High	"Normal"	P	High	"Normal"	P	Added	Placebos	P
Number of patients	94	95		95	94		95	94	
Admission value	45.9	45.8	—	46.4	45.3	.5	46.0	44.7	.5
S.D.	13.2	13.0		12.8	13.1		13.6	15.8	
First week after normal TSB	6.6	8.3	.05	7.5	7.4	.5	7.9	7.0	.3
S.D.	5.6	5.9		6.1	5.5		6.2	5.4	
Second week after normal TSB	4.7	5.8	.1	5.0	5.6	.3	5.3	5.2	—
S.D.	3.8	5.2		4.5	4.5		4.3	4.8	

4.9 *Effects of treatment on symptoms and signs*

As discussed previously (Section 3.6) the influence of "doctor effects" on the data obtained for symptoms, liver size and tenderness, splenomegaly and spider angiomata was so great that attempts to interpret differences in these factors in terms of treatment effects seem unwarranted. Data from the second study are presented in Tables XIII and XIV, Appendix II. There are no striking differences.

The weight changes during the first 3 hospital weeks are presented in Table XIV, Appendix II. The patients on the high-calorie diets gained more weight than the "normal"-calorie group during the first 2 weeks only.

4.10 *Summary of the results of the second study*

1. Carefully collected dietary data demonstrated strict adherence to the prescribed diets.

2. Numerous checks on the method of randomization showed it to have been effective.

3. Several analyses of the effects of caloric intake, protein composition of the diet, and supplementary choline and vitamins on the duration of acute infectious hepatitis revealed the following:

a) Patients fed a high-protein diet (19 per cent protein calories) throughout their illness had a mean duration of illness 14 per cent shorter than the duration of patients fed a "normal"-protein diet (11 per cent protein calories). The probability that a difference of this size or greater might occur by chance is less than one in twenty.

b) Patients fed a high-calorie diet (4000 cal.) did not have a significantly shorter duration of illness than those fed a "normal"-calorie diet (3000 cal).

c) Patients given supplementary choline and a Multivitamin preparation did not have a shorter duration of illness than patients who were given placebos.

d) There were no demonstrable interactions among the three dietary factors.

4. Asymptomatic bromsulphalein and serum bilirubin relapses occurred in 4 per cent of the patients without any significant differences among the treatment groups.

5. There were significantly more rapid falls of both total and prompt direct serum bilirubins in the high-protein groups than in the "normal"-protein groups. Questionably more rapid falls were observed in patients receiving supplements as compared with those given placebos.

PART FIVE

THIRD STUDY: [20] THE EFFECTS OF STRENUOUS EXERCISE DURING CONVALESCENCE

5.1 *Design*

The purpose of the third study was to determine if the duration of hospitalization could safely be shortened by eliminating the 1 to 3 weeks usually necessary for patients to recuperate from the effects of strict bed rest. Half of the second study patients, all of whom had been at *ad lib.* rest, were accordingly started on strenuous physical reconditioning as soon as their total serum bilirubins reached 1.5 mg. per 100 ml. or less, and their bromsulphalein retentions were 5 per cent or less. The other half were observed in the hospital as controls. *The patients in the early exercise group developed significantly more minor abnormalities, but these were considered of little clinical importance because they disappeared while exercise was continued.*

Following admission to one of the eight treatment groups of the second study by the procedure outlined in Section 4.1, half of the patients in each dietary group were randomly assigned to each of the two exercise groups. The randomization was restricted to pairs in order to keep the two groups equal in size as the second study progressed.

All patients in the second study were transferred to the Physical Reconditioning Center (P.R.C.) at Nara, Japan, in either an "early" or a "late" group. Elective operations and dental work were not done until after the patients had completed their reconditioning program. Transfer was requested for patients in the "early" group as soon as they fulfilled the criteria for the start of convalescence (total serum bilirubin below 1.5 mg. per 100 ml. and bromsulphalein retention in 45 minutes below 5 per cent). Various administrative procedures then resulted in a delay of 1 to 7 days before actual transfer took place, the average interval being 3 days for the "early"

[20] For his help in the performance of this study the authors wish to thank Hunter A. Soper, 1st Lt., M.C., U.S.A.R.

group. Transfer was requested for the "late" group on the 8th day of convalescence and these patients were actually transferred, on the average, on the 12th day. As shown in Table XVI, Appendix II, the mean serum bilirubin levels at the time of transfer of the "early" group are significantly higher than those of the "late" group, and the latter are significantly higher than the values of the first study patients at the time of transfer. The mean serum bilirubin levels of all three groups of patients, at the start of exercise, were significantly higher than normal.

At the P.R.C. the hepatitis patients joined in the active reconditioning program designed for all patients convalescing from hospitalization in Southwest Japan. The mornings were spent attending classes and movies, engaging in various types of graduated calisthenics and reconditioning exercises, and taking part in short marches and drills in the camp area. On Mondays the subjects took a 7.5-mile, 3-hour hike over flat terrain. On Wednesdays they took a 5-mile march in 2 hours over rougher terrain, and on Fridays they were assigned a 9.5-mile road march over rugged mountain terrain to be completed in 3½ hours. On Tuesdays, Thursdays, and Saturdays, they participated in organized athletics such as basketball, volley ball, soccer, and soft ball. There were no restrictions on week-end and evening passes. Although patients were admonished not to drink alcoholic beverages, no action was taken if they chose to disregard the warnings.

Although the reconditioning program was designed to allow increasing activity from the beginning to the end of each week, many of the patients were transferred at the middle or end of the week, and thus engaged in the more strenuous exercise immediately. Patients in the "early" group were kept at the P.R.C. for a total of 2 weeks so that they might be under observation the same length of time as the "late" group transferred approximately a week later. Between convalescence and transfer to the P.R.C. those in the "late" group were allowed *ad lib.* activity throughout the hospital.

Patients were seen twice a week by one of the authors or by a doctor of the P.R.C. staff. A brief history and physical examination were performed and the same observations made as described in Section 2.4. The bromsulphalein test was done weekly and blood for other liver function tests was drawn twice a week. The tests were performed in the same laboratory (Kyoto) as were those of the first and second studies. The resulting data were analyzed with respect to three time periods as follows:

Period I: The week immediately preceding convalescence, including three semi-weekly days on which clinical or laboratory observations were made.

Period II: The first week of exercise at the P.R.C. for the "early" group and the last week in the hospital before transfer for the "late" group. For most patients there were two observations in this period.

Period III: The second week of strenuous exercise for the "early" group and the first week at the P.R.C. for the "late" group.

5.2 *Elimination of patients from the study*

Although 192 patients were included in the original randomization as performed on admission to the second study, 10 patients have been excluded from the third study analyses for the following reasons: Three patients (one in the "early" group, two in the "late") were demonstrated after admission not to have infectious hepatitis. Three patients still had abnormal bromsulphalein tests 120 days after admission (all in the "early" group) and were sent to limited duty without physical reconditioning. Four patients in the "early" exercise group, because of an administrative oversight, were transferred more than 1 week after convalescence. In addition, in the "late" group, the transfers of three patients were delayed more than 1 week by oversight and four patients were transferred late because they developed partial or complete relapses in the hospital. These seven patients are included in the analyses of the period II data but are left out of the over-all laboratory curves and period III analyses. Thus, in comparisons involving periods I and II as defined above, there were 88 patients in the "early" group and 94 in the "late." In the period III analyses there were 88 in the "early" group and 87 in the "late."

5.3 *Effectiveness of the randomization*

The randomization was not as effective as in the first and second studies. This is probably at-

tributable both to the original restriction of the randomization to pairs and to the larger number of patients removed from the study after assignment to a treatment regimen. For 3 of the 25 variables examined (see Table VI, Appendix II) there was a significant difference between the two groups. The "early" group had a higher mean bromsulphalein retention and fewer positive thymol flocculations on admission than the "late" group. Although not significant, the admission total serum bilirubin was also higher in the "early" group (8.95 mg. per 100 ml. compared wtih 7.96 mg. per 100 ml.). These results suggest that, by chance, the "early" group included sicker patients at the time of admission to the second study, and this impression is confirmed by the fact that their average duration of illness was 34 days as compared with 28 days for the "late" group ($P = 0.02$). However, as illustrated in Figures 25 and 26, the mean serum bilirubins and bromsulphalein retentions were essentially the same for the two groups at the start of the convalescent period.

5.4 *Effects of physical reconditioning on clinical and laboratory findings*

It was the opinion of the medical officers in charge of the reconditioning program that the hepatitis patients had relatively fewer complaints than those patients convalescing from battle wounds, epidemic hemorrhagic fever, or other illnesses. Nevertheless, there were some differences among the hepatitis patients with respect to the distributions of changes in symptoms and liver size, as shown in Table XVIII. During period II symptoms appeared more often in the "early" group undergoing exercise then in the "late" patients who remained in the hospital. Of the 10 patients in the "early" group who developed symptoms during their first week at the P.R.C., 3 had mild anorexia only, 2 had mild malaise when active but were asymptomatic at rest, 4 complained of mild epigastric distress on exertion, and 1 had both mild pain and malaise. The proportion of patients in whom previous symptoms disappeared

TABLE XVIII

Third study: Changes in symptoms, liver size (by 2 cm. or more), total serum bilirubin (by 0.25 mg. per 100 ml.), prompt direct serum bilirubin (by 0.05 mg. per 100 ml.), and bromsulphalein retention (by 1 per cent or more)

	Period II*			Period III†		
	"Early"	"Late"	P	"Early"	"Late"	P
Number of patients	88	94		88	87	
Symptoms						
Appeared	10	1		14	10	
No change	66	79	.02	68	74	.4
Disappeared	12	14		6	3	
Liver size						
Increase	7	2		7	13	
No change	48	67	.05	68	52	.06
Decrease	33	25		13	22	
Total serum bilirubin						
Increase	19	2		3	13	
No change	58	62	.001	57	59	.01
Decrease	11	30		28	15	
Prompt direct serum bilirubin						
Increase	4	2		3	11	
No change	28	15	.05	36	43	.001
Decrease	56	77		49	33	
Bromsulphalein retention						
Increase	18	4		22	32	
No change	27	35	.01	24	30	.05
Decrease	43	55		42	25	

* At the end of period II the "early" group had exercised for one week and the "late" group had remained in the hospital as controls.

† At the end of period III the "early" group had exercised for two weeks and the "late" group had exercised for one week.

during period II was about the same in the two groups. During period III in which both groups were at the P.R.C., the pattern of changes in symptoms was about the same for the two groups and all new symptoms were benign.

Table XVIII also shows a significant difference between the distributions of change in liver size for the two groups during period II. There were more decreases as well as increases in liver size in the "early" group with fewer patients showing no change. In only one of the seven patients in the "early" group who had increases in liver size was the increase greater than 2 cm. In period III the differences were not significant although the "late" group, then in their first week of reconditioning, tended to show more fluctuations in liver size. *No patient in either group developed tenderness of the liver during reconditioning.*

It seems likely that some of the changes in symptoms and liver size after transfer to the P.R.C. reflect differences among observers, but no data are available to test this assumption.

Complete laboratory "relapses," defined by the consecutive occurrence of at least two abnormal bromsulphalein or total serum bilirubin tests, were observed in 4 per cent of the patients. This rate was similar to that found in the first study (7 per cent) in which the patients started physical reconditioning an average of 19 days later in their course. No patient in either the "early" or "late" group developed recurrent hepatitis with jaundice during or shortly after the period of reconditioning. Two patients in the "early" group and five in the "late" group had asymptomatic bromsulphalein "relapses," but two of the latter occurred before the start of strenuous exercise. Sixteen per cent of the "early" group and only 4 per cent of the "late" had one total serum bilirubin determination above normal after the start of convalescence ($P = 0.02$). The incidence of partial bromsulphalein "relapses" was approximately the same for each group, 9 per cent and 12 per cent, respectively.

Graphs of the changes in mean total and prompt direct serum bilirubin and bromsulphalein retention are shown in Figures 25 and 26, in which the two vertical lines separate the three time periods defined in Section 5.1. There was a distinct

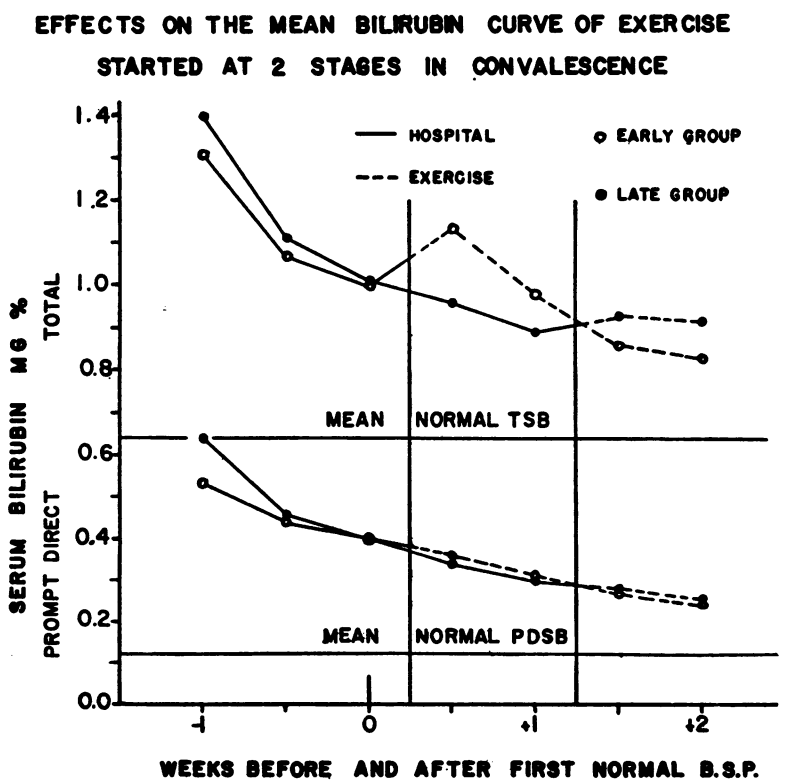

FIGURE 25

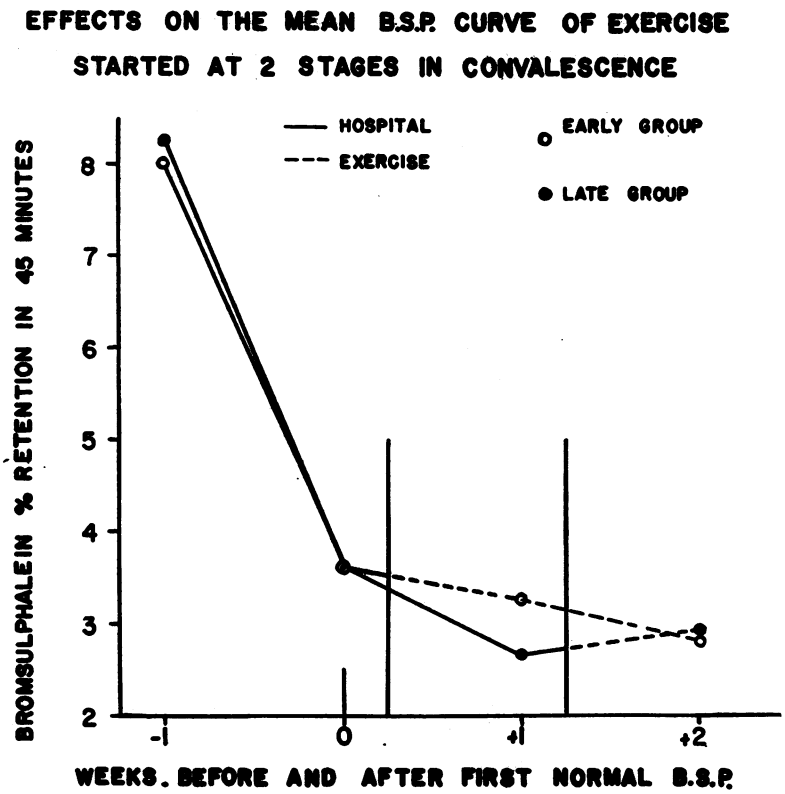

FIGURE 26

bounce in the mean total serum bilirubin shortly after the "early" group started active exercise in period II, and a much smaller bounce for the "late" group in period III. There were slight changes in the same direction in the prompt direct bilirubin, and bromsulphalein retention declined more slowly in the "early" group during period II. Note that the bounces in the "early" group were transient and that the tests resumed their downward trend during period II while strenuous exercise was continued. The thymol and zinc turbidity tests and the thymol and cephalin flocculations were not affected by exercise.

The statistical significance of these distinct but small changes in laboratory tests is indicated in Table XVIII. During period II the "early" group had more increases and fewer decreases in serum bilirubin level and bromsulphalein retention than did the "late" group, while in period III the converse was true.

The general tendency for tests which rose at the onset of strenuous exercise to return to lower levels while exercise was continued is illustrated in Figure 27. In none of the 14 patients whose total serum bilirubins rose above 1.5 mg. per 100 ml. after the start of exercise was there any rise above normal (5 per cent) in bromsulphalein retention. In the time between the start of exercise and the elevated total serum bilirubin, five patients had decreases in liver size of 2 cm. or more, three had increases, and six were unchanged. None of these 14 patients had symptoms or liver tenderness. All of them continued in the reconditioning program for 2 weeks and were then discharged to duty.

5.5 *Summary*

The effects of 2 weeks of strenuous physical reconditioning were observed in 88 patients early in their convalescence from acute infectious hepatitis. This group of patients, when compared with a control group kept in the hospital, showed distinct bounces in total serum bilirubin and bromsulphalein retention, as well as the appearance of minor symptoms and some non-tender hepatomegaly during the first week of reconditioning.

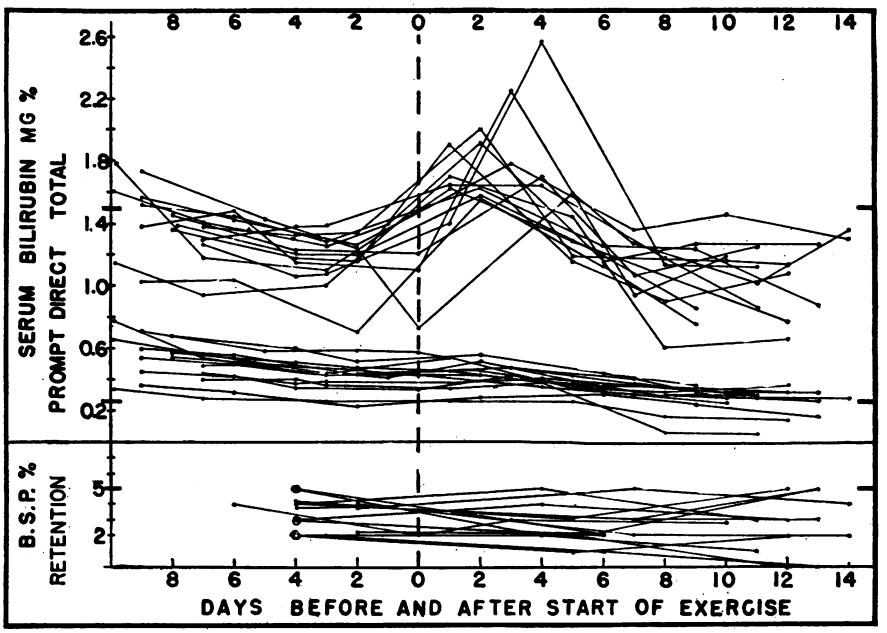

FIG. 27. CHANGES IN THE SERUM BILIRUBIN AND BROMSULPHALEIN TESTS OF THE 14 PATIENTS IN THE "EARLY" EXERCISE GROUP WHOSE TOTAL SERUM BILIRUBIN ROSE ABOVE NORMAL

Although statistically significant, these changes were not considered to be of clinical importance because they were small, they usually disappeared during the second week of reconditioning, they were seldom combined in the same patient, and they were not associated with unequivocal residual abnormalities in the follow-up study.

There was thus no evidence in this controlled study that strenuous exercise early in convalescence had precipitated a clinical relapse of infectious hepatitis.

PART SIX

FOURTH STUDY: FOLLOW-UP

6.1 *Design*

One of the principal arguments cited in favor of strict and prolonged rest in bed in the treatment of hepatitis has been a purported increased occurrence of disability among patients allowed out of bed "too soon." For this reason it was considered especially important to perform an adequate follow-up study to determine the effects of treatment on the later health of the patients. The following principles guided its design and execution: 1) Rather than attempt to obtain some information of varying completeness and accuracy about all of the patients in the studies, a random sample was selected and a vigorous attempt was made to contact every patient selected, no matter what his location. 2) It was assumed that the patients examined would be a representative sample and that extraneous factors and events in the interval between discharge and follow-up would be by chance equally distributed among the treatment groups. 3) Whenever possible patients were examined by one of the doctors who took part in the original studies and blood sera were sent to one laboratory for examination. 4) Conclusions were based on the incidence of significant interval illness and on the prevalence of abnormalities at the time of examination. *The only significant findings were an increased occurrence of abnormalities among the patients treated in the second study with a high protein, high carbohydrate diet.*

6.2 *Location and examination of patients*

One hundred patients (25 "blocks" of 4) were selected by means of a table of random numbers from the first study and 88 patients (11 "replicates" of 8) from the second study. Thus each

treatment group was equally represented in the follow-up study.

The addresses of the 188 patients were obtained by letters to the nearest relatives; 105 answered the first letter, 54 a second, and 8 more answered a third letter, making a total of 167 responses (89 per cent). Addresses of the remaining 21 patients were obtained from the Adjutant General's office.

One hundred forty patients (74 per cent) were examined by three of the former study ward doctors (J. G. C., N. D., and R. W. R.) on trips throughout the United States. Frozen serum specimens for liver function tests were sent to the follow-up laboratory in Boston. Forty-eight patients still in military service were examined at their Army posts; ninety-two had been separated from service and were seen at local hospitals, in doctors' offices, or at their homes. Although occasional civilian patients were found only after extensive inquiries at local post offices and corner drug stores, none refused to cooperate once located.

Twenty-nine patients (15 per cent) who would not have returned to the United States before the estimated closing date of the study were examined by one of the authors in Sasebo, Japan, or in Korea. These 29 patients were part of a group of 147 examined in Sasebo and compared with 460 "normal" soldiers rotating home from Korea (Section 6.8). Four patients had been reassigned to Europe before they could be found and were examined at the Army Hepatitis Center in Germany. To avoid the expense of a final circuitous trip throughout the country at the end of the study, it was arranged to have 10 patients examined by the staffs of various Army Hospitals and sera sent in the frozen state to the laboratory in Boston.

Data were incomplete on seven patients (4 per cent). The serum specimens from three patients seen in Korea were lost in transit to the laboratory in Sasebo. Three other patients refused a bromsulphalein test, and one test was unsatisfactory because of extravascular infiltration during the injection. Data from these seven are presented when available, but have been omitted from the final abnormality classifications.

A total of five patients (3 per cent) were not seen. One is somewhere in California; one is working as a merchant seaman; three were missed in the Far East and did not rotate home until after the study was completed.

TABLE XIX

Distribution of patients according to treatment group and location of follow-up examination

Treatment group†	Examined by research team: USA	Examined by research team: Japan or Korea	Examined by others	Not seen	Total selected for follow-up	Total seen
A. First study						
DR	20	3	1	1	25	24
Dr	21	1	3		25	25
dR	18 (1*)	2	4 (1*)	1	25	24
dr	21	1	2	1	25	24
Total	80	7	10	3	100	97
B. Second study						
Cps	11				11	11
CpS	6	4 (1*)		1	11	10
CPs	4	7 (2*)			11	11
CPS	7	3		1	11	10
cps	8	2	1		11	11
cpS	9 (1*)	1	1		11	11
cPs	7	3 (1*)	1		11	11
cPS	8	2	1		11	11
Total	60	22	4	2	88	86
Total for both studies	140 (2*)	29 (4*)	14 (1*)	5	188	183

* Numbers in parentheses refer to patients in whom data were incomplete.
† Capital letter indicates forced or high level treatment group, small letter the *ad lib.* or low level of treatment. D = diet; R = rest; C = carbohydrate; P = protein; S = supplements.

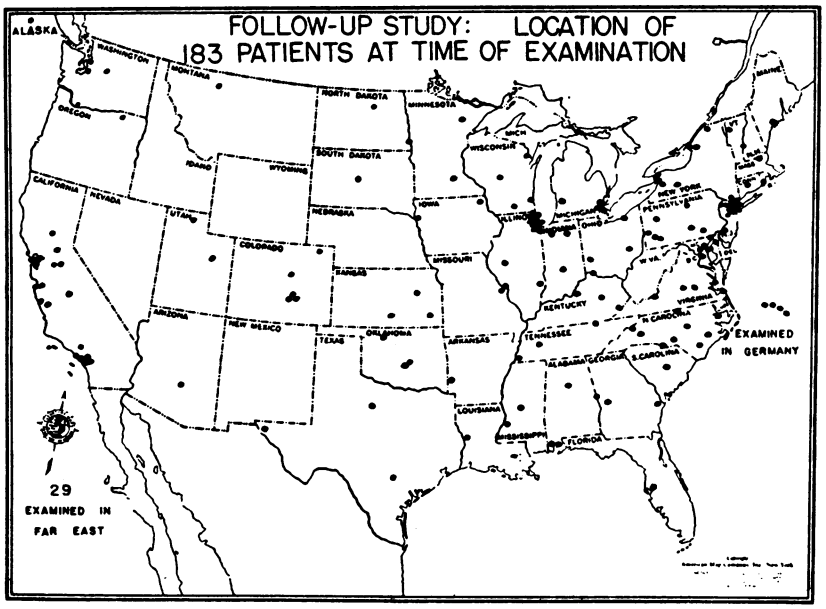

FIGURE 28

Outline map reprinted by permission of the American Map Company, Inc., New York.

Thus some information was obtained on 183 (97 per cent) of the 188 patients in the random sample, and complete information with reliable laboratory data on 176 (94 per cent). The distribution of the above patients by treatment groups is presented in Table XIX. The widely scattered geographic distribution of the patients at the time of examination is illustrated in Figure 28.

TABLE XX

Definition of the point system for classification of abnormalities found in the follow-up examinations

Finding	Severity	Point score
Symptoms: (anorexia, nausea, vomiting, malaise, liver pain)	No symptoms, or one mild symptom	0
	One moderate symptom and/or two or more mild symptoms	1
	Two or more symptoms of moderate or greater severity	2
Signs:		
Liver size	Not palpable or felt less than 3 cm. below right costal margin (corrected for location of upper border)	0
	Palpable 3 to 5 cm. below costal margin	1
	Palpable 6 cm. or more below costal margin	2
Liver tenderness	Tender to palpation or fist percussion	1
Spider angiomata	More than one	1
Spleen size	Any palpable enlargement	1
Laboratory tests:		
Bromsulphalein retention	More than 5% in 45 minutes	2
Total serum bilirubin	Above 1.08 mg./100 ml. (Far East)	
	Above 1.50 mg./100 ml. (U. S. A.)	2
Prompt direct serum bilirubin	Above 0.19 mg./100 ml. (Far East)	
	Above 0.26 mg./100 ml. (U. S. A.)	2
Thymol turbidity	Above 5.5 Shank-Hoagland units (Far East)	
	Above 6.5 Shank-Hoagland units (U. S. A.)	1
Cephalin flocculation	More than 2+ in 24 hours	1
Thymol flocculation	More than 2+ in 24 hours	1
Maximum points obtainable by one patient		16

6.3 *Criteria of abnormality*

Since the syndromes of "chronic" and "recurrent" hepatitis are ill-defined entities, specific and arbitrary criteria of abnormality had to be defined before analysis of the follow-up data. In order to make the evaluations of abnormality as reproducible as possible, a point system of scoring was evolved. The relative weights given to the abnormal symptoms, signs and liver function tests were based on the authors' ideas about the clinical importance of each (Table XX).

The definitions of abnormal liver function tests were based on the 99 per cent upper limit of normality derived from the Kyoto series of 279 and the Sasebo series of 460 "normal" soldiers (Table I, Text and Appendix II). The former group of normals were the reference group for the patients examined in the United States, and the latter for the 29 examined in Sasebo. There is no apparent explanation for the slight differences between the two series of normals.

6.4 *Effectiveness of the randomization*

The effectiveness of the method of random sampling used for this study was tested by comparing the follow-up sample with the remainder of the patients with respect to the mean values of three quantitative variables—age on admission to the hospital in Kyoto, total serum bilirubin on admission, and duration of acute illness from admission to convalescence (Table XVII, Appendix II). Unfortunately, there were significant departures from randomness in the samples drawn from each of the original studies. For each discrepancy, however, the sample was either older than the remainder, or the patients were more severely ill during the acute course, or both. Hence, any bias introduced by the sampling procedure might be expected to increase the likelihood of residual disability in the sample, rather than to lead to underestimation of the occurrence of abnormalities. Within the sample the treatment groups were reasonably comparable with respect to point scores at the time of discharge to duty. The average scores of 1 and 2 points (see Table XVII, Appendix II) reflect the fact that the majority of patients in these studies were allowed to return to duty with a variety of minor abnormalities. In fact, 16 per cent of the follow-up sample from the first study and 14 per cent of the second study sample had point scores of 3 or more at the time of discharge.

6.5 *The interval between discharge and the follow-up examination*

For the sample of 95 patients from the first study on whom complete follow-up data were obtained, the interval between discharge from the study and follow-up examination ranged from 7 to 18 months with an average of 12 months. For the sample of 81 second study patients the interval varied from 2 to 16 months with an average of 8 months. Within each sample the average intervals were similar for the several treatment groups, as shown in Table XVII, Appendix II.

During the interval, 38 (22 per cent) of the 176 patients with complete follow-up information were hospitalized for more than 1 day (Table XVIII, Appendix II). In only 19 of these patients was the loss of time from duty or work associated with gastrointestinal or abdominal complaints and in only nine did it seem at all likely that the "disability" might have been related to the previous hepatitis. Attempts were made to obtain the medical and hospital records for these nine instances of interval illness, and eight records or abstracts were received. In four of the eight patients no evidence of residual or recurrent hepatitis had been found during hospitalization. The remaining four patients had been found to have physical and/or laboratory abnormalities which suggested recurrent or chronic hepatitis, but in no instance was there definite evidence for a diagnosis of "infectious hepatitis with jaundice." Interval disability attributable to the patients' hepatitis was so rare, therefore, that its occurrence could not be used to compare the treatment regimens.

6.6 *Comparisons of treatment groups at the time of follow-up examinations*

A) *Specific abnormalities.* The individual abnormalities listed in Table XIX, Appendix II, occur more commonly among the *ad lib.* rest group in the first study but this difference is less striking when the abnormalities are graded according to clinical importance in Table XXI below. The dietary treatment groups in the first study are similar.

TABLE XXI

Comparison of treatment regimens with respect to abnormalities existing at the time of follow-up examinations *

A. First study

Status on follow-up	Point score	Treatment regimen: Diet — Forced No.	Forced %	*Ad lib.* No.	*Ad lib.* %	P	Rest — Strict No.	Strict %	*Ad lib.* No.	*Ad lib.* %	P
Normal	0	26	53	23	50		28	61	21	43	
Equivocal	1 or 2	16	33	16	35	.9	12	26	20	41	.2
Abnormal	3 or above	7	14	7	15		6	13	8	16	
Total patients		49		46			46		49		

B. Second and third studies

Status on follow-up	Point score	Therapeutic regimens: Protein — High No.	High %	"Normal" No.	"Normal" %	P	Calories — High No.	High %	"Normal" No.	"Normal" %	P
Normal	0	17	42	28	68		24	62	21	50	
Equivocal	1 or 2	18	45	12	29	.04	10	26	20	48	.05
Abnormal	3 or above	5	13	1	3		5	12	1	2	
Total patients		40		41			39		42		

Status on follow-up	Point score	Supplements — Added No.	Added %	Placebos No.	Placebos %	P	Exercise — "Early" No.	"Early" %	"Late" No.	"Late" %	P
Normal	0	19	48	26	63		22	55	23	56	
Equivocal	1 or 2	17	42	13	32	.3	14	35	16	39	.7
Abnormal	3 or above	4	2	2	5		4	10	2	5	
Total patients		40		41			40		41		

C. Comparison of first and second studies

Status on follow-up	Point score	First study No.	First study %	Second study No.	Second study %	P
Normal	0	49	52	45	56	
Equivocal	1 or 2	32	34	30	37	.3
Abnormal	3 or above	14	15	6	7	
Total patients		95		81		

D. Ward comparison—second study

Status on follow-up	Point score	High pro. High cal.	High pro. "Normal" cal.	"Normal" pro. High cal.	"Normal" pro. "Normal" cal.
Normal	0	6	11	18	10
Equivocal	1 or 2	9	9	1	11
Abnormal	3 or above	4	1	1	0
Total patients		19	21	20	21

* Data complete on 176 of the 188 patients selected for follow-up.

In the sample of patients from the second and third studies there was a tendency for those in the high-protein, high-calorie treatment group (CP) to present more abnormal findings for most of the measurements, but the individual differences were not large. The patients who had received vitamin and choline supplements were similar to those who had been given placebos. Among patients from

the "early" reconditioning group there were eight instances of liver tenderness while the "late" group had none, but these two groups were similar with respect to all of the other variables. The second study patients, all treated with *ad lib.* rest, had a slightly lower prevalence of abnormalities than the patients of the first study.

B) *Abnormalities by point scores.* Arbitrarily, those patients with no abnormality points were designated "normal," those with 1 or 2 points "equivocal," and those with 3 or more points "abnormal." Comparisons among treatment groups have been made for the percentage distributions of patients in these three categories and "chi-square" tests of significance have been applied with the results shown in Table XXI. There were no significant differences among the treatment groups in the first study. In the second study the high-protein regimen produced significantly more equivocal and abnormal patients than the "normal"-protein diets, while the high-calorie diets tended to yield more abnormals than the "normal"-calorie groups. The table of ward comparisons demonstrates that these differences were largely due to the poor showing of a single ward (CP) on which the high-protein, high-calorie diets were served. The third study comparison of "early" and "late" reconditioning groups did not demonstrate any striking differences. A comparison of the first and second studies showed no significant differences.

6.7 *Results of additional follow-up examinations*

Eleven patients were hospitalized in the United States for further investigation of abnormalities found in the follow-up examination in either the Far East or the United States. Ten of them were sent to Walter Reed Army Hospital and one to the Veterans Administration Hospital in Phoenix, Arizona.

All but one of the patients had improved by the time they were admitted for study, the interval between the routine follow-up examination and

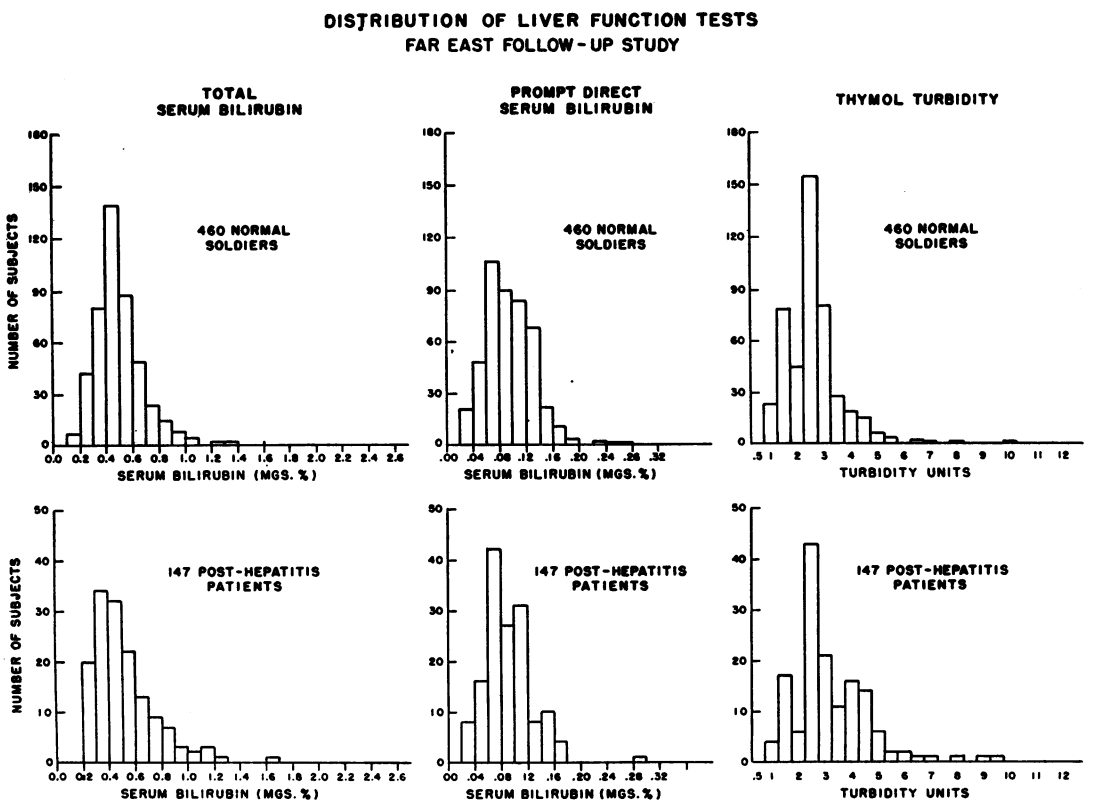

FIG. 29. COMPARISON OF LIVER FUNCTION TESTS IN 147 FORMER HEPATITIS PATIENTS ROTATING HOME FROM KOREA THROUGH SASEBO, JAPAN, AND 460 "NORMAL" SOLDIERS

TABLE XXII

Physical findings of 147 post-hepatitis patients compared with 460 "normal" soldiers

	Post-hepatitis		"Normal" controls		P
	Number	%	Number	%	
Liver not palpable	102	69	405	88	
1–2 cm.	20	14	27	6	
3–5 cm.	22 } 25	15 } 17	25 } 28	5 } 6	<.001
>5 cm.	3 }	2 }	3 }	1 }	
Liver tenderness	15	10	2	0.5	.01
Spleen palpable	2	1	5	1	—
Spider angiomata	13	8	10	2.5	.02

subsequent hospitalization varying from 1 to 3 months. Eight of the 11 patients had liver biopsies; the livers of seven were essentially normal and changes consistent with "chronic active hepatitis" were noted in one. Discharge diagnoses were "no liver disease" in eight of the patients, "inactive hepatitis" in two, and "chronic hepatitis" in one.

Since many of the factors which led to the hospitalization of these particular patients were beyond the control of the research team, these results are not intended for use in the interpretation of the effects of previous therapy on the occurrence of residual abnormalities. However, these supplementary hospital studies certainly suggest that the arbitrarily defined "abnormalities" found in the follow-up study may have little clinical significance.

6.8 *Comparisons of post-hepatitis patients with "normal" soldiers*

Because of the possibility that sufficient of the randomly selected patients could not be found in the follow-up study outlined above, facilities were set up to examine former patients as they rotated through Sasebo, Japan, on their way back to the United States. Since the selection of patients examined did not depend on chance alone, the results could not be used to assess the efficacy of the various treatments. The former patients, however, could be compared with rotating soldiers who had not had hepatitis during their stay in the Far East.

TABLE XXIII

Distributions of urine urobilinogen in 115 post-hepatitis patients and 50 "normal" soldiers

Ehrlich units *per hour*	Post-hepatitis		"Normals"	
	Number	%	Number	%
0.10–0.29	14	12	4	8
0.30–0.49	39	34	11	22
0.50–0.69	33	29	20	40
0.70–0.89	11	10	7	14
0.90–1.09	8	7	6	12
1.10–1.29	2	2	0	0
1.30–1.49	2	2	2	4
1.50–1.69	3	3	0	0
1.70–1.89	2	2	0	0
>1.89	1	1	0	0
Total patients	115		50	

One hundred and forty-seven of the former patients and 460 "normals" were examined in Sasebo by one of the authors (C. W. S.). Liver function tests were carried out by one of the former Hepatitis Center technicians.[21] The 2-hour uro-

[21] Thanks are due Dr. Noriaki Wakizaka for performing the laboratory determinations.

TABLE XXIV

Distributions of cephalin and thymol flocculation tests in 147 post-hepatitis patients and 460 "normal" soldiers

	Cephalin flocculation					Thymol flocculation				
	Post-hepatitis		"Normals"			Post-hepatitis		"Normals"		
	Number	%	Number	%		Number	%	Number	%	
0	134	91	413	90	0	119	81	410	89	
1+	10	7	43	9	1+	22	15	34	7	
2+	2	2	3	1	2+	4	3	14	3	
3+	1	1	0	0	3+	2	1	2	—	
4+	0	0	1	—	4+	0	0	0	0	
Total	147		460			147		460		

TABLE XXV

Comparisons of the means of liver function tests in the 147 post-hepatitis patients and 460 "normal" soldiers

Test	Post-hepatitis patients	"Normal" soldiers
Serum bilirubin—*mg./100 ml.*		
Total	0.51	0.50
Prompt direct	0.09	0.09
Thymol turbidity		
Shank-Hoagland units	3.0	2.5
Urine urobilinogen*		
Ehrlich units per hour	0.62	0.63

* This test was done on only 115 post-hepatitis patients and 50 "normal" soldiers.

bilinogen test (30) was added to the tests previously performed. The patients were examined from 2 to 15 months after discharge from the hospital (mean 8 months). Eighty per cent had been discharged more than 6 months previously.

Thirty-one of the 147 patients (21 per cent) complained of various combinations of anorexia, nausea, vomiting, malaise, fatigue, and pain. Symptoms at the time of the examination of the "normal" patients were not recorded, but it seems likely that they had fewer complaints than the hepatitis patients. Physical signs (Table XXII) were more common in the post-hepatitis group, the most striking difference being the frequency of hepatic tenderness. Liver function tests in the two groups are compared in Figure 29 and in Tables XXIII, XXIV and XXV. The distributions and means of the total and prompt direct serum bilirubin, cephalin flocculation and thymol flocculation, thymol turbidity and urine urobilinogen were quite similar for the post-hepatitis and "normal" groups.

6.9 *Summary*

1. One hundred and eighty-eight patients were selected at random from the original group of 450 for follow-up examinations. Ninety-seven per cent, or 183 of the patients, were examined and complete information was obtained on 94 per cent (176 patients).

2. Approximately 5 per cent of the sample, equally distributed among the treatment groups, lost more than one day from duty or work because of complaints which were possibly attributable to hepatitis, but no case of recurrent jaundice was seen.

3. The patients on the *ad lib.* rest regimen had more individual abnormalities than those on strict bed rest, but when these were graded according to clinical importance, the difference was not significant.

4. There was no difference between the patients treated with the forced high-protein and *ad lib.* diets in the first study. Those patients in the second study from the high-protein, high-calorie ward showed more equivocal and distinct abnormalities than the patients from the other three wards.

5. Subsequent hospitalization of 11 "abnormal" patients showed all but one to be essentially normal.

6. One hundred and forty-seven former patients were compared with 460 "normal" controls as they rotated through Sasebo, Japan, on their way back to the United States. The patients showed an increased frequency of symptoms, hepatomegaly, liver tenderness and spider angiomata, but the distributions of liver function tests were the same as in the controls.

PART SEVEN

RETROSPECTIVE ANALYSES OF THE EFFECTS OF REST AND DIET

The results presented in Parts Three and Four are those of controlled experiments in which the patients were assigned to treatment groups at random and the general plan of analysis was decided before the results were available. During the conduct of these controlled studies, numerous subsidiary data were gathered in the expectation that their analyses might further elucidate any treatment effects demonstrated. This section is concerned with retrospective studies suggested by the data or by the conclusions of others. The patients have been grouped for analysis not at random before the start, but systematically and "after the fact." Therefore, the results should be looked upon as suggestive rather than conclusive, and of limited value from the standpoint of probability statements. ***The results are generally negative and in no way qualify the conclusions drawn from the first and second studies.***

TABLE XXVI

First study: Relation of rest effects to the duration of symptoms before admission and the height of the total serum bilirubin on admission

	Strict bed rest			*Ad lib.* rest		
	Number of patients	Mean adm. TSB	Mean duration of illness	Number of patients	Mean adm. TSB	Mean duration of illness
Symptoms 10 days or less	71	7.7	30	73	7.9	26
Symptoms 11 to 21 days	55	7.7	32	54	8.6	28
Admission TSB 1 to 6.9 mg./100 ml.	70	4.1	23	58	3.8	20
Admission TSB 7 to 12.9 mg./100 ml.	39	10.0	37	48	9.6	31
Admission TSB 13+ mg./100 ml.	17	17.8	42	21	17.8	45

7.1 *Relation of the stage and severity of illness to the effects of rest*

The belief that strict bed rest should be continued after the patient with acute hepatitis no longer desires to stay in bed is so firmly entrenched in current medical practice that the failure to confirm it in the first study warrants some further inspection of the data. To investigate whether enforced bed rest might still be essential early in the course of the disease the patients were divided into two approximately equal groups: those with any symptoms for 10 days or less before admission and those who had been sick for from 11 to 21 days. The data presented in Table XXVI reveal that the *ad lib.* rest patients had a shorter duration of illness in the hospital irregardless of how long they had been sick before admission. When the patients were divided according to the severity of illness as represented by the total serum bilirubin on admission (Table XXVI) the *ad lib.* rest groups had shorter durations in the low and medium bilirubin ranges, but slightly longer durations in the high ranges. None of these differences is significant.

7.2 *The effects of pre-hospitalization activity on the duration of subsequent illness*

An attempt was made to record on admission to the hospital each patient's activity on each day of his illness before admission. The number of days in which the patient's activity was more than one-third his usual activity, from the onset of symptoms and from the onset of jaundice to hospitalization, were then plotted in scattergrams against the duration of the acute illness in the hospital. No suggestive correlations were apparent.

7.3 *Relation of the stage and severity of the illness to the effects of diet*

An early dietary effect was demonstrated in both of the present studies by the fact that the trends of the mean serum bilirubins began to diverge within 3 to 4 days of the start of treatment (Figures 10 and 26). This early effect was further illustrated by the fact that the *ad lib.* and "normal"-protein groups each had significantly more patients whose serum bilirubins rose after admission to the hospital. Thus, in the two studies there were 35 patients on the *ad lib.* and "normal"-protein regimens with rising bilirubin levels and only eight on the forced and high-protein diets (see Table VIII, Appendix II). In 27 (63 per cent) of these 43 patients, the total serum bilirubin had risen 1 mg. per 100 ml. or more by 4 days after admission, and in 37 (86 per cent) the rise was apparent by the end of the first week. If one therefore assumes that the difference in percentage of patients with rising serum bilirubins is a distinct treatment effect rather than chance occurrence, and this seems likely in view of the fact that a difference of equal magnitude and direction was found in both studies, then one must also assume that the dietary effect takes place, at least in part, in the first week of treatment, or during the acute stage in which the serum bilirubin may still be rising.

To investigate further the relationship between the observed dietary effects and the stage of illness in which treatment was started, the patients in

TABLE XXVII

Relation of dietary treatment effects to duration of symptoms before admission

	First study			Second study		
	Forced diet	*Ad lib.* diet	Per cent shortening of illness by forced diet	High protein diet	"Normal" protein diet	Per cent shortening of illness by high protein diet
Symptoms 10 days or less:						
Number of patients	69	75		47	51	
Mean admission TSB	7.2	8.4		8.5	8.1	
Mean duration of illness	24	31	23	28	35	20
Symptoms 11 to 21 days:						
Number of patients	59	50		47	44	
Mean admission TSB	9.0	7.1		8.8	8.2	
Mean duration of illness	28	34	18	30	34	12

each study were divided into two groups, those who had symptoms for 10 days or less before admission and those who had been sick from 11 to 21 days. The data are presented in Table XXVII. The overall duration of illness does not differ in those sick a short or a long time before admission. In both studies, however, the dietary effect is slightly greater in those admitted to the study early in the course of their illness.

To determine whether the treatment effect might vary according to the height of the admission total serum bilirubin, the patients were divided into three groups, those with low, moderate, and high admission levels (Table XXVIII). In both studies the treatment effect was greatest in the middle range of bilirubin levels. It was least apparent at the high bilirubin levels, but the number of patients in this group was small.

For practical purposes the severity of the illness might also be judged by the magnitude of the patient's complaints and the degree of hepatomegaly on admission. The results of analyses of dietary treatment effects in the second study with respect to these criteria of severity are presented in Table XXIX. Since both measurements are susceptible to "doctor effects" (see Sections 3.1 and 5.1), the patients on each ward were ranked according to severity of symptoms and liver size and then divided at the middle rank into two groups designated as "severe" and "mild." The patients with the more severe symptoms and larger livers did have higher admission bilirubin

TABLE XXVIII

Relation of dietary treatment effects to the total serum bilirubin on admission

	First study			Second study		
	Forced diet	*Ad lib.* diet	Per cent shortening of illness by forced diet	High protein diet	"Normal" protein diet	Per cent shortening of illness by high protein diet
Admission TSB (1 to 6.9 mg./100 ml.)						
Number of patients	64	64		44	50	
Mean admission TSB	3.8	4.1		—	—	
Mean duration of illness	19	25	24	24	28	14
Admission TSB (7 to 12.9 mg./100 ml.)						
Number of patients	42	45		32	27	
Mean admission TSB	9.4	10.0		—	—	
Mean duration of illness	28	39	28	29	40	28
Admission TSB (13+mg./100 ml.)						
Number of patients	22	16		18	18	
Mean admission TSB	18.4	17.0		—	—	
Mean duration of illness	43	44	2	43	49	12

TABLE XXIX

Second study: Relation of dietary treatment effects to the severity of symptoms and size of the liver on admission

	High protein diet			"Normal" protein diet			Per cent shortening of illness by high protein diet
	Number of patients	Mean adm. TSB	Mean duration of illness	Number of patients	Mean adm. TSB	Mean duration of illness	
"Severe" symptoms*	46	9.4	31	47	8.9	38	18
"Mild" symptoms	48	8.0	27	48	7.5	30	10
"Severe" hepatomegaly*	48	9.3	31	48	8.5	36	14
"Mild" hepatomegaly	46	8.0	28	47	7.9	32	12

* To avoid the influence of "doctor effects," the patients on each ward were ranked according to symptoms and liver size and then divided at the middle ranks.

levels and slightly longer acute illnesses. The protein effect was the same regardless of the severity of the illness.

From the standpoint of severity of illness on admission the six patients on the forced-fed wards who required tube feedings were entirely similar to the nine patients on the *ad lib.* wards whose intake in the first 4 hospital days was less than 2,000 calories or 70 grams of protein. Yet the mean durations of illness of each group were respectively 33 and 51 days. Although the numbers involved are small, the figures suggest that the severely anorectic patients on the forced-diet wards might have had more prolonged illnesses if they had not been tube fed.

It should be pointed out, however, that none of the patients in these studies were in the precoma or comatose stages in which the *deleterious* effects of a high-protein diet on the central nervous system—in cirrhosis of the liver—have been demonstrated (31).

PART EIGHT

GENERAL SUMMARY, DISCUSSION, AND RECOMMENDATIONS

8.1 *Rest effects*

A. *Summary of results*

1. Patients hospitalized with acute infectious hepatitis improved as rapidly when allowed to be up and about their wards at will as did patients kept at strictly enforced bed rest.

2. Asymptomatic laboratory relapses occurred early in convalescence with equal frequency for both groups of patients.

3. There was no evidence that *ad lib.* ambulation was detrimental irrespective of the stage or severity of the patients' illness.

4. Patients started on an active physical reconditioning program early in convalescence had increases in symptoms, signs and laboratory tests of small degree and transient nature. Since they disappeared as exercise continued, they were not considered of clinical importance.

5. The incidence of chronic disability and significant residual abnormalities observed in a follow-up study was no greater for patients permitted *ad lib.* ambulation and started on strenuous physical rehabilitation early in convalescence than it was for patients treated in the more conventional conservative manner.

B. *Discussion of results*

The conclusion drawn from these studies that it is entirely unnecessary to enforce bed rest in the treatment of acute infectious hepatitis is at variance with the great majority of interpretations of previous data expressed in the literature (1, 2, 5, 28, 32). It is important, therefore, to discuss possible explanations for this discrepancy.

It does not seem plausible that the results of the present study are statistical artefacts. The study was well controlled, except for the fact that "ward and doctor effects" could not be completely excluded. There was no evidence that the strict bed rest patients were by chance more severely ill. The doctor who decided on the eligibility of a patient for admission to the study had no knowledge of the treatment he would receive until after he was admitted. Numerous randomization checks revealed the groups to be similar with respect to many variables other than the treatments.

Although as always in infectious hepatitis the variability in duration of the acute disease was large, so was the number of patients included in this study, and the "confidence limits" make it extremely unlikely that a clinically important difference in favor of strict bed rest would be observed on repetitions of the study under similar circumstances. Careful follow-up studies of the patients in the hospital, at the physical reconditioning center, in Japan at the time of their rotation to the United States, and after their return have revealed no evidence that the patients treated with *ad lib.* rest have had an increased incidence of significant residual abnormalities. Long-term effects must remain for the time being a matter for conjecture, but there is no suggestion in follow-up data now available on World War II patients (33) that long-term residuals will be common enough to reverse the present conclusion that strict bed rest is no longer necessary.

The lack of effectiveness of strict bed rest noted in this study did not appear to be due to significantly different clinical material or a milder form of the disease than reported in other epidemics. To illustrate this fact data from descriptions of epidemics of infectious hepatitis among military personnel in post-war Germany, and during World War II in the United States, Great Britain, Italy, and the Middle East (1–3, 34–36) are presented in Table XX, Appendix II. As might be expected, there was considerable variation in the manner in which the data were handled in each of these reports, and some liberties have been taken in the tabulation to make them as comparable as possible. Symptoms were essentially the same in all with the exception that in post-war Germany the onset has been appreciably more insidious. Within the limits of the different standards of measurement and methods of handling the patients, the duration of jaundice and hospitalization were similar in all of these epidemics. Certainly by these criteria the patients in the present studies were no less sick. To obtain quantitative data comparable to that of the present study, the laboratory records of 100 randomly selected patients[22] who had hepatitis in post-war Germany were reviewed. The admission total serum bilirubins and the duration from admission to a bilirubin of 1.5 mg. per 100 ml. or less are compared in Table XXX with 253 first study patients. The differences in the mean initial serum bilirubins and the durations of jaundice are not striking. It seems unlikely, therefore, that any such small differences between epidemics in comparable populations could result in a need for enforced bed rest in one group and not in the other.

The only striking difference between the present series of patients and those studied during World War II lies in the incidence of relapses. Return of jaundice within 2 or 3 months after it had once disappeared was never seen in the present study and occurred in 5 per cent or more of the patients studied in Great Britain (34) and Italy (1). This plus the fact that the precipitation of relapses by exercise early in convalescence was not observed in the present studies, as contrasted with the series in Italy (1), suggests that the epidemic behavior of infectious hepatitis may have changed since World War II. Another possible explanation for the relatively high incidence of relapses with jaundice during World War II may be that anorectic patients were occasionally treated with intravenous plasma which may have contained the virus of homologous serum jaundice. In addition, the transmission of the hepatitis viruses by

[22] The authors wish to thank Dr. W. P. Havens, Jr. for supplying these records.

TABLE XXX

Comparison of hepatitis patients in post-war Germany with first study patients

	Number of patients	Mean duration of illness before admission *days*	Mean admission TSB *mg. per 100 ml.*	Duration to first normal TSB*	
				Mean *days*	S.D. *days*
Japan and Korea (first study)	253	10	8.1	23	15
Germany	100	14	7.4	27	16

* 1.5 mg. per 100 ml. or less.

syringes and needles had not then been clearly demonstrated. Thus some of the relapses may have been reinfections with a different strain of virus.

Two other possibly important differences may be conjectured. First, more of the World War II patients may have had homologous serum jaundice and it is conceivable, although improbable, that in this disease bed rest is more effective than it is in infectious hepatitis. Finally, the patients in some World War II epidemics were probably more fatigued and less well fed when they acquired their hepatitis than the patients in the present studies. However, McFarlan (37) could demonstrate no relation between fatigue and diet before onset and the severity of the disease among British troops in World War II, and retrospective analyses of the present data revealed none.

If the conclusions of the present study are accepted, and the patient material and disease are not too different from that reported by others, a re-examination of the data on which the concept of strict bed rest has been based is indicated. Only two "controlled" studies are available for comparison (1, 5, 7), and in both of these studies the patients on bed rest who had a shorter duration of acute illness also received a high-protein diet, whereas patients on a modified rest program received an *ad lib.* diet. Thus the entire effect may have been due to diet.

In a retrospective study (2) interpreted as emphasizing the importance of bed rest, the total duration of illness for patients entering the hospital less than 30 days after onset was distinctly shorter than for those who were hospitalized after 30 days or more of illness. The patients were Navy personnel who were transferred to one hospital as soon as a diagnosis of hepatitis was made, and delays in transfer were attributed to delays in reaching port or difficulties in establishing the diagnosis. Since the pre-admission regimen was assumed to be one of *ad lib.* rest and all patients were kept strictly in bed after admission, it was concluded that restriction of activity early in the illness had appreciably shortened the duration. An equally plausible explanation for the difference has nothing to do with restriction of activity. It seems probable that the original group of patients, who could not be transferred early for various reasons, included some who recovered within 30 days and therefore never were transferred. Thus the group of late transfers may well have been overloaded with patients who were destined to have prolonged illnesses irrespective of how they were treated.

Another type of retrospective observation on which a great deal of emphasis has been placed is exemplified by a case report (1) of a patient whose icteric index was approximately 25 on admission, fell to normal during 3 weeks of bed rest, and rose to 70 after 2 weeks of exercise about the ward. Such time-related events may lead to useful hypotheses to be tested in controlled studies, but by themselves are not sufficient evidence for a cause and effect relationship.

Recently two "controlled" experiments from the Army Hepatitis Center in Germany have suggested that, at least in the type of patient material encountered there, rest did not have to be as prolonged as heretofore thought necessary. In the first (3), patients were exercised mildly and cautiously at all stages in the disease and adverse effects were encountered only in those with total serum bilirubins above 3 mg. per 100 ml. In the second (4), the effects of physical reconditioning in patients with persistent bromsulphalein retentions between 5 per cent and 10 per cent were compared with the effects in patients with less than 5 per cent retention, and no differences were found. It was suggested that mild elevation of the bromsulphalein test in the presence of a total serum bilirubin of 1.0 mg. per 100 ml. or under should not be a contraindication to the start of ambulation. No one, however, has previously suggested that bed rest should be *ad lib.* throughout the illness.

It should be emphasized that the ambulatory patients in the present studies were never forced to stay out of bed or to perform any labor, and were confined to their hospital wards. *The study offers no evidence, therefore, that rest is not advantageous when the patient feels sick.* It is still probable that enforced activity during the acute phase of hepatitis, as in any infectious disease, will make the patient feel worse, and may possibly prolong the disease. It should also be emphasized that the regimen of *ad lib.* rest was not instituted until an average of 10 days after the onset of symptoms, 7 days after the onset of dark urine and 4 days after first hospitalization. The data in Table

XXVI, however, suggest that the time of starting treatment is not an important factor.

The third study satisfactorily demonstrated that patients who have been at *ad lib.* rest throughout their acute illness may be returned with safety to their normal activity as soon as their total bilirubins have been 1.5 mg. per 100 ml. or less for 1 week and their bromsulphalein retention 5 per cent or less. Exercise started at this time did not result in an increased incidence of relapses or residual disability. That this regimen of *ad lib.* rest in bed and earlier return to duty results in a substantial saving in the duration of hospitalization is illustrated by the following data: The average duration of hospitalization of all patients transferred to the physical reconditioning center in the first study was *56 days;* in the second study the 94 patients in the early reconditioning group were discharged after *34 days.* Thus, disregarding any potential dietary savings, 22 days were eliminated from the duration of hospitalization. Part of this saving in time may be attributed to the elimination of all possible administrative delays and the postponement of elective minor surgery and dental work until reconditioning had begun. The greatest saving, however, resulted from the elimination of the physical disability that results from prolonged rest in bed.

8.2 *Diet effects*

A. *Summary of results*

1. In the first study, patients forced to eat a diet supplying an abundance of calories, protein and vitamins throughout hospitalization improved more rapidly than did those patients who ate only as much as they chose of a regular hospital diet.

2. In the second study it was observed that the duration of hepatitis was shorter for those patients forced to eat a high-protein diet (19 per cent protein calories) than for those who consumed the "normal"-protein diet (11 per cent protein calories). The duration of illness was similar for patients eating 3000 and 4000 calories, and for those who received supplemental choline and vitamins and those who did not.

3. Asymptomatic laboratory relapses occurred with equal frequency irrespective of the composition of the diets.

4. During the first 2 weeks of treatment, there was a more rapid decline of the serum bilirubin in the forced-diet groups of the first study, and in the high-protein groups of the second study.

5. Although first study patients (forced and *ad lib.*) were similar when seen in follow-up, second study patients who received the high-protein and high-calorie diet showed a slightly higher incidence of mild residual abnormalities.

B. *Discussion of results*

The 22 per cent reduction in the duration of the acute disease by the forced diet noted in the first study was highly significant. This indicates that repetitions of the study would almost certainly yield similar dietary results. From the clinical standpoint, however, this reduction is not very impressive when compared with the effects of more specific therapy in other infectious diseases. In civilian medicine the potential saving of a week on the average, in the absence of any evidence for the prevention of death or chronicity, might not be worth the extra trouble of forcing the patient to eat. From the military standpoint, however, an average saving of 1 week during an epidemic period when thousands of cases occur each year represents a substantial saving in man power and expense.

The second study was designed, in part, to gain some information as to whether the absolute amount of protein or percentage of protein calories was more important. The variability in duration of illness encountered in the second study was so large in relation to the number of patients available that this problem could not be specifically solved. But a reorientation of results from the second study supplied some evidence for discussion. Table XXXI shows that there was a linear decrease in duration of the disease as the amount of protein in the diet was increased. Although this comparison was not included in the original design of the study and disregards caloric levels, it does suggest that actual content of protein was important in shortening the duration of illness. On the other hand, as shown in Table XI, the protein effect was the same at both caloric levels, indicating the effect of percentage composition of the diet. The question cannot therefore be answered by the data of this study.

The smaller dietary effects encountered in the

TABLE XXXI

Second study: Relation of protein content of diet to duration of illness

		Number of patients	Protein content		Calories	Mean duration of illness
			grams	% of calories		
High calorie, high protein	(CP)	42	190	19	4,000	28
"Normal" calorie, high protein	(cP)	42	140	19	3,000	30
High calorie, "normal" protein	(Cp)	42	110	11	4,000	33
"Normal" calorie, "normal" protein	(cp)	42	80	11	3,000	35

second study than in the first, and the differences in follow-up findings, make desirable an examination of other differences between the two studies. Data presented in Table V, Appendix II, suggest that the patient material differed in the two studies. The mean duration of symptoms and of jaundice before admission were slightly longer in the second study, although the duration of hospitalization elsewhere was the same. In spite of the fact that they were admitted somewhat later in their course, significantly more of the patients in the second study complained on admission of malaise, nausea, and vomiting. The mean prompt direct serum bilirubin on admission was significantly higher in the second study. Conversely, the mean thymol and zinc turbidities were lower, as were the percentages of patients with positive cephalin and thymol flocculations. During the period of the second study fewer patients became ill while in active combat, there were fewer instances suggestive of "point epidemics" in combat units than in the first study, and the admission rate at the Hepatitis Center was lower. Perhaps related to these changes the variability of durations of illness was somewhat greater in the second study than in the first. However, the duration of illness in the hospital was about the same in both studies, the overall geometric means being 25 days in the first study and 27 days in the second.

Since dietary intakes of patients in the second study were restricted to narrow ranges, the high-level diets differed from the forced diet in the first study in that the minimum levels were higher and there were no patients eating more than the prescribed amounts. The "normal" diets were unlike the *ad lib.* diet in the first study in that there were no patients eating less than 2700 calories or 70 grams of protein, and there were no excessive intakes. Thus the dietary intakes were different enough to make a comparison of the effects in the two studies unwarranted.

Whatever the reasons for these differences between the two studies and whatever their influence on the treatment effects, the fact remains that the effect of the high-protein diet on the duration of illness in the second study was not very much better than that of the "normal"-protein diet, and even that advantage must be qualified by the results of the follow-up study.

The beneficial results arising from the forced feeding of a diet rich in protein which were demonstrated so conclusively in these studies are difficult to reconcile with studies recently reported by Leone and his co-workers (38). These workers have obtained some evidence from observations on prisoner volunteers participating in studies of viral hepatitis that a high-protein, low-fat diet started within a few days of the onset of symptoms may increase the severity and prolong the duration of illness. There are several obvious differences between the dietary study on prisoners and the present studies, one or more of which might contribute to the divergent results. It seems unlikely, in view of the data presented in Tables XXVIII, XXIX, and XXX, that the differences in the conclusions of the two studies can be explained by the factors of time of starting treatment and the severity of illness. The possibility of differences due to the type of virus or to the fat content [23] of the special diets of Leone may warrant further investigation.

[23] In a series too small for statistical validity, Hoagland, Labby, Kunkel, and Shank (6) found that 15 patients on a high-protein, low-fat diet had an acute illness averaging 8 days longer than an equivalent number on a high-protein, high-fat diet.

8.3 *Recommendations*

When the results of the above studies and those of Leone, and his co-workers (38) were presented to the Committee on Hepatitis of the Commission on Liver Disease of the Armed Forces Epidemiological Board, recommendations were drawn up for revision of the treatment of acute infectious hepatitis in the Armed Forces. The following recommendations were therefore sent by the Epidemiological Board to The Surgeon Generals of the Armed Forces:

The following recommendations for the treatment of acute infectious hepatitis are general principles and may require modification for individual patients under particular circumstances. They embody a distinct change in the presently accepted rest regimen and little or no change in dietary treatment. They are based on the conclusions of a carefully controlled study of enlisted military personnel (age range, 17 to 45, median 21) with acute infectious hepatitis. Their applicability to the more severe forms of the disease in older or less well nourished patients has not been established.

Since physical activity to the point of fatigue may be harmful, patients with acute hepatitis should be hospitalized as soon as the diagnosis is made. They should be urged to rest in bed as long as acute symptoms persist. Once they begin to feel well, regardless of the degree of jaundice, they should not be forced to stay in bed more than 1 hour after each meal. Restriction to the hospital ward, however, is essential to decrease undue activity or exertion. Allowing *ad lib.* activity on the ward (without any required exertion) circumvents the usual delay necessary for recuperation from the effects of prolonged rest in bed and appreciably shortens the period of hospitalization.

Patients so treated may be discharged from the hospital and physical reconditioning may be undertaken after the total serum bilirubin concentration (Ducci and Watson (17)) is below 1.5 mg. per 100 ml. and the bromsulphalein retention in 45 minutes below 6 per cent for a period of not less than 1 week. Patients whose bromsulphalein retention stabilizes between 5 and 10 per cent may be discharged from the hospital with safety. Those with persistently higher levels will require individual management.

Following discharge from the hospital it is well to follow all patients for 2 weeks with weekly physical examinations, serum bilirubins and bromsulphalein tests. Recurrent abnormalities will occur rarely and are probably indications for rehospitalization.

The optimal diet in the treatment of infectious hepatitis consists of about 3000 calories containing approximately 150 grams each of protein and fat. Intakes above this level should be *ad lib.* Although fried and greasy foods may cause indigestion, the fat contained in meat, eggs, and dairy products is not harmful and adds greatly to the palatability of the diet. During the stage of severe anorexia the patient should be urged to take frequent small feedings. Intravenous glucose solutions should be administered when necessary to maintain a minimal caloric fluid intake. Although the forcing of a high-protein, high-fat diet, by stomach tube if necessary, has been demonstrated to hasten recovery on the average, critically ill patients with fulminating disease or impending hepatic coma may be harmed by excess dietary protein. In these few patients, therefore, it is probably unwise to administer more than a maintenance quantity of protein.

Intravenous protein hydrolysates, plasma or blood transfusions have no place in the nutritional therapy of patients with uncomplicated infectious hepatitis.

APPENDIX ONE

Summary of Statistical Methods[24] *Used in Basic Analyses of the First and Second Studies*

A. First study

1. ***Experimental design.*** The first study was designed as a 2×2 factorial experiment in randomized blocks. Two treatment factors, diet and rest, were each represented at two levels, *"ad lib."* and "forced." Blocks of four patients each were formed from patients admitted to the hospital at about the same time, and each block comprised a complete replicate of the four treatment combinations. Duration of illness from hospital admission to convalescence was chosen as the primary measure of treatment effects.

2. ***Preliminary estimation of the size of the experiment.*** Retrospective observations on clinical records at the

[24] This summary is intended for those readers who are familiar with the applications of the theory and techniques of "analysis of variance" in biological experiments.

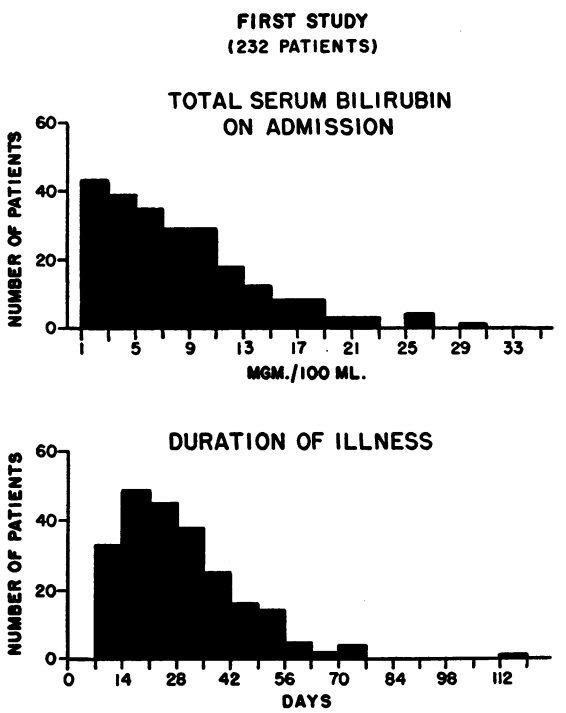

FIGURE 1 (Appendix I)

Hepatitis Center in Kyoto (see Sec. 1.2) provided information which was essential to the planning of the controlled studies. The records of 80 patients, who satisfied the criteria for admission to the first study (Sec. 2.1), were used to estimate the variability in duration of illness. This group had a mean duration of illness of 34 days and a standard deviation of ± 16 days, hence a coefficient of variation of 47 per cent. These preliminary data also demonstrated a reasonably linear relationship between the total serum bilirubin on admission and the duration of hospitalization, with a correlation coefficient of about + 0.6. By using this correlation in an analysis of covariance, it was expected that the coefficient of variation for duration of illness might be reduced to about 38 per cent.

Because of the varied clinical impressions of the investigators and others about the effects on duration of illness to be expected from the treatments under study, it seemed desirable to avoid fallacious acceptance of a null hypothesis if, in fact, a "real" treatment effect of 7 days or more might exist. Therefore, the sensitivity of the experiment was planned to detect such an effect as significant at the 5 per cent level with a Type II error of 5 per cent or less. To achieve this sensitivity in the face of the variability described above, it was estimated that at least 50 replicates or 200 patients would be required.

3. *Analyses of covariance.* Frequency distributions of the independent variable (x), admission total serum bilirubin, and the dependent variable (y), duration of illness in days, are shown in Figure 1. The analysis of covariance for these data is presented in Table I. In this analysis the differences among the regression coefficients in the "block × treatment" interaction terms were not significant. Hence, an average regression coefficient of + 1.850 was used for estimating the reduced error mean square. However, the three independent components of error variance, *i.e.*, the "block × treatment" interactions, differed significantly after reduction for regression, according to Bartlett's test (39) for homogeneity of vari-

Table I, Appendix I

First Study: Analysis of Covariance (Duration of Illness in Days)

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio		$\bar{r}$*	b†
		$[x^2]$	$[xy]$	$[y^2]$	Sum of Squares	Degrees of Freedom	Mean Square	F	P		
Total	231	6928.36	11811.00	54775.50							
Blocks	57	2304.40	3547.30	12577.00	7244.14	57	127.09				
Treatments	3	42.96	- 210.02	2209.81	3115.62	3	1038.54	7.26	<.001		
Diet	1	10.35	- 147.00	2088.00	2661.23	1	2661.23	18.61	<.001		
Rest	1	21.48	- 41.99	82.09	309.51	1	309.51	2.16	.10		
Diet x Rest	1	11.12	- 21.02	39.72	155.17	1	155.17	1.08			
Error	171	4581.00	8473.72	39988.69	24314.41	170	143.03			+ 0.63	1.850
Block x Diet	57	1794.00	3708.45	13455.50	5789.60	56	103.39			+ 0.76	2.067
Block x Rest	57	1461.53	2396.74	10988.41	7068.02	56	126.21			+ 0.60	1.640
Block x Diet x Rest	57	1325.47	2368.52	15534.78	11302.40	56	201.83			+ 0.52	1.787
Deviations from Individual Regressions					24160.02	168	143.81				
Differences among Individual Regressions					154.39	2	77.19				
Reduction due to Average Regression					15674.28	1	15674.28	109.59	<001		
Non-additivity					687.90	1	687.90	4.92	<05		
Remainder					23626.51	169	139.80				

* Correlation coefficient
† Regression coefficient

Table II, Appendix I

First Study: Analysis of Covariance (Duration of Illness in Log Days)

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio		r*	b†
		$[x^2]$	$[xy]$	$[y^2]$	Sum of Squares	Degrees of Freedom	Mean Square	F	P		
Total	231	6928.356	178.440	12.197							
Blocks	57	2304.401	54.977	2.762	1.474	57	0.026				
Treatments	3	42.957	- 3.817	0.609	0.848	3	0.283	9.09	<.001		
Diet	1	10.349	- 2.372	0.544	0.682	1	0.682	21.91	<.001		
Rest	1	21.484	- 1.032	0.050	0.123	1	0.123	3.95	<.05		
Diet x Rest	1	11.123	- 0.414	0.015	0.047	1	0.047	1.51	>.20		
Error	171	4580.998	127.280	8.826	5.290	170	0.031			+0.63	0.028
Block x Diet	57	1793.996	54.128	3.164	1.531	56	0.027			+0.72	0.030
Block x Rest	57	1461.531	37.627	2.396	1.427	56	0.025			+0.64	0.026
Block x Diet x Rest	57	1325.472	35.525	3.267	2.314	56	0.041			+0.54	0.027
Deviations from Individual Regressions					5.272	168	0.031				
Differences among Individual Regressions					0.018	2	0.009				
Reduction due to Average Regression					3.536	1	3.536	113.64	<.001		
Non-additivity					0.019	1	0.019				
Remainder					5.271	169	0.031				

* Correlation coefficient
† Regression coefficient

Table III, Appendix I

First Study: Treatment Comparisons with Separate Components of Error

A. Duration of Illness in Days

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio	
		$[x^2]$	$[xy]$	$[y^2]$	Sum of Squares	Degrees of Freedom	Mean Square	F	P
Blocks x Diet	57	1794.00	3708.45	13455.50	5789.60	56	103.39		
Diet					2724.25	1	2724.25	26.35	<.001
Blocks x Rest	57	1461.53	2396.74	10998.41	7068.02	56	126.21		
Rest					273.57	1	273.57	2.17	>.10
Blocks x Diet x Rest	57	1325.47	2368.52	15534.78	11302.40	56	201.83		
Diet x Rest					149.12	1	149.12		

B. Duration of Illness in Log Days

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio	
		$[x^2]$	$[xy]$	$[y^2]$	Sum of Squares	Degrees of Freedom	Mean Square	F	P
Blocks x Diet	57	1793.996	54.128	3.164	1.531	56	0.027		
Diet					0.692	1	0.692	25.33	<.001
Blocks x Rest	57	1461.531	37.627	2.396	1.427	56	0.025		
Rest					0.115	1	0.115	4.52	<.05
Blocks x Diet x Rest	57	1325.472	35.525	3.267	2.314	56	0.041		
Diet x Rest					0.045	1	0.045	1.09	>.20

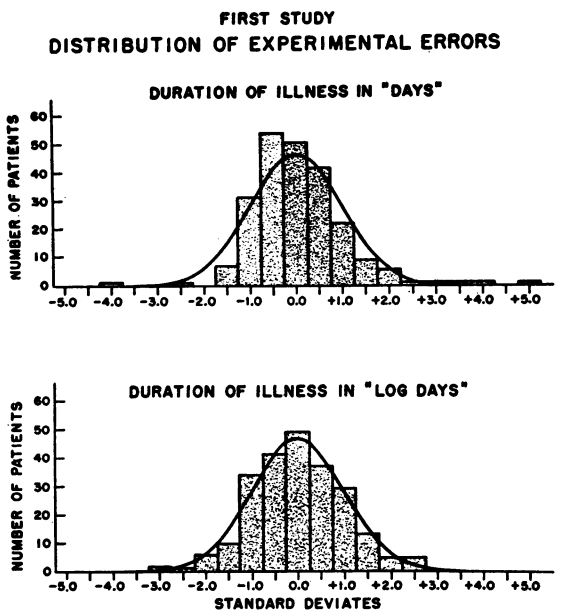

FIGURE 2 (Appendix I)

ances. Rather than use a pooled estimate of error variance for tests of significance of the treatment effects, as done in Table I, it is more appropriate in the face of heterogeneous errors to test each treatment effect against its corresponding subdivision of error variance, as is done in Table IIIA. In the present case, both procedures give similar results, although the latter test is less precise.

The discovery of error heterogeneity led to further investigation of the data with respect to the three basic assumptions involved in the "analysis of variance" under infinite models. (An infinite model is essential in the present instance because of the use of "covariance.")

a) Homogeneity of error variance—heterogeneity is present in these data by Bartlett's criterion.
b) Additivity of block and treatment effects—Tukey's test (40) for non-additivity was significant at the 5 per cent level.
c) Normal distribution of residual errors—the upper histogram in Figure 2 shows the distribution of residual errors measured in days' duration of illness with best fitting normal curve superimposed. A chi-square test for "goodness of fit" demonstrated significant departure from normality, the observed distribution being leptokurtic and positively skew.

The failure of data from the first study to satisfy the assumptions implicit in the mathematical model on which the tests of significance are based led to a change in metameter for the dependent variable from "days" to "log days." The effect of the transformation on the distribution of adjusted durations of illness is shown in Figure 3, and the effect on the distribution of residual errors is shown in Figure 2. The latter distribution on the transformed scale does not depart significantly from normal. The corresponding analysis of covariance is displayed in Table II, in which the subdivisions of error variance are now homogeneous and the test for non-additivity is not significant. There is a distinct "clinical" justification for the transformation to log days. Since any reduction in duration of illness might be proportional to the total duration, a constant percentage reduction seems more applicable than a fixed absolute reduction.

4. *Sensitivity of the experiment.* The Type II error in the first study was found to be approximately 0.01 for a Type I error of 0.05, as estimated by the use of Tang's "Tables of the Power Function of Analysis of Variance" (41).

B. Second study

1. *Experimental design.* The second study was designed as a $2 \times 2 \times 2$ factorial experiment in randomized blocks with the three-factor interaction completely confounded with blocks. Three dietary factors—total calories, percentage protein calories, and supplementary choline and vitamins—were each represented at two levels. Admission procedure and measurements of treatment effects were similar to those used in the first study.

2. *Preliminary estimate of the size of the experiment.* Estimates of variability obtained from the first study were used to predict the number of replicates required to detect a 20 per cent reduction in duration of illness with a Type I error of 0.05 and Type II error of not more than 0.05.

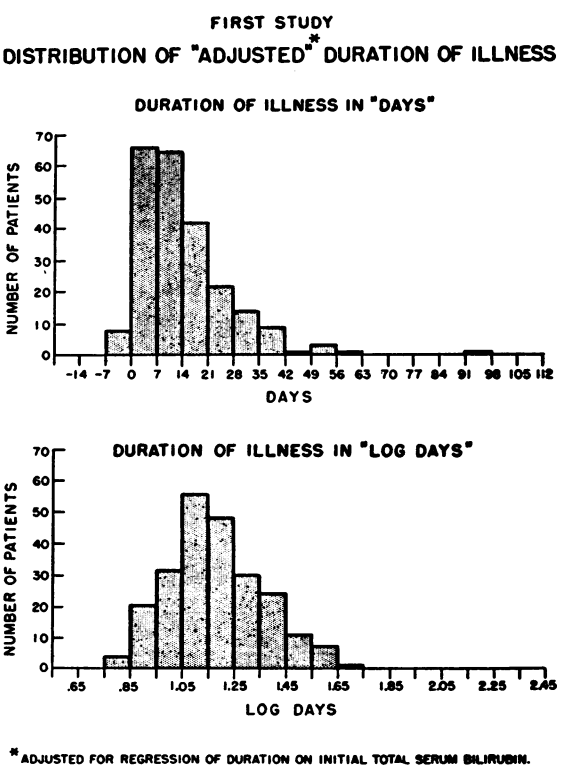

FIGURE 3 (Appendix I)

Table IV, Appendix I

Second Study: Analysis of Covariance (Duration of Illness in Days)

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio		r*	b′
		[x²]	[xy]	[y²]	Sum of Squares	Degrees of Freedom	Mean Square	F	P		
Total	167	5078.14	7788.54	45849.12							
Blocks	41	1105.80	1883.19	12410.12							
Replicates	20	593.04	1062.39	6181.12	4303.59	20	215.18				
Cal x Pro x Supp	1	15.42	83.02	446.88	227.47	1	227.47				
Rep x Cal x Pro x Supp	20	497.33	737.78	5782.12	4687.63	19	246.72				
Treatments	6	193.38	278.31	2069.57	1669.49	6	278.25				
Calories	1	20.37	-19.50	18.67	121.25	1	121.25				
Protein	1	3.07	67.83	1500.02	1303.76	1	1303.76	6.75	<.05		
Supplements	1	4.90	21.87	97.52	43.22	1	43.22				
Cal x Pro	1	52.93	96.55	176.10	5.86	1	5.86				
Cal x Supp	1	59.40	127.25	272.60	24.95	1	24.95				
Pro x Supp	1	52.71	-15.68	4.67	165.92	1	165.92				
Error	120	3778.96	5627.04	31369.43	22990.52	119	193.20			+0.52	1.489
Blocks A x Cal	20	514.31	559.05	3297.00	2689.31	19	141.54			+0.43	1.087
Blocks B x Cal	20	704.09	1386.88	5856.67	3124.86	19	164.47			+0.68	1.973
Blocks A x Pro	20	603.14	1246.70	7047.24	4470.30	19	235.28			+0.60	2.067
Blocks B x Pro	20	501.10	711.77	4655.14	3644.12	19	191.80			+0.47	1.420
Blocks A x Supp	20	431.97	346.58	4827.14	4549.07	19	239.42			+0.24	0.802
Blocks B x Supp	20	1024.36	1376.06	5686.24	3837.72	19	201.99			+0.58	1.343
Deviations from Individual Regressions					22315.40	114	195.75				
Differences among Individual Regressions					675.12	5	135.02				
Reduction due to Average Regression					8378.91	1	8378.91	43.37	<.001		

* Correlation coefficient

′ Regression coefficient

Table V, Appendix I

Second Study: Analysis of Covariance (Duration of Illness in Log Days)

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio		r*	b′
		[x²]	[xy]	[y²]	Sum of Squares	Degrees of Freedom	Mean Square	F	P		
Total	167	5078.140	113.973	8.512							
Blocks	41	1105.797	29.846	2.204							
Replicates	20	593.041	17.618	1.296	0.787	20	0.039	1.26	>.20		
Cal x Pro x Supp	1	15.421	1.073	0.075	0.033	1	0.033	1.06	>.20		
Rep x Cal x Pro x Supp	20	497.335	11.155	0.834	0.584	19	0.031				
Treatments	6	193.384	2.939	0.320	0.283	6	0.047				
Calories	1	20.371	-0.286	0.004	0.026	1	0.026				
Protein	1	3.067	0.800	0.209	0.176	1	0.176	4.92	<.05		
Supplements	1	4.903	-0.020	0.000	0.003	1	0.003				
Cal x Pro	1	52.931	1.033	0.020	0.000	1	0.000				
Cal x Supp	1	59.405	2.141	0.077	0.012	1	0.012				
Pro x Supp	1	52.707	-0.728	0.010	0.065	1	0.065	1.82	>.10		
Error	120	3778.958	81.189	5.988	4.244	119	0.036			+0.54	0.021
Blocks A x Cal	20	514.307	8.506	0.558	0.417	19	0.022			+0.50	0.017
Blocks B x Cal	20	704.093	18.859	1.067	0.562	19	0.030			+0.69	0.027
Blocks A x Pro	20	603.138	17.375	1.446	0.945	19	0.050			+0.59	0.029
Blocks B x Pro	20	501.097	9.182	0.750	0.581	19	0.031			+0.46	0.018
Blocks A x Supp	20	431.966	7.499	1.105	0.975	19	0.051			+0.33	0.017
Blocks B x Supp	20	1024.357	19.768	1.062	0.681	19	0.036			+0.60	0.019
Deviations from Individual Regressions					4.162	114	0.037				
Differences among Individual Regressions					0.082	5	0.016				
Reduction due to Average Regression					1.744	1	1.744	48.91	<.001		

* Correlation coefficient

′ Regression coefficient

Table VI, Appendix I

Second Study: Treatment Comparisons with Separate Components of Error

A. Duration of Illness in Days

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio	
		$[x^2]$	$[xy]$	$[y^2]$	Sum of Squares	Degrees of Freedom	Mean Square	F	P
Blocks x Cal	40	1218.40	1945.93	9153.67	6045.77	39	155.02		
Calories					130.73	1	130.73		
Pro x Supp					181.36	1	181.36	1.17	>.20
Blocks x Pro	40	1104.24	1958.47	11702.38	8228.85	39	211.00		
Protein					1265.55	1	1265.55	6.00	<.05
Cal x Supp					7.66	1	7.66		
Blocks x Supp	40	1456.32	1722.64	10513.38	8475.75	39	217.33		
Supplements					52.48	1	52.48		
Cal x Pro					20.99	1	20.99		

B. Duration of Illness in Log Days

Source of Variation	Degrees of Freedom	Sum of Squares and Products			Error of Estimate			Variance Ratio	
		$[x^2]$	$[xy]$	$[y^2]$	Sum of Squares	Degrees of Freedom	Mean Square	F	P
Blocks x Cal	40	1218.400	27.364	1.625	1.011	39	0.026		
Calories					0.027	1	0.027	1.03	>.20
Pro x Supp					0.071	1	0.071	2.73	>.10
Blocks x Pro	40	1104.235	26.557	2.195	1.556	39	0.040		
Protein					0.171	1	0.171	4.30	<.05
Cal x Supp					0.008	1	0.008		
Blocks x Supp	40	1456.323	27.267	2.167	1.657	39	0.042		
Supplements					0.003	1	0.003		
Cal x Pro					0.000	1	0.000		

3. *Analysis of covariance.* Tables IV, V, and VI present the analyses of covariance for both the original and transformed measurements of duration of illness. The analysis suggests that no reduction in error variance was achieved by restricting the size of block to four patients, since the mean square for "Replicate × Cal × Pro × Supp interaction" does not significantly exceed the error variance.

4. *Sensitivity of the experiment.* The Type II error in the second study was found to be approximately 0.05 for a Type I error of 0.05.

APPENDIX II

Supplementary Tables

Table 1, Appendix II

Distribution of Liver Function Tests in 279 "Normal" Soldiers - Kyoto and Sasebo Series

Total Serum Bilirubin					Thymol Turbidity				
		Kyoto Series History		Sasebo			Kyoto Series History		Sasebo
mgm/100 ml	Normal	Equivocal	Total	Series	Units	Normal	Equivocal	Total	Series
.10- .19	0	1	1	77	.5	1	3	4	0
.20- .29	5	5	10	42	1.0	17	3	20	23
.30- .39	22	9	31	80	1.5	5	4	9	79
.40- .49	37	7	44	139	2.0	56	18	74	44
.50- .59	34	17	51	88	2.5	30	10	40	155
.60- .69	34	15	49	49	3.0	29	12	41	81
.70- .79	27	6	33	24	3.5	27	10	37	28
.80- .89	16	3	19	15	4.0	13	3	16	19
.90- .99	15	8	23	8	4.5	13	1	14	15
1.00-1.09	8	2	10	4	5.0	4	0	4	7
1.10-1.19	3	0	3	0	5.5	7	3	10	4
1.20-1.29	1	0	1	2	6.0	0	0	0	0
1.30-1.39	1	0	1	2	6.5	3	5	8	2
1.40-1.49	0	0	0	0	7.0	0	0	0	1
1.50-1.59	0	0	0	0	7.5	0	0	0	0
1.60-1.69	1	0	1	0	8.0	0	0	0	1
1.70-1.79	1	0	1	0	8.5	0	0	0	0
1.80-2.49	0	0	0	0	9.0	1	0	1	1
2.50-2.59	1	0	1	0	9.5-11.5	0	0	0	0
					12.0	0	1	1	
	206	73	279	460		206	73	279	460

Prompt Direct Serum Bilirubin					Zinc Turbidity			
.02-.03	2	3	5	21	2	1	2	3
.04-.05	11	5	16	48	3	8	6	14
.06-.07	25	12	37	108	4	22	5	27
.08-.09	33	13	46	90	5	19	7	26
.10-.11	39	12	51	84	6	55	17	72
.12-.13	33	9	42	68	7	38	15	53
.14-.15	22	10	32	23	8	21	4	25
.16-.17	21	2	23	11	9	19	2	21
.18-.19	11	2	13	3	10	10	4	14
.20-.21	5	4	9	0	11	5	5	10
.22-.23	1	0	1	2	12	3	4	7
.24-.25	1	0	1	1	13	2	2	4
.26-.27	2	0	2	1	14	1	0	1
.28-.29	0	0	0		15-17	0	0	0
.30-.31	0	1	1		18	0	1	1
	206	73	279	460		204	74	278

ΔpH/hr.	Cholinesterase				Thymol Flocculation				
.40- .49	5	1	6		0	132	49	181	410
.50- .59	5	2	7		1 +	70	21	91	34
.60- .69	46	11	57		2 +	3	2	5	14
.70- .79	49	18	67		3 +	0	1	1	2
.80- .89	33	19	52		4 +	1	0	1	0
.90- .99	45	17	62			206	73	279	460
1.00-1.09	16	2	18						
1.10-1.19	3	2	5		Cephalin Flocculation				
	202	72	274						
					0	193	65	258	413
					1 +	4	4	8	43
					2 +	8	4	12	3
					3 +	1	0	1	0
					4 +	0	0	0	1
						206	73	279	460

Table II, Appendix II

Sample Diet Check Sheet: Forced Diet Wards, First Study

FOOD		SECONDS	REFUSALS	TOTAL	CHO	PRO	FAT
Amount	Weight						
1 cup Chilled Tomato Juice	(150)			1	6	2	
2 Poached Eggs	(100)			1		12	12
1 slice Toast	(30)			1	16	3	1
1 pat Butter	(8)			1			7
1 tablespoon Jam	(20)			1	13		
Evaporated Milk	(15)			1	2	1	1
1 shaker sugar	(1t)			1	5		
1 carton Milk	(240)			1	12	8	9
	TOTAL				54	26	30
Special Eggnog	(260)			1	21	21	13
1 teaspoon Sugar	(5)			1	5		
2 servings Baked Chicken - 180	(190)		40	150		42	14
1 dipper Mashed Potatoes	(60)			1	10	1	4
1 serving Baked Tomatoes	(100)			40	2		
1 spoon Old-Fashioned Coleslaw	(40)		all				
1 serving Corn Bread	(80)			1	38	6	7
1/2 pat Butter	(4)			1			3
1 spoon Lemon Meringue Pudding	(80)			1	34	2	2
Evaporated Milk	(15)			1	2	1	1
1 shaker sugar	(1t)			1	5		
1 carton Milk	(240)			1	12	8	9
	TOTAL				183	107	83
Special Eggnog Plus	(200)			1	16	16	10
Ice Cream	(75)			1	16	3	10
2 pieces Steak - 150	(150)			150		41	20
1 spoon Scalloped Potatoes	(80)			1	12	2	5
1 spoon Buttered Peas	(60)			1	5	2	
1 spoon Mixed Vegetable Salad	(40)		all				
1 teaspoon Oil & Vinegar	(5)		all				
1/2 slice Bread	(15)			1	8	2	1
1/2 pat Butter	(4)			1			3
1 spoon Apple Crisp	(80)			1	24	6	2
Evaporated Milk	(15)			1	2	1	1
1 shaker sugar	(1t)			1	5		
1 carton Milk	(240)	1		2	24	16	18
	TOTAL				295	196	153
Special Eggnog plus	(200)			1	16	16	10
Ice Cream	(75)			1	16	3	10
1 slice Bread 1/2 pat Butter 60 Roast Beef — Sandwich	(30) (4) (60)		all all all				
	TOTAL GRAMS				327	215	173

Total Calories: 3725

Total % Protein Calories: 23.1%

Table III, Appendix II

Sample Diet Check Sheet: Ad Lib Wards, First Study

FOOD		SECONDS	REFUSALS	TOTAL	CHO	PRO	FAT
Amount	Weight						
1 cup Chilled Tomato Juice	(150)		1/2	75	3	1	
1 box Assorted Dry Cereal Puff Wheat	(15)			1	11	2	
1 Poached Egg on	(50)			1		6	6
1 slice Toast	(30)			1	16	3	1
1 slice Toast	(30)			1	16	3	1
1 pat Butter	(8)			1			7
1 tablespoon Jam	(20)			1	13		
Evaporated Milk	(15)			1	2	1	1
1 shaker sugar	(2t)			2	10		
1 carton Milk	(240)			1	12	8	9
	TOTAL				83	24	25
1 cup Fruit Juice - Orange	(150)			1	18	1	
1 ladle Bean Soup	(180)		all				
1 tablespoon Croutons	(10)		all				
1 serving Fried Fish	(65)			65	5	13	8
1 tablespoon Tartar Sauce	(20)			1			10
1 dipper Mashed Potatoes	(120)		all				
1 serving Green Beans	(60)			1	3		
1 spoon Old-Fashioned Coleslaw	(30)			1	2		3
1 serving Corn Bread	(80)				38	6	7
1 pat Butter	(8)			1			7
1 spoon Lemon Meringue Pudding	(120)			1	52	2	2
Evaporated Milk	(15)		all				
1 shaker sugar	(2t)			2	10		
1 carton Milk	(240)			1	12	8	9
	TOTAL				223	54	71
1 cup Fruit Juice	(150)						
1 ladle Salmon Chowder	(150)		all				
1 Cracker	(10)		all				
1 piece Grilled Steak	(80)	70	20	130		35	17
1 spoon Scalloped Potatoes	(100)			1	15	3	6
1 spoon Buttered Peas	(40)			1	5	2	
1 spoon Mixed Vegetable Salad	(35)		all				
1 teaspoon Oil & Vinegar	(5)		all				
1 slice Bread	(30)			1	16	3	1
1 pat Butter	(8)			1			7
1 serving Turnover	(80)	1		2	54	5	21
Evaporated Milk	(15)		all				
1 shaker sugar	(2t)			2	10		
1 carton Milk	(240)			1	12	8	9
Lemon Sauce	(10)	1		2	10		
1 small Strawberry Sundae	( )				67	6	18
1 cup Fruit Juice	(150)				18	1	
	TOTAL GRAMS				430	117	150

Total Calories: 3538
Total % Protein Calories: 13.2%

Table IV, Appendix II

Accuracy of the Dietary Calculations

A. Comparison of mean data obtained by calculation (aides), weighing (dietitians), and chemical analysis.

		Calculated by the aides	Weighed by the dietitians	Analyzed by the chemists
		First Study		
Forced Diets (4 days averaged)	CHO-gm.	308	306	306*
	Pro "	189	190	205
	Fat "	168	161	134
	Calories	3504	3427	3253
Ad Lib Diets (4 days averaged)	CHO-gm.	367	366	370*
	Pro "	119	122	136
	Fat "	130	123	106
	Calories	3120	3055	2981
		Second Study		
Ward 23 High calorie High protein (3 days averaged)	CHO-gm.	357	357	339*
	Pro "	185	181	196
	Fat "	184	182	144
	Calories	3821	3795	3433
Ward 41 Normal calorie Normal protein (3 days averaged)	CHO-gm.	311	299	291*
	Pro "	71	68	80
	Fat "	105	107	90
	Calories	2469	2458	2293

B. Rank correlations between calculated and chemically analyzed whole days' diets.

Study	Number of diets	Rank correlation coefficient Protein	Fat
First	8	.79	.96
Second	6	.67	.80

C. Mean differences between methods.

Comparison		Mean difference in Grams	S.E.	P
Protein -	Calculated minus analyzed	-14.	6.6	.05
	Calculated minus weighed	+ 1.	1.7	.6
Fat -	Calculated minus analyzed	+28.	4.2	.001
	Calculated minus weighed	+ 4.	1.5	.02

* Calculated from the difference between the sum of the protein and fat calories and the total calories.

Table V, Appendix II

Distributions of Clinical and Laboratory Findings on Admission by First Study Treatment Groups, and Comparisons of First and Second Studies

Treatment Regimens*	DR	Dr	dR	dr	P	First Study Mean	First Study S.D.	2nd Study Mean	2nd Study S.D.	P
Quantitative Variables										
"Doctor Effect" Improbable										
1. Age in years	23	23	24	23	.4	23	3.7	23	3.9	.3
2. Duration of hospitalization prior to Kyoto admission in days	4	4	4	3	.2	4	2.7	4	2.1	.4
3. Weight in pounds on admission	149	155	150	148	.08	150	21.6	152	19.1	.3
4. Admission total serum bilirubin mgm./100 ml.	8.29	8.10	7.46	8.50	.9	8.07	5.6	8.32	5.4	.6
5. Admission prompt direct serum bilirubin mgm./100 ml.	4.13	3.91	3.71	4.11	.9	3.96	2.8	4.70	3.2	.01
6. Admission thymol turbidity in units	10.1	10.3	9.6	9.4	.8	9.6	4.7	8.4	5.1	.001
7. Admission zinc turbidity in units	12.0	13.6	9.6	12.8	.1	12.6	4.5	9.8	4.6	.001
"Doctor Effect" Possible										
8. Loss of weight between arrival in Korea and admission, in pounds	13	12	12	13	.9	12.5	9.9	10.9	8.4	.09
9. Duration of symptoms before admission	11	10	10	11	.7	10	4.6	12	5.4	.01
10. Duration of icterus before admission	7	8	7	8	.9	7.5	4.0	8	4.2	.02
11. Number of days before admission on which patient ate one meal or less per day	8	8	9	8	.5	8	4.3	8	4.8	.8
12. Number of days from onset of symptoms to hospitalization in which the patient's activity was more than 1/3 of normal	6	5	5	7	.02	6	4.4	7	5.5	.001
13. Same from onset of jaundice to hospitalization	4	3	3	4	.2	3	3.4	5	3.8	.5
Qualitative Variables										
"Doctor Effect" Improbable										
1. Race - % white	91	83	86	81	.4	85		81		.3
2. Source of infection - % Korea	95	97	98	91	.2	94		93		.7
3. % with past history of liver disease	12	10	2	8	.1	8		8		—
4. Cephalin flocculation - % positive on admission	69	69	71	69	.9	69		37		.001
5. Thymol flocculation - % positive on admission	52	60	48	52	.5	53		34		.001
"Doctor Effect" Possible										
History in 120 days before admission										
6. % with other diseases	35	56	49	42	.1	45		46		.8
7. % with subnormal food intake	9	19	14	27	.06	17		16		.8
8. % with active physical exertion	6	38	24	20	.001	22		14		.03
9. % with fatigue	5	10	29	20	.002	16		13		.4
10. % receiving parenteral injections	95	94	79	78	.003	87		88		.7
11. % with moderate to severe alcohol consumption	47	32	40	13	.008	33		45		.01
Present Illness										
12. % with 2 or more severe symptoms	37	44	52	34	.03	42		32		.03
13. % with food intake decreasing significantly in the 3 days before admission when compared with the previous 3 days	20	21	8	21	.002	17		14		.4
14. % with anorexia on admission	74	68	71	69	.9	71		79		.5
15. % with malaise on admission	52	70	70	33	.003	56		71		.001
16. % with liver pain on admission	42	62	49	44	.09	49		50		.8
17. % with nausea on admission	46	41	30	31	.2	37		50		.007
18. % with vomiting on admission	12	8	6	5	.4	8		18		.002
19. % with moderate hepatomegaly on admission	46	48	26	47	.03	42		46		.4
20. % with marked hepatomegaly on admission	40	34	61	53	.01	47		46		.8
21. % with hepatic tenderness on admission	68	69	73	75	.8	71		63		.07
Total Number of Patients	65	64	63	65		257		189		

*See footnote to Table VII, Appendix II for explanation of symbols referring to treatment regimens.

Table VI, Appendix II

Distributions of Clinical and Laboratory Findings on Admission by Treatment Groups in the Second and Third Studies

Treatment Regimens:	CPS	CPs	cPS	cPs	CpS	Cps	cpS	cps	P*	E+	e+	P
Total patients	24	23	24	23	24	24	23	24	—	95	94	
Quantitative Variables												
"Doctor Effect" Improbable												
1. Age in years	24	22	25	22	24	24	23	24	.4	23	23	—
2. Duration of hospitalization prior to Kyoto admission in days	4	5	3	4	4	4	3	5	.3	4	4	—
3. Weight in pounds on admission	154	151	151	152	146	155	154	153	.9	153	151	.6
4. Admission total serum bilirubin mgm./100 ml.	8.58	7.90	9.34	8.37	7.46	10.46	7.45	7.02	.6	8.95	7.96	.2
5. Admission prompt direct serum bilirubin mgm./100 ml.	4.54	4.40	4.98	4.42	4.36	6.31	4.33	4.11	.1	5.02	4.37	.2
6. Admission thymol turbidity in units	9.6	7.5	7.4	7.7	8.1	8.9	8.0	9.9	.9	8.0	8.5	.3
7. Admission zinc turbidity in units	10.5	9.8	9.1	9.3	9.1	9.9	10.6	11.0	.9	10	10	—
8. Admission bromsulphalein retention, % in 45 minutes	48	46	44	46	42	50	50	40	.06	48	43	.02
9. Admission cholinesterase, pH/hr.	.69	.65	.67	.68	.61	.58	.65	.62	.5			
"Doctor Effect" Possible												
10. Loss of weight between arrival in Korea and admission, in pounds	9	9	10	9	12	10	14	13	.3	10	11	.5
11. Duration of symptoms before admission	12	14	12	10	13	10	12	13	.3	12	12	—
12. Duration of icterus before admission	7	10	9	9	9	7	8	9	.3	9	9	—
13. Number of days before admission on which patient ate one meal or less per day	10	11	7	6	10	8	7	8	.01	8	8	—
14. Number of days from onset of symptoms to hospitalization in which the patient's activity was more than 1/3 of normal	8	9	8	6	5	4	9	10	.01	7	7	—
15. Same from onset of jaundice to hospitalization	4	7	6	5	4	2	5	6	.01	5	5	—

Qualitative Variables	CP	cP	Cp	cp	P**	S	s	P#			
"Doctor Effect" Improbable											
1. Race - % white	72	89	90	74	.04	84	79	.4	78	85	.2
2. Source of infection -% Korea	98	91	90	94	.4	94	93	.8	93	94	.8
3. % with past history of liver disease	9	9	10	6	.9	8	10	.6	6	11	.3
4. Cephalin flocculation - % positive on admission	33	36	40	43	.9	35	41	.4	35	41	.4
5. Thymol flocculation - % positive on admission	28	35	35	38	.8	35	33	.7	27	41	.05
"Doctor Effect" Possible											
History in 120 days before admission											
6. % with other diseases	49	38	42	53	.4	46	45	.9	51	40	.2
7. % with subnormal food intake	21	19	15	12	.6	17	15	.8	17	15	.7
8. % with active physical exertion	6	19	13	17	.004	11	17	.4	13	15	.7
9. % with fatigue	20	7	28	2	.002	14	15	.8	18	10	.1
10. % receiving parenteral injections	94	77	85	98	.008	87	89	.9	91	86	.3
11. % with moderate to severe alcohol consumption	31	49	46	53	.06	41	47	.5	43	46	.7
Present Illness											
12. % with 2 or more severe symptoms	62	21	19	26	.01	33	31	.8			
13. % with food intake decreasing significantly in the 3 days before admission when compared with the previous 3 days	23	6	10	15	.04	13	13	—			
14. % with anorexia on admission	92	74	88	64	.003	82	77	.5			
15. % with malaise on admission	89	72	73	49	.003	73	69	.6			
16. % with liver pain on admission	64	55	44	38	.06	43	57	.06			
17. % with nausea on admission	62	53	44	40	.2	50	50	—			
18. % with vomiting on admission	23	17	15	17	.7	14	22	.1			
19. % with moderate hepatomegaly on admission	28	60	38	60	.003	45	47	.8			
20. % with marked hepatomegaly on admission	70	32	52	30	.003	46	46	—			
21. % with hepatic tenderness on admission	81	74	85	13	.001	63	64	.9			

* Probability values for differences among the 8 treatment groups.
** Probability values for difference between wards.
\# Probability values for differences within wards.

+ E = early exercise group.
e = late exercise group. See footnote to Table VII for explanation of other treatment symbols.

Table VII, Appendix II

Patients Removed from Studies in Basic Analyses

Treatment groups*		Reason for removal	Admission total serum bilirubin	Start of convalescence
		A. FIRST STUDY		
1	dR	Clinical infectious mononucleosis with rising and falling heterophile agglutination and many atypical cells on smear.	1.4	14
2	dR	Lymphogranuloma venereum. Liver function tests normal.	0.9	7
3	Dr	No symptoms, signs, or laboratory findings of hepatitis. Malingering suspected.	0.3	7
4	dr	Committed for acute psychosis on 48th day. TSB normal. BSP 7%.	19.4	51 (earliest) 58 probable
5	Dr	Emergency leave day 32, BSP 2, TSB 1.3 Needed one more normal TSB.	14.5	32 - 35
6	dR	True ambulation day unknown due to possible mix-up of bloods. Either 43 days or 10 days plus 33-day relapse.	6.7	10 or 43
7	dR	Same as #6. Either 102 days or 29 plus 73-day relapse.	8.7	29 or 102
		B. SECOND STUDY		
1	cPs	E. Histolytica in stools. Persistent fever and localized hepatic tenderness. Treated with chloraquin and terramycin. Dropped from observation.	17.7	unknown
2	CPs	E. Histolytica in stools. Severe localized hepatic tenderness. Treated with chloraquin and terramycin.	12.0	27
3	cpS	Heterophile positive. May have had hepatitis but TSB remained around 3 mg% with normal PDSB and BSP until discharge 78 days after admission. No reticulocytosis.	3.3	78
4	cps	Last replicate of 8 removed to close study.	6.9	22
5	cPs	Same	5.1	33
6	CPS	Same	2.4	30
7	CpS	Same. Dietary figures for only 6 days.	1.1	35
8	CPs	Same	5.8	38
9	cPS	Same. BSP still 6 when study ended.	15.6	62
10	cpS	Same. BSP still 7 when study ended.	5.9	61
11	Cps	Same	17.5	47

*In this and following tables where treatment groups are indicated by code, the capital letter indicates the forced regimen or high level of dietary intake and the small letter the ad lib regimen or "normal" dietary intake. Thus:

First Study: D = forced diet; d = ad lib diet; R = forced rest; r = ad lib rest

Second Study: P = high protein; p = "normal" protein; C = high calorie; c = "normal" calorie; S = choline and vitamin supplements; s = placebos

Table VIII, Appendix II. The effect of treatment on the incidence of patients whose serum bilirubin levels rose after admission.

	First Study						Second Study								
	Diet			Rest			Protein			Calories			Supplements		
	Forced	Ad Lib.	P	Strict	Ad Lib.	P	High	"Normal"	P	High	"Normal"	P	Added	Placebos	P
Total serum Bilirubin															
Total Patients	129	128		128	129		94	95		95	94		95	94	
Number rising*	5	18		11	12		3	17		12	8		5	15	
% rising	4	14	.01	9	9	-	3	18	.001	13	9	.4	5	16	.02
Prompt Direct Serum Bilirubin															
Total Patients	129	128		128	129		94	95		95	94		95	94	
Number rising**	5	16		10	11		3	13		9	7		5	15	
% rising	4	12	.01	8	8	-	3	14	.01	10	7	.6	5	16	.02

* By 1 mg. per 100 ml. or more **by 0.5 mg. per 100 ml. or more

Table IX. Thymol and zinc turbidities: Mean admission, convalescent and discharge values.

	First Study										Second Study*									
	Diet					Rest					Protein				Calories				Supplements			
	Forced		Ad Lib.			Forced		Ad Lib.			High		"Normal"		High		"Normal"		High		"Normal"	
	Mean	S.D.	Mean	S.D.	P	Mean	S.D.	Mean	S.D.	P	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Thymol Turb.																						
Admission	9.8	4.9	9.4	4.5	.5	9.5	4.5	9.8	4.7	.6	8.0	5.1	8.7	5.2	8.5	5.2	8.2	5.1	8.3	4.7	8.5	5.4
Convalescence	7.1	3.5	5.9	3.2	.005	6.3	3.3	6.8	3.5	.1	4.5	2.7	4.7	3.0	4.8	3.1	4.3	2.6	4.6	2.8	4.5	2.9
Discharge	4.5	2.6	4.3	2.5	.5	4.1	2.5	4.6	2.8	.1	3.4	1.6	3.3	2.0	3.5	2.0	3.2	1.7	3.4	1.9	3.3	1.7
Zinc Turb.																						
Admission	12.9	4.5	12.3	3.3	.3	12.0	4.4	13.2	3.5	.05	9.6	4.9	10.0	4.3	9.8	4.4	9.9	4.5	9.7	4.1	10.0	4.8
Convalescence	12.0	4.4	10.1	4.0	.002	10.6	3.8	11.6	4.7	.1	7.8	4.1	7.3	1.7	7.9	2.2	7.2	3.7	7.3	4.1	7.8	1.4
Discharge	9.1	3.6	8.9	3.6	.7	8.6	3.4	9.3	4.0	.1	6.8	3.1	6.9	3.2	7.2	2.9	6.6	3.1	6.6	3.4	7.0	3.1
Total Patients	129		128			128		129			94		95		95		94		95		94	

*None of the differences between treatment groups were significant

Table X, Appendix II The percentage of patients with abnormal flocculation and turbidity tests

	First Study (257 Patients)				Second Study (189 Patients)					
	Diet		Rest		Protein		Calories		Supplements	
Test and Time Performed	Forced %	Ad Lib %	Forced %	Ad Lib %	High %	"Normal" %	High %	"Normal" %	Added %	Placebos %
Cephalin Flocculation										
Admission	69	68	69	68	34	41	36	39	34	40
Highest	82	84	83	88	41	50	42	50	41	51
Convalescence	24	15	18	21	1*	9*	4	6	3	7
Discharge	6*	1*	2	4	0	0	0	0	0	0
Thymol Flocculation										
Admission	55	50	49	55	32	37	32	37	35	33
Highest	63	55	57	61	38	46	40	45	43	41
Convalescence	43	38	40	41	15	21	19	17	15	21
Discharge	24	27	22	29	8	16	14	10	12	12
Thymol Turbidity										
Admission	71	70	71	70	50	56	51	55	54	52
Highest	76	74	75	75	54	58	56	56	54	58
Convalescence	49	38	42	46	14	20	17	17	16	18
Discharge	17	14	12	18	7	7	7	6	6	7
Zinc Turbidity										
Admission	42	37	35	43	20	22	18	24	19	22
Highest	59	46	46	59	28	24	25	31	27	29
Convalescence	37*	14*	18	24	9	5	9	5	8	6
Discharge	14	11	9	16	2	5	4	3	3	4
Mean Duration of:**										
Acute illness	25	32	30	28	28	34	31	32	31	32
Observation	62	65	64	63	49	54	50	54	50	56

* Differences significant at the 5% level
** Arithmetic means

Table XI, Appendix II

Comparison of flocculation and turbidity tests in first and second studies

	% of patients with abnormal tests			Mean number of units		
	1st study	2nd study	P	1st study	2nd study	P
Cephalin flocculation						
Admission	69	37	.001			
Highest	83	46	.001			
Convalescence	20	5	.001			
Discharge	3	0	.01			
Thymol flocculation						
Admission	52	34	.001			
Highest	59	42	.001			
Convalescence	41	18	.001			
Discharge	25	12	.001			
Thymol turbidity						
Admission	71	53	.001	9.5	8.5	.001
Highest	75	67	.07			
Convalescence	44	17	.001	5.5	4.5	.002
Discharge	15	7	.007	4.5	3.5	.001
Zinc turbidity						
Admission	39	21	.001	13	10	.001
Highest	53	28	.001			
Convalescence	21	7	.001	11	8	.001
Discharge	13	4	.001	9	7	.001
Total Patients	257	189		257	189	
Mean duration of acute illness				29 days	31 days	
Mean duration of observation				64 "	52 "	

Table XII

Mean eosinophil counts (first study) and cholinesterase values (second study) during the first two weeks of hospitalization.

	Eosinophil counts (number per ml)				Cholinesterase (Δ pH per hour)			
	Diet		Rest		Protein		Calories	
	Forced	Ad Lib	Forced	Ad Lib	High	"Normal"	High	"Normal"
Admission	91	95	103	88	.68	.61	.63	.65
Day 3-6	119	100	100	90	.65	.63	.65	.63
Day 7-10	104	115	119	104	.72	.65	.70	.67
Day 11-14	118	134	144	116	.74	.72	.72	.74
Convalescence					.84	.78	.81	.81
Discharge					.85	.82	.85	.82
Number of Patients	37	43	30	50	93	92	93	92

Table XIII, Appendix II

Effects of treatment on symptoms during the first three weeks of hospitalization

	First Study				Second Study					
	Diet		Rest		Protein		Calories		Supplements	
	Forced	Ad lib.	Forced	Ad lib.	High	"Normal"	High	"Normal"	Added	Placebos
Anorexia										
Admission										
Number of patients	128	127	128	127	94	95	95	94	95	94
% with symptoms	71	70	73	68	83	76	90	69	82	77
% with severe symptoms	9	14	10	13	27	15	35	6	21	20
7 - 8 days										
Number of patients	127	127	128	126	94	95	95	94	95	94
% with symptoms	16	20	25	11	26	26	35	17	28	23
% with severe symptoms	0	2	2	0	0	1	1	0	0	1
13 - 15 days										
Number of patients	110	116	117	109	88	90	87	91	91	87
% with symptoms	7	10	9	8	9	10	14	6	9	10
% with severe symptoms	1	1	1	1	0	1	0	1	0	1
20 - 22 days										
Number of patients	76	98	91	83	67	74	70	71	73	68
% with symptoms	3	3	3	2	11	5	10	6	4	12
% with severe symptoms	0	0	0	0	2	0	1	0	0	2
Malaise										
Admission										
Number of patients	128	127	128	127	94	95	95	94	95	94
% with symptoms	61	51	61	51	81	61	81	61	73	69
% with severe symptoms	24	12	23	13	29	14	35	7	24	18
7 - 8 days										
Number of patients	127	127	128	126	94	95	95	94	95	94
% with symptoms	13	24	25	11	17	27	34	11	21	23
% with severe symptoms	6	3	8	1	3	0	3	0	2	1
13 - 15 days										
Number of patients	110	116	117	109	88	90	87	91	91	87
% with symptoms	9	14	17	6	8	10	12	7	6	13
% with severe symptoms	0	3	3	0	0	0	0	0	0	0
20 - 22 days										
Number of patients	76	98	91	83	67	74	70	71	73	68
% with symptoms	1	6	7	1	10	14	14	10	8	16
% with severe symptoms	0	0	0	0	0	0	0	0	0	0
Liver Pain										
Admission										
Number of patients	128	127	128	127	94	95	95	94	95	94
% with symptoms	52	46	45	53	60	41	54	47	43	57
% with severe symptoms	16	22	24	14	18	8	17	10	15	12
7 - 8 days										
Number of patients	127	127	128	126	94	95	95	94	95	94
% with symptoms	12	11	10	13	12	8	10	10	13	7
% with severe symptoms	1	4	1	3	3	0	2	1	3	0
13 - 15 days										
Number of patients	110	116	117	109	88	90	87	91	91	87
% with symptoms	5	4	4	5	3	4	2	6	6	2
% with severe symptoms	0	3	1	2	1	0	0	1	1	0
20— 22 days										
Number of patients	76	98	91	83	67	74	70	71	73	68
% with symptoms	3	3	3	2	2	4	2	4	3	3
% with severe symptoms	0	0	0	0	0	0	0	0	0	0
Nausea and Vomiting										
Admission										
Number of patients	128	127	128	127	94	95	95	94	95	94
% with nausea	44	31	38	36	57	42	53	47	50	50
% with vomiting	10	6	9	6	20	16	19	17	14	22
7 - 8 days										
Number of patients	127	127	128	126	94	95	95	94	95	94
% with nausea	3	8	9	2	10	7	10	7	6	11
% with vomiting	1	0	1	0	0	3	3	0	1	2
13 - 15 days										
Number of patients	110	116	117	109	88	90	87	91	91	87
% with nausea	1	5	4	2	3	2	3	2	1	5
% with vomiting	0	2	1	1	0	1	0	1	1	1
20 - 22 days										
Number of patients	76	98	91	83	67	74	70	71	73	68
% with nausea	0	3	2	1	6	3	4	4	3	6
% with vomiting	0	1	1	0	0	1	0	1	0	2

Table XIV, Appendix II The effects of treatment on the frequency of hepatomegaly liver tenderness, spider angiomata and splenomegaly, and on weight gain during the first 3 hospital weeks

	First Study (257 Patients)				Second Study (189 Patients)					
	Diet		Rest		Protein		Calories		Supplements	
	Forced %	Ad Lib %	Forced %	Ad Lib %	High %	"Normal" %	High %	"Normal" %	Added %	Placebos %
Admission										
No enlargement	15	6	13	8	5	11	6	9	9	7
3-5 cm.	48	37	37	48	44	48	33	60	45	47
>5 cm.	37	57	50	44	51	41	61	31	46	46
Tenderness	68	74	70	72	78	49	83	44	63	64
7-9 Days										
No enlargement	12	10	12	10	8	21	9	20	11	19
3-5 cm.	63	38	45	56	53	58	47	64	60	51
>5 cm.	25	52	43	34	39	21	44	16	29	30
Tenderness	25	38	31	31	32	33	46	18	34	29
14-16 Days										
No enlargement	30	10	23	17	18	52	17	52	28	36
3-5 cm.	59	42	41	60	58	41	56	43	59	45
>5 cm.	11	48	36	23	24	7	27	5	13	19
Tenderness	8	21	15	14	12	14	19	6	15	10
21-23 Days										
No enlargement	42	19	33	28	29	67	36	59	44	52
3-5 cm.	50	48	47	52	54	25	46	33	45	33
>5 cm.	8	33	20	20	17	8	18	8	11	15
Tenderness	5	13	11	7	7	30	33	15	8	11
Splenomegaly	10	18	10	18	23	5	14	15	12	17
Spider Angiomata	30	20	20	29	39	20	34	26	27	33
Weight on admission	151	149	149	151	152	152	151	153	151	153
Mean gain in pounds										
First week	4	2	4	3	1	2	3	0	2	1
Second week	4	1	2	3	2	1	2	1	1	2
Third week	1	2	2	1	1	1	1	2	2	1
Total pounds gained	9	5	8	7	4	4	6	3	5	4

Table XV, Appendix II

The effects of two weeks of increasing ambulation on liver function tests and liver size and tenderness of the strict bed rest patients compared with the equivalent period in the course of the patients who were ambulatory throughout

	Strict Bed Rest	Ad lib Rest	P
I Liver Function Tests			
Total Serum Bilirubin			
Mean convalescent value ± 1 S. D.	1.01 ± .25	1.02 ± .26	
Mean change in first week	+.001	+.01	.8
Mean change in second week	-.12	-.09	.4
Prompt Direct Serum Bilirubin			
Mean convalescent value ± 1 S. D.	0.36 ± .12	0.38 ± .11	
Mean change in first week	-.021	-.025	.8
Mean change in second week	-.11	-.11	—
Bromsulphalein Retention			
Mean convalescent value ± 1 S. D.	3 ± 2.0	3 ± 2.0	
Mean change in first week	-.03	-.4	.1
Mean change in second week	-.7	-.8	.7
Total Patients	128	129	
II Clinical Findings - % of patients			
Return of minor symptoms	6	8	.5
Increase in size of liver by 2 cm. or more	5	3	.5
Appearance of liver tenderness	10	7	.5
Bromsulphalein "relapses"	6	2	.1
Total patients	126	127	

Table XVI

Total and prompt direct serum bilirubins on discharge to the Physical Reconditioning Center: comparison of the normal series with the first study patients and with the early and late groups in the third study

	Number	Range	Mean	S.D.	S.E.
Normal Series					
TSB	279	0.15 to 2.55	0.64	0.26	.028
PDSB	279	0.03 to 0.31	0.12	0.05	.005
First Study					
TSB	189	0.35 to 1.52	0.78	0.26	.019
PDSB	189	0.06 to 0.36	0.19	0.07	.005
Third Study - early exercise group					
TSB	88	0.33 to 1.48	1.00	0.23	.024
PDSB	88	0.14 to 0.71	0.40	0.11	.012
Third Study - Late exercise group					
TSB	86	0.30 to 1.40	0.89	0.23	.025
PDSB	86	0.11 to 0.49	0.30	0.10	.011

TABLE XVII, APPENDIX II

Comparison of follow-up sample with the remainder of the study patients with respect to mean values for age on admission, initial total serum bilirubin and duration of acute illness from admission to convalescence; comparisons of treatment groups in the sample according to the mean points (abnormality score) at discharge to duty and the interval from discharge to follow-up examination

Treatment group*	Number in sample	Mean age *yrs.*		Mean TSB *mg./100 ml.*		Mean duration *days*		Mean points for sample at discharge to duty	Mean interval *mos.*
		Sample	Rem.	Sample	Rem.	Sample	Rem.		
First study:									
DR	25	23	22	9.0	7.9	33	29	2	12
Dr	25	23	24	7.0	7.7	29	37	1	13
dR	25	25†	21	9.4	7.6	29	23	1	12
dr	25	24	23	8.9	7.5	29	25	1	12
Second study:									
CPS	11	23	24	7.1	9.8	23	31	2	8
CPs	11	22	22	9.4	7.2	31	25	1	9
cPS	11	26	23	10.0	8.4	30	30	2	8
cPs	11	22	23	6.3	9.4	29	34	1	9
CpS	11	24	24	7.4	7.3	33	29	1	8
Cps	11	27†	22	13.5†	7.9	49†	30	1	8
cpS	11	23	24	8.8	6.2	36	34	1	8
cps	11	23	24	7.2	7.6	27	36	1	10
Third study:									
E	44	24	23	10.3†	7.8	37	31	1	9
e	44	24	23	7.9	8.0	28	29	2	8

* See footnote to Table VII for explanation of abbreviations.
In addition, E = "early" and e = "late" exercise groups.
† Difference between the sample and remainder is significant at the 5 per cent level.

TABLE XVIII, APPENDIX II

Patients hospitalized in the interval between discharge and follow-up examination

Patients hospitalized for more than one day for:	First study				Second study							
	Diet		Rest		Protein		Calories		Supplements		Exercise	
	Forced	*Ad lib.*	Forced	*Ad lib.*	High	Normal	High	Normal	Added	Placebos	Early	Late
Complaints possibly related to hepatitis	5	3	5	3	1	0	1	0	1	0	1	0
Complaints probably not related to hepatitis	3	3	1	5	3	1	4	0	1	3	3	1
Complaints not related to hepatitis	6	4	7	3	4	5	3	6	4	5	8	1
Total patients hospitalized	14	10	13	11	8	6	8	6	6	8	12	2
Total patients followed	49	46	46	49	40	41	39	42	40	41	40	41

TABLE XIX, APPENDIX II

Results of follow-up study: Distribution of patients according to treatment group and abnormalities in symptoms, signs, and laboratory tests

		First study					Second and third studies								Both studies total	
		DR	dR	Dr	dr	Total	Cp	CP	cp	cP	S	s	E	e	Total		
Total patients examined		24	24	25	24	97	21	21	22	22	42	44	43	43	86	183	
Abnormalities on follow-up	Points																
Mild–moderate symptoms	1	4	5	7	5	21	1	7	1	1	5	5	7	3	10	31	17
Severe symptoms	2	3	2	2	4	11	0	1	1	0	2	0	1	1	2	11	6
Hepatomegaly 3–5 cm.	1	2	2	2	3	9	1	6	6	3	10	6	9	7	16	25	14
Hepatomegaly >5 cm.	2	1	1	0	1	3	0	1	0	1	1	1	1	1	2	5	3
Liver tenderness	1	2	4	4	3	13	1	3	2	2	4	4	8	0	8	21	11
More than one spider	1	0	0	1	1	2	0	2	0	1	2	1	1	2	3	5	3
Splenomegaly	1	1	0	0	0	1	0	1	0	0	1	0	0	1	1	2	1
Total serum bilirubin	2	0	0	2	1	3	0	1	0	2	3	0	0	3	3	6	3
Prompt direct serum bilirubin	2	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1	1
Bromsulphalein test*	2	1	0/22	1	3	5	0/20	2/19	1	2/21	2	3	3	2	5	9	5
Cephalin flocculation	1	0	0	1	0	1	1	0	1	1	1	2	0	3	3	4	2
Thymol turbidity	1	0	1	2	2	5	1	1	1	1	2	2	2	2	4	9	5
Thymol flocculation	1	0	0	0	1	1	1	0	0	1	1	1	2	0	2	3	2
Total abnormality points																	
0		15	13	11	10	49	18	6	10	11	19	26	22	23	45	94	53
1		4	4	7	7	22	1	5	7	2	10	5	7	8	15	37	21
2		2	2	3	3	10	0	4	4	7	7	8	7	8	15	25	14
3		2	2	3	0	7	0	2	0	0	1	1	1	1	2	9	5
4		0	1	0	2	3	0	0	0	1	1	0	1	0	1	4	2
5		1	0	1	0	2	1	1	0	0	1	1	1	1	2	4	2
6		0	0	0	2	2	0	1	0	1	0	1	0	1	1	3	2
Total patients with complete data		24	22	25	24	95	20	19	21	21	40	41	40	41	81	176	

* The second number indicates the number of patients who had the test performed. In all other instances the total number is the same as at the top of the column.

TABLE XX, APPENDIX II

Characteristics of epidemics of infectious hepatitis among military personnel in various locales

Location	Korea and Japan	Germany (3)	United States (2)	Great Britain (34)	Italy (1) (36)	Middle East (35)
Dates	1951–52	1947–49	1944–45	1943–45	1943–44	1942–44
Number of patients	454	3,614	200	200	101 and 1,172	200
Per cent incidence of:						
Anorexia	95	Only 20% had acute onset	92	94	87	82
Malaise	92		68	58		82
Nausea	89		79	78	84	75
Liver pain	75		57	36		
Vomiting	64	Rare	58	50	51	33
Fever	53	Rare	42		61	53
Diarrhea	20		10	11	33	9
Per cent of patients with no symptoms prior to onset of jaundice	3 or 27 (a)	? High	10			16.5
Mean total duration of jaundice*—days	32	37 (d)		19	14–28	27
Mean duration of hospitalization—days	56 (b)	60	ca. 35	33	50–60	30
Per cent incidence of acute relapses						
Total	5.6	0.7 (c)	18.5	11.5	10–15	1.5
With jaundice	0	?	"Few"	ca. 7.5	5	
Mortality	0 in 454, (.2% in 2,448)	.2%	0	0	.2–.4%	0

(a) First figure—no symptoms prior to onset of clinical jaundice.
Second figure—no symptoms prior to onset of dark urine.
(b) First study only.
(c) Listed as per cent with "moderately severe" relapses.
(d) Estimated from data supplied by Dr. W. P. Havens, Jr. in which the duration from admission to a bilirubin of 1.5 mg./100 ml. was 27 days, and the duration of symptoms before admission 14 days.
* Since different criteria for the duration of jaundice were used in each study, these figures are approximations.

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