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Normal and Pathologic Erythrocyte Survival

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I. ERYTHROCYTE SURVIVAL UNDER NORMAL AND PATHOLOGIC CONDITIONS

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1. Introduction

There have been remarkable advances during the past ten years in our understanding of the hemolytic anemias. Various factors have led to these advances. Clinicians have become increasingly aware of the frequency of increased red cell destruction in a variety of diseases. Physiologists and physical chemists have become increasingly more interested in the fundamental nature of hemolytic processes. Tracer techniques have been developed or refined for directly following the fate of "marked" red cells in vivo in normal and abnormal states.

This report is primarily concerned with results of red cell tracer studies in normal man and in patients with various hemolytic syndromes.

2. Red Cell Tracer Techniques

Certain general requirements apply to all substances used for red cell tracer studies: (1) The labelling substance must be incorporated into the red cells only during their formation, or if the label is a substance used to mark red cells already circulating it must be taken up equally well by cells of all ages. If the "tag" is administered to be incorporated into cells during their formation, it is advantageous to obtain "sharp" labelling, that is, the dosage and time of administration should be adjusted so that labelled cells are produced over as short a period of time as possible. (2) The labelling substance must remain "fixed" in the red cells until they disintegrate, but at the same time the "tag" must not alter the metabolism of the red cells in any way so as to cause possible alterations in the life of the cell. (3) Upon disintegration of the "tagged" red cells, the labelling substance must not be reutilized in the development of new cells.

Two general types of tags are in use to follow the fate of red cells: (1) isotopic, and (2) the naturally occurring agglutinogens of the red cells. Radioactive iron (Fe^{55} and Fe^{59}), radioactive carbon (C^{14}) and heavy nitrogen (N^{15}) (a stable isotope) are used in humans. Radioiron has limited application because it does not satisfy the third criterion listed above.

Shemin and Rittenberg reported in 1945[1] that the amino acid, glycine, is a specific precursor of the protoporphyrin of hemoglobin. This opened a new avenue of approach both to studies of porphyrin metabolism and red cell dynamics. Glycine labelled with N^{15} in the amino group or C^{14} in the alpha carbon position is fed or can be given intravenously. Normally the level of the isotope builds up in the peripheral blood hemoglobin for around 25 days so the labelling is not as "sharp" as may be desired. Otherwise, this method seems to satisfy the three criteria. However, there may be some reutilization of at least the protoporphyrin nitrogen which is of no great consequence in normals but possibly may be of significance in hemolytic syndromes. We expect a study now in progress to give information on this point. These isotopic tracer studies are very expensive, time consuming, and require access to elaborate equipment for measurement of the concentrations of the isotopes.

Much more versatile and widely used specifically for observing red cell survival is the Ashby differential agglutination technique[2-4] which utilizes the naturally occurring agglutinogens of the red cells. It appears safe to assume that the agglutinogens remain with the red cell until the cell disintegrates, and there is no evidence that the agglutinogen material is reutilized as such in the production of new cells. The main problems in using the technique are concerned with the availability of appropriate potent anti-sera, the finding of suitable donor-recipient combinations and the avoidance of unusual donor-recipient incompatibilities which may lead to erroneous conclusions.

In this method red cells that are

compatible but serologically identifiable are transfused, and the rate of their disappearance is followed. For example, the fate of Group O cells can be determined when given to a Group A recipient. Serial blood samples are drawn, the recipient's cells removed by agglutination with anti-A serum, and the donor cells which remain freely suspended are counted. These values are plotted against time on graph paper. The resulting slope shows the pattern of disappearance of the transfused cells and, from this slope, the average life of the transfused red cells can usually be calculated. By cross transfusion studies in hemolytic syndromes, it is possible to determine whether faulty cells or abnormal environmental factors are primarily the cause of the increased rate of red cell destruction.

The Ashby method has been most useful to demonstrate the general processes of destruction in various hemolytic syndromes. However, except for a few simple cases, mathematical treatment of the curves to deduce quantitatively the mechanisms involved have proved formidable[5] although recent[6-9] proposals may be helpful. A necessary requisite for quantitative analysis is a smooth curve. With frequent sampling, the use of the potent anti-sera, and the counting of large numbers of unagglutinated cells (1000-4000)[7,8] this condition will more frequently be met.

A third type of human red cell labelling has been described by Jope[10]. The disappearance of sulfhemoglobin from the blood was followed in persons who had been exposed to T.N.T. The disappearance slope was linear and the sulfhemoglobin disappeared in an average time of 116 days in six subjects. It was assumed, therefore, that the sulfhemoglobin was retained until destruction of the red cells, and it appeared that the life of the red cell was not impaired by the presence of the abnormal hemoglobin. However, Jope's observations have not been confirmed. Moreover, Brown[11] points out that the equations[10] for derivations of the spectrophotometric constants contain an error and therefore cannot be used as given. Brown has found that the sulfhemoglobin disappears in a curvilinear manner. This may indicate that the sulfhemoglobin is reverted to normal hemoglobin or that affected cells have an altered life span. Dod, Bierman and Shimkin[12] noted an exponential disappearance curve of sulfhemoglobin in rabbits, and that anemia developed in 3 of 7 rabbits in whom sulfhemoglobinemia was produced. The method of sulfhemoglobinization of red cells as a tracer technique does not appear promising at present.

3. Applications and results of red cell tracer studies

General Statement

World War II with its demands for whole blood transfusions served as a great stimulus to development of methods to observe the survival of red cells. It became quickly apparent that blood had to be tested in vivo in order to evaluate the results of various blood banking methods on the viability of the stored cells. The Ashby technique was efficaciously applied to these ends especially by the English group. At the same time, the method was obviously a means to study normal cell survival, various hemolytic syndromes and transfusion reactions. Radioiron tagged donor cells were used in this country to test various methods of preserving red cells, but, partly because of reutilization of the tag, this method did not lead so easily to the other observations. By means of tagged cells the in vivo effects on red cell survival of various agents such as X-ray, ACTH and cortisone as well as of others can be followed.

Normal erythrocyte survival

It is now generally accepted that the normal life span of the erythrocyte in man is between 100 and 120 days. The life span figures have been established mainly by means of the Ashby differential agglutination technique[7,13-16] by glycine-N^{15} studies[17,18] and also by radioiron.[19] These figures agree with some of the estimates made on the basis of bile pigment excretion.[20,21] However, it

may be remarked that Schiødt[20] concluded in 1938 from a review of all evidence available at that time, including pigment excretion studies, that the duration of life of the red cell was about 30 days.

Figure 1, although a study in a patient with leukemic-reticuloendotheliosis (see L.H. below) serves to illustrate normal types of survival curves found by means of serologically identifiable transfused cells (Ashby technique) and by the labelling of the patient's own cells by feeding N^{15} marked glycine. In the case of transfused cells where the sample contains cells of all ages, the linear type of disappearance slope can most simply be explained by the fact that the red cells have a constant life-span[6,7,14,15]. This type of slope results if a fixed number, i.e., the cells equivalent to one day's production, are eliminated each day. The slope of this line gives the rate of destruction and the point where the line cuts the time axis of the graph gives the average life-span of the red cells. In this example the average life-span of the transfused cells is about 110 days, the rate of destruction of these cells about 0.91 per cent per day.

Because it is likely there is some variation of life-span from cell to cell produced on a particular day, a "tailing out" at the end of the Ashby curve can be expected, and indeed occurs at times. However, accuracy of the counts is poor in this region because the unagglutinable count, which itself can show some variation, makes up a large part of the free cell count. Mollison[7] concludes, partly on the basis of observations on 14 subjects taken about 120 days after transfusion, that transfusion experiments suggest there is comparatively little variation in red cell life. A calculation based on the presence of 2 per cent of transfused cells at 120 days indicates 95 per cent of the cells live 120 $\pm$ 12 days.

In the case of the N^{15} curve, a comparatively small population of red cells is tagged. In this instance (Fig. 1) analysis of the curve indicates the average life-span of the patient's cells to be about 110 days. The fact that the normal N^{15} curves are "plateau" in type rather than random decay slopes indicates that the cells do have a life span, that their death is a function of age.[17] This confirms the deductions from the linear Ashby slopes. One point of discrepancy is the early time at which the N^{15} level begins to fall, in this example, after about 50 days. This is in keeping with normal curves reported by London et al[18] where the N^{15} began to fall after forty to sixty days. The second and third quarters of the cell population were concluded[18] to die between 106 and 141 days. This could indicate that there is a wide variation in the life-span of a given population of red cells and is at variance with the conclusions drawn from the study of the survival of transfused cells. Mollison[7] points out that the assumption in N^{15} red cell studies that there is no reutilization of N^{15} may not be valid. Therefore, precise information as to the exact variability of life-span of a population of red cells can not be determined by this method. He suggests that very frequent Ashby counts towards the end of the survival curve with mathematical analysis may lead to the best answer.

Normal erythrocyte destruction

Previous to the use of red cell tracer methods it could not be established whether a cell lived a certain length of time, then disintegrated, or whether an active destructive system removed a certain proportion of cells each day regardless of their age. Schiødt[20] expressed these ideas in 1938 and favored the longevity theory. Now that the tracer methods have established the longevity theory as fact, further progress can be made as to the mechanisms of red cell destruction.

Ponder[5] points out that the process which ends in the destruction of the red cell under normal conditions presumably is an intrinsic one, i.e., one that takes place in the red cell itself. He urges the idea of "wear and tear" by buffeting about in the circulation be replaced by

the idea of a cell aging continuously, and of the aging process as involving a using up of enzymes essential to the cell's integrity. The methemoglobin reductase mechanism[22] may be one such system affected by age. The idea that the life of the red cell is limited by the degradation of its metabolic processes is an improvement over the idea of wear and tear due to movement in the circulation. However, the nature of the terminal event which removes the red cell under normal conditions is yet debatable. Rous[23] stated in 1923 that only two methods had so far been described whereby worn-out red cells left the circulation--fragmentation and phagocytosis, and that hemolysis had not been proven a factor in normal blood destruction. Ponder[5] states that even now the evidence for normal red cell destruction by hemolysis is unimpressive. However, at present a number of normally occurring substances are recognized at least as potential lysins.

Erythrocyte survival under pathologic conditions

Hemolytic anemias primarily due to faulty red cells (intrinsic defects)

This group is characterized in cross transfusion studies by normal survival of cells transfused to the patient but a diminished survival of the patient's cells in normal recipients:

(1) Hereditary spherocytosis[24-29]
(2) Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria[30]
(3) Sickle cell anemia[31,32]
(4) Thalassemia major (Cooley's anemia)[33]
(5) Congenital hemolytic anemias of unclassified type[7,34,35]
(6) Elliptocytosis (possibly in some cases)[36]
(7) Although pernicious anemia is not primarily a hemolytic anemia in the usual sense, shortened survival of the cells has been found.[37,38] However, recent reports[8,39] indicate there is also some shortening of survival of normal cells in patients with pernicious anemia.

Of this group of hemolytic anemias we have studied erythrocyte survival in two patients with hereditary spherocytosis and in two patients with paroxysmal nocturnal hemoglobinuria.

Hereditary spherocytosis

The first patient was studied with glycine-N^{15} in collaboration with D. S. Amatuzio and C. J. Watson and will be reported in detail elsewhere. The patient was a 73-year old professor emeritus (J.B.) who had a classical personal and family history of hereditary spherocytosis. Physical examination revealed mild icterus and an enlarged spleen which extended to the iliac crest. In November 1949, with acute urinary retention, transurethral resection, and a transfusion reaction, the tempo of the disease was apparently increased. For the following 3 months, during which period the N^{15} observations were made, the patient had persistent jaundice, anemia, reticulocytosis, and an increased fecal urobilinogen excretion. The patient having agreed to be a subject for isotopic tracer studies of hemoglobin metabolism, glycine-N^{15} was administered orally over a 3 3/4 day period beginning December 21, 1949. Blood and stool samples were collected at appropriate intervals for 154 days. All stools were collected in 3 day periods during the first 28 days.

Crystalline protoporphyrin was prepared from the hemoglobin of the blood specimens[40] and stercobilin was extracted from the stools.[41] The N^{15} content of these samples was determined by means of the mass spectograph.[42]

We are concerned in this report primarily with the red cell survival pattern as indicated by the N^{15} concentrations in the circulating hemoglobin.

Figure 2 is a graph of the hemoglobin protoporphyrin N^{15} values plotted against time. The curve indicates a random type of disappearance of the N^{15}. On the assumption that the N^{15} tag remains with the red cell hemoglobin until the cell

disintegrates, it can be concluded that the red cells in this patient with hereditary spherocytosis die in their own environment, indiscriminately, regardless of age. To derive the average life of the red cells a further assumption must be made, namely, that during the decline of the N^{15} concentration no newly formed cells marked with N^{15} are added to the circulation. With these two major assumptions the average life of the red cells is calculated to be about 37 days. Splenectomy had been performed on the 68th day. The average life was calculated using an extrapolation from the 68th day conceived on the basis that splenectomy had not been done.

It is of interest to compare this 37 day average life figure with an estimation made from urobilinogen excretion. During the first 28 days of the study, the patient had an average hemoglobin of 9.7 gm/100 ml of blood. Blood volume was calculated to be 5100 ml from surface area using the chart of Gibson et al.(43) These figures indicate that there was an average circulating hemoglobin mass of 495 gm. Fecal urobilinogen was quantitatively determined(44) in nine 3 day stool collections made during this period and averaged 1133 mg/day (range, 820-1590). The "apparent" wastage of hemoglobin (2.39 gm Hb equivalent to 100 mg fecal urobilinogen)(45) was found to be 27 gm/day. From this and the circulating hemoglobin mass, it could be estimated that about 5.5 per cent of the circulating hemoglobin was destroyed each day. This suggests that the average life of the red cells was about 18 days.

Studies of red cells from patients with hereditary spherocytosis transfused to normals have indicated shorter average survival than found in this N^{15} study. This discrepancy may have been due to several possibilities, one of which was that newly formed cells tagged with N^{15} were entering the circulation during the decline phase of the N^{15} concentration. This, of course, would decrease the rate and extent of fall of the N^{15} concentration giving a falsely long average life of the red cells.

The second investigation of cell survival and hemoglobin metabolism in hereditary spherocytosis includes the simultaneous use of the N^{15} and Ashby methods. It is currently in progress in conjunction with R. J. Goldish, P. T. Lowry and C. J. Watson. The Ashby study portion of the work has been essentially completed and a preliminary report of these findings is given here. The patient was a 65 year old farm laborer (J.P.) who was admitted to the Minneapolis Veterans Administration Hospital because of mild congestive heart failure and auricular fibrillation on an arteriosclerotic basis. He was found also to have typical physical and laboratory findings of hereditary spherocytosis. The spleen extended to the iliac crest. Hemoglobin was 11 gm/100 ml. Reticulocytes ranged from 6.7 per cent to 14.3 per cent. A sibling was found also to have typical findings of hereditary spherocytosis.

The patient's blood group was O $Rh^{+}M$. Aoproximately 500 ml. of blood were removed February 7, 1952 and given to a normal recipient of blood group A $Rh^{+}M$. This recipient had previously received blood of group A $Rh^{+}N$ for a survival study. The elimination slope indicated that the normal blood was disappearing at a normal rate.

Immediately after the blood was removed from the patient, it was replaced by O $Rh^{+}N$ blood. By the use of appropriate anti-sera, the fate of normal blood was followed in the patient, while the patient's blood was observed in a normal person who at the same time was showing a normal rate of removal of normal blood.

Figure 3 shows the results of the cross transfusion study. Normal blood was eliminated by the patient in a normal pattern indicating normal environmental factors. On the other hand, the patient's blood was rapidly removed from the normal recipient which showed that the patient's cells were defective. The cells disappeared in a random manner, indicating that cells of all ages were affected. The long tailing out of the curve shows a wide variation of the cells in the susceptibility to destruction. The average survival of these hereditary spherocytic

cells in a normal, calculated by the area method,[6,46] was 8 days.

It is of interest to compare this figure with an estimate of average red cell life based on fecal urobilinogen excretion in this patient. For certain observations as a part of the total study, the patient was receiving aureomycin, so the determination of fecal urobilinogen during the investigation was precluded. However, calculations of the "apparent" wastage of hemoglobin were made in October and November, 1951 and January, 1952. The "W" values were 7.8 per cent, 5.4 per cent and 5.8 per cent respectively, averaging 6.3 per cent. Average red cell life in the patient on the basis of this figure was about 16 days. It will be most interesting to compare these figures with the average life indicated by the disappearance of the hemoglobin N^{15} when those values become available.

With respect to the mechanisms of increased red cell destruction in hereditary spherocytosis, certain findings are pertinent. Emerson et al[47] found, in splenectomized patients with this disease, that the splenic pulp contained a high proportion of red cells markedly susceptible to hemolysis in hypotonic solution and to mechanical trauma when compared to those in the peripheral blood. They also transfused patients with hereditary spherocytosis with serologically identifiable cells several days before splenectomy. Study of red cells from the splenic pulp showed a distinctly greater proportion of the patient's cells than found in the peripheral blood.

Young et al[48] perfused 3 spleens with mixtures of normal and hereditary spherocytic cells which were serologically identifiable. They found that the spherocytic cells were selectively removed by the spleens. It was their belief that the spheroidal cells were readily trapped in the splenic pulp because the abnormal thickness of the cells did not permit them to escape easily through slit-like openings into the venous sinusoids.

Moreover, Schrumpf[28] found that cells from a patient with hereditary spherocytosis transfused to a splenectomized individual had a nearly normal life span.

These findings point up the role of the spleen in this disease and indicate why splenectomy is so effective.

Paroxysmal nocturnal hemoglobinuria

We have studied* the survival of normal cells in two patients who proved to have chronic hemolytic anemia with paroxysmal hemoglobinuria. In each instance, the survival of the transfused cells was essentially normal. These findings proved of aid in the correct diagnosis in each instance. The first patient was a 25 year-old male (W.W.) who had had anemia since 1945. Since 1947, there had been several episodes of passing "dark" urine. In 1949, a splenectomy had been done elsewhere for possible familial hemolytic anemia but without effect. He had laboratory findings consistent with hemolytic anemia, including reticulocytosis and elevated fecal urobilinogen excretion. To help rule out an acquired, that is, "extrinsic", type of hemolytic anemia, the Ashby study was undertaken. Observance of normal disappearance of the transfused cells coupled with the elevated fecal urobilinogen excretion (362 to 793 mg/day) indicated that the problem was one of intrinsically defective cells. Appropriate laboratory tests including the Ham acid-serum test[49] established the correct diagnosis.

The second patient was a 61 year old man (N.N.) who had had symptoms of anemia for 2 years. He had hepato-splenomegaly and leukopenia. The patient was of a stoical type and had some speech difficulty. A history of hemoglobinuria was not elicited. That he had hemolytic anemia was obvious from laboratory examinations. He was suspected of having leukemia or lymphoma with a "symptomatic" hemolytic anemia. An Ashby study was started and revealed, surprisingly, a normal rate of elimination of the transfused cells. This led to closer examination and, indeed, hemoglobinemia and hemoglobinuria were found. Normal sur-

vival of transfused cells in the face of constant hemoglobinemia indicated that the patient's cells were defective. They proved to satisfy the criteria for cells of paroxysmal nocturnal hemoglobinuria.(49)

Cells from our first patient were transfused to a normal but due to a donor-recipient combination of blood groups unsatisfactory for the Ashby technique, the study was unsuccessful.

Normal survival of transfused cells in paroxysmal nocturnal hemoglobinuria was first reported by Dacie and Firth in 1943(50) and has been confirmed in additional reports.(4,51,53)

Hemolytic anemias due to abnormal environmental factors ("extrinsic" or acquired hemolytic anemia)

Survival studies of transfused cells in hemolytic anemias not due to malformation of the red cells consistently have shown a shortened survival time. This demonstrates that abnormal environmental (extrinsic) factors are important in these hemolytic syndromes on the presumption that the transfused and the patient's cells are affected in similar fashion.

Various agents cause hemolytic syndromes, however, hyperimmune bodies are the most frequent type encountered. A variety of hyperimmune reactions are found. The use of the Coombs anti-human globulin test has increased the incidence of demonstrating the presence of a red cell "coating" presumably by hyperimmune bodies in these acquired hemolytic anemias.

That the patient's cells are fundamentally normal has been demonstrated by substantially normal survival of these cells in normal recipients.(25) However, if the cells are "heavily coated", there may be a rapid disappearance of variable percentages of the cells with normal survival of the remainder.(54,55)

Idiopathic acquired hemolytic anemia

We have observed* the survival of transfused cells in 3 patients with idiopathic acquired hemolytic anemia and have found a shortened survival in each instance.

The first patient, (,) was a 28 year old student who had a 2 week history of easy fatiguability, headache and chilly sensations. The spleen was palpable 2 cm below the costal margin and was tender. Laboratory study showed: hemoglobin 9.8 gm/100 ml of blood; reticulocytes 14 per cent, serum bilirubin 0.2 (1 min.) and 1.5 (total mg/100 ml; red cell osmotic fragility increased; cold agglutinin titer 1:16; Coombs test, negative direct, positive indirect; positive trypsinated cell test; fecal urobilinogen (4 day specimen) 1300 mg/day. He was blood group B $Rh^{+}N$ and was given 2000 ml of B $Rh^{+}M$ blood for an Ashby study.

Figure 4 shows the disappearance slope of these cells. The average life calculated by the area methos was 16 days. This slope plots as a straight line on semi-logarithmic graph paper and so is exponential in type. This indicates a steady rate of removal of the transfused cells and that there is random destruction of cells of all ages.

In this case where the removal of transfused cells is rapid and the slope of disappearance exponential, the survival of the transfused cells is presumably a good estimate of the patient's own average cell life.(7) Because quantitative fecal urobilinogen determinations were made in successive 4 day stool collections during the Ashby study, an opportunity was afforded to compare the estimates of red cell turnover by the two methods. The average "apparent" wastage figure from the bile pigment excretion during the period of study was 4.5 per cent compared with 6.2 per cent ($\frac{1}{\text{Av. red cell life}} \times \frac{100}{1}$ from the Ashby data, a ratio of 0.73.

Because of the reported favorable results,(56-58) the effect of ACTH and Cortisone on red cell survival was investigated in the second patient with idiopathic acquired hemolytic anemia. The patient was a 23 year-old college student, (,) who for 3 weeks before admission, had had weakness, fatigue, dyspnea on exertion and a low grade fever. The spleen was not

palpable. Laboratory data revealed: hemoglobin 8.3 gm/100 ml of blood, reticulocytes 43 per cent, increased osmotic fragility of the erythrocytes, serum bilirubin 0.2 (1 minute) and 1.7 (total) mg/100 ml, Coombs test negative direct and indirect, negative trypsinated cell test, and a cold agglutinin titer 1:8. Because he had received aureomycin before admission the fecal urobilinogen results were unreliable.

The patient's blood group was O Rh+N. He received O Rh+M blood for cell survival studies. The results are shown in Figure 5.

The first study of survival of transfused blood lasted from 2/26/51 to 4/3/51. During this time there was an average hemoglobin of 12.7 gm/100 ml of blood with 11.6 per cent reticulocytes. Average life (area method used in each instance) of the transfused cells was 12.8 days. At the end of this period, the Coombs test was found positive direct and indirect as well as a positive trypsinated cell test.

During the second period, 4/5/51 to 5/15/51, an average of 153 mg/day of cortisone were administered intramuscularly for 30 days. The hemoglobin level dipped from 10.3 to 5.8 then climbed to 10.6, reticulocytes started at 17.8 per cent and peaked to 39.3 per cent with an average of 28.5 per cent, and fecal urobilinogen output averaged 1816 mg/day in successive 4 day stool collections ("apparent" hemoglobin wastage = 9.9 per cent. The Coombs and trypsinated cell tests became negative. The average life of the transfused red cells was 12.9 days.

During the third period, 5/16/51 to 7/9/51, 80 mg/day of ACTH was given intramuscularly for 30 days. Hemoglobin averaged 12.6, reticulocytes 10.2 per cent, and fecal urobilinogen 1011 mg/day ("apparent" hemoglobin wastage = 3.0 per cent). The average life of the transfused red cells was 18.6 days.

These studies indicate that there was no change in the environmental factors during cortisone therapy as regards the survival of transfused blood. There may have been some change during the ACTH therapy. (The "marked" blood used in these studies, unfortunately, was crossmatched only in the usual manner and not checked with the indirect Coombs testing technique.) Coincidentally or not, there was a remission following the ACTH therapy which has continued to the present time.

In the third patient, transfused cells had an average life of 27.6 days.

Erythrocyte survival in leukemia and Hodgkins disease

Where hemorrhage is excluded, anemia results from shortened red cell survival, decreased production of red cells, or a combination of these two factors. Red cell tracer studies have been used to elucidate the mechanisms of the anemia in leukemia and have shown shortened red cell survival almost regularly in the small number of patients examined (59-62). This confirms numerous previous reports that hemolytic anemia occurs in leukemia. (63-64)

The mechanisms of anemia were studied in a patient with leukemic reticuloendotheliosis by means of simultaneous Ashby and N^{15} methods. The N^{15} phase of the investigation was made by P. T. Lowry as a part of certain observations on hemoglobin metabolism that will be reported separately. The patient, (L.H.) (private patient of Dr. C. J. Watson), a 53 year old white woman, was first admitted to the University Hospitals May 1, 1949. She had skin lesions of sporotrichosis, anemia, mild granulocytopenia and increased urinary porphyrins. The sporotrichosis responded to therapy. However, the splenomegaly, anemia, granulocytopenia and increased urinary porphyrin excretion persisted. There was also a mild reduction in platelets. The mechanism of the anemia was not clear. Reticulocytes were normal or slightly increased in number but the fecal urobilinogen values were not elevated. The Coombs test was negative. Accordingly, both glycine-N^{15} and serologically iden-

tifiable red cells were given in mid-May 1950 to see if there was a shortened survival of the patient's red cells, and if so, whether the reason was primarily faulty cells, or abnormal environmental factors.

Ten grams of glycine containing 62 atom per cent of N^{15} were administered orally over a two day period. The patient was blood group B Rh+M. Three units of B Rh+N blood were transfused for the Ashby study. Blood volume determined by the Evans Blue dye method(65) was 4300 ml. During the period of study, the hemoglobin averaged 11.3 gm/100 ml of blood, reticulocytes 2.6 per cent, and fecal urobilinogen 99 mg/day in 6 determinations.

Figure 1 shows the results of the red cell survival studies which, as mentioned above, indicate normal life spans (about 110 days in each instance) of both the patient's and the transfused cells. This shows that in this case of leukemia, the patient was producing red cells normal at least with respect to life span. One patient with chronic lymphatic leukemia studied with glycine-C^{14} by Berlin(62) gave essentially the same results. Since both the patient's and the transfused red cells had a normal survival time, there was no evidence that abnormal environmental factors were the cause of the anemia in this patient. Since there was also no evidence of hemorrhage, the anemia must have been due to a decreased rate of red cell production. Bone marrow study (by R.D.Sundberg) did not indicate this. Red cell regeneration appeared reasonably active, the normoblasts were relatively increased (32.2 per cent). The slightly decreased rate of rise of the hemoglobin N^{15} concentration was consistent with a decreased rate of red cell production. "Apparent" hemoglobin wastage calculated from the urobilinogen values was about 0.5 per cent/day while the rate of red cell breakdown indicated by the cell survival studies was about 0.9 per cent/day, a ratio of 0.55.

The survival of transfused cells was investigated* in several patients with leukemia and Hodgkins disease. The results are summarized in Table I. In 6 of the 7 patients, there was an increased rate of destruction of the transfused cells. The elimination curves were not smooth and did not lend themselves to detailed analysis. However, most of them were essentially curvilinear. In two cases, the slope was essentially linear, in H.D. with a rapid rate of disappearance while in E.P., the rate was practically normal. These results indicate, as has been shown by others,(56,59-61) that the anemia of leukemia is rather frequently associated with an increased rate of red cell destruction due to abnormal environmental factors. Evidence of hyperimmune bodies is often found in these patients.

The effect of cortisone on the survival of transfused red cells was studied in R.R., a patient with Hodgkins disease. He was a 34 year-old white man whose disease was diagnosed by lymph node biopsy in 1948. The red cell survival studies were made January through April 1951 at a time when the patient had persistent fever, splenomegaly, anemia, reticulocytosis and increased fecal urobilinogen excretion. The patient was blood group A Rh+M, and was given for each study 4 units of A Rh+N blood which had been cross matched only in the usual manner. The results of the first study are recorded in Table I. Cortisone was then administered intramuscularly in an average dose of 150 mg/day for 62 days and the survival of transfused red cells restudied. During this period of study, there was marked clinical improvement with abatement of the fever and the patient experienced a feeling of well being. Average laboratory values were as follows: hemoglobin 13.6 gm/100 ml of blood; reticulocytes 3.8 per cent, and the fecal urobilinogen in successive 4 day stool collections was 559 mg/day. An average "apparent" wastage figure was 1.9 per cent/day in contrast to 4.1 per cent/day before cortisone. The average life of the transfused red cells was now 33.5 days compared with 23.6 days before cortisone. These results suggest that, in this patient, cortisone was of beneficial effect on the hemolytic anemia. Figure 6 shows the red cell survival curves in this case.

Summary and Conclusions

1. Tracer methods of study of red cell survival have been briefly outlined as well as some of the results of the use of these techniques.

2. The results of some of our investigations of red cell survival were as follows:

   a. Red cell survival was studied with glycine-N^{15} in a patient with hereditary spherocytosis. Based upon two major assumptions relating to the method of study, the average life was found to be about 37 days.

   b. By means of the Ashby differential agglutination technique, the average survival of red cells from another patient with hereditary spherocytosis when transfused to a normal was about 8 days.

   c. The survival of transfused red cells in two patients with paroxysmal nocturnal hemoglobinuria was normal.

   d. In three patients with idiopathic acquired hemolytic anemia transfused red cells had decreased average life, demonstrating the presence of abnormal environmental factors as a cause of increased red cell destruction in this disease.

   e. Transfused blood had decreased survival in 6 of 8 patients with leukemia or Hodgkins disease.

   f. Simultaneous Ashby and N^{15} studies in a patient with leukemic reticulo-endotheliosis showed normal survival of both the patient's and donor cells. The N^{15} curve indicated that at least in this patient with leukemia normal cells were produced by the bone marrow. The results of the study suggested that the anemia was due to decreased production of red cells.

   g. The effect of ACTH and cortisone on the survival of transfused cells in hemolytic syndromes was examined in two patients. Cortisone appeared to be beneficial in the patient with Hodgkins disease but not in the patient with idiopathic acquired hemolytic anemia. ACTH may have been of some benefit in the latter.

   h. Where adequate fecal urobilinogen studies could be made, the results quite regularly predicted the the shortened survival of red cells cells as elicited by the red cell tracer studies. Quantitative comparison could be made in only 2 instances. The fecal urobilinogen values indicated a smaller per cent per day destruction of red cells than did the tracer studies, in one 0.73 and in another 0.55 as much.

Acknowledgments:

Studies marked with an asterisk (*) were made with E. F. Englund, M.D., Minneapolis, who was a Resident in Medicine at the time.

R. L. Evans, Ph.D., of the Mathematics and Mechanics Department analyzed certain of the curves and gave much helpful advice for which it is a pleasure to thank him.

The author wishes to express his appreciation and thanks to Frances Severance Loomis for her valuable technical aid.

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References

1. Shemin, D. and Rittenberg, D. J.Biol.Chem.,159:567:1945.
2. Ashby, W. J.Exper.Med.,29:267:1919.
3. Young, L. E., Platzer, R. F., and Rafferty, J. A., J.Lab.Clin.Med.,32:489:1947.
4. DeGowin, E. L., Sheets, R. F., and Hamilton, H. E., J.Clin.Invest.,29:693:1950.
5. Ponder, E. Blood, 6:559:1951.
6. Dornhorst, A. C.

Figure 1

Ashby and N^{15} Studies in Leukemic Reticulo-endotheliosis

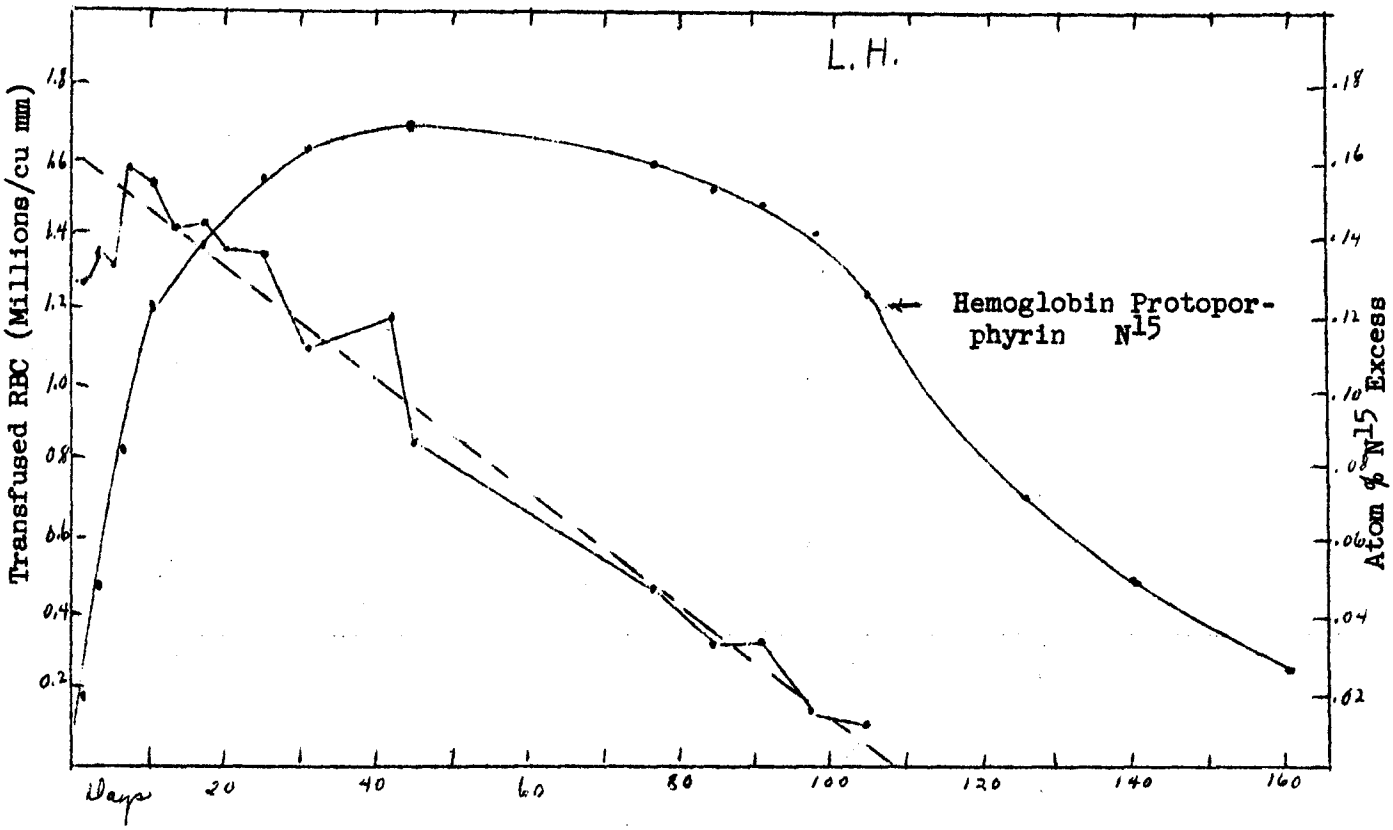


Figure 2

N^{15} Study of Hereditary Spherocytosis

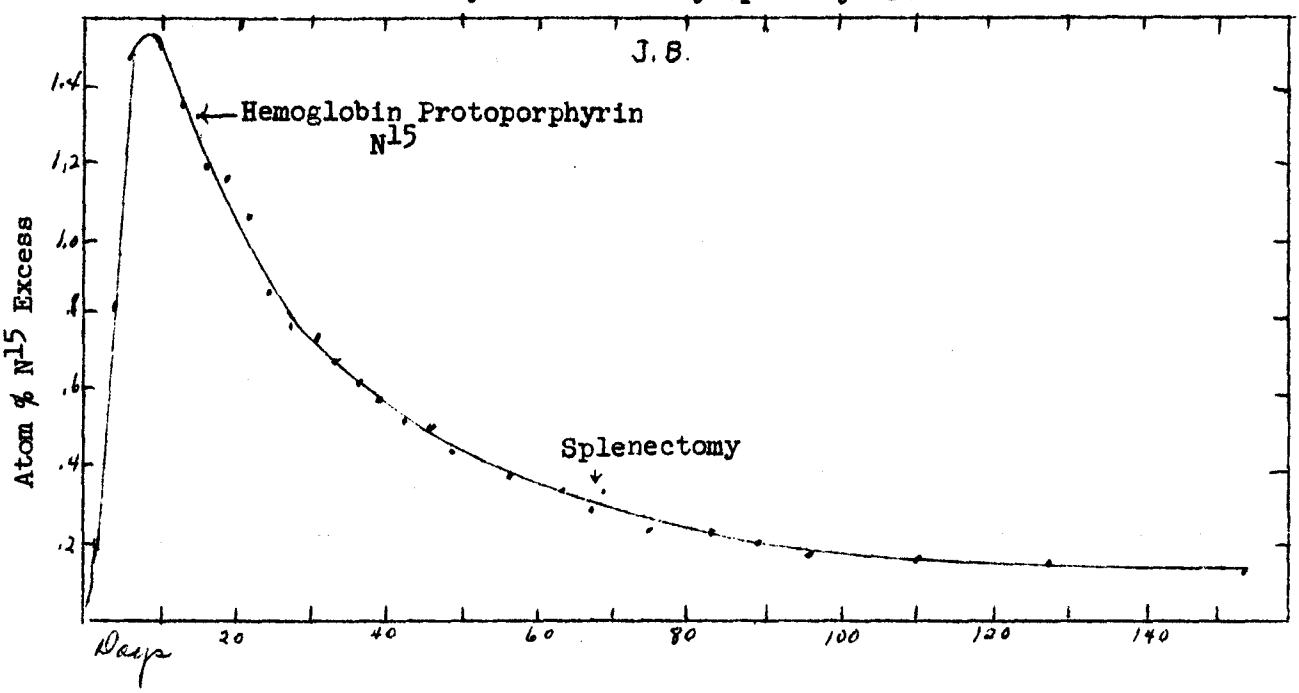
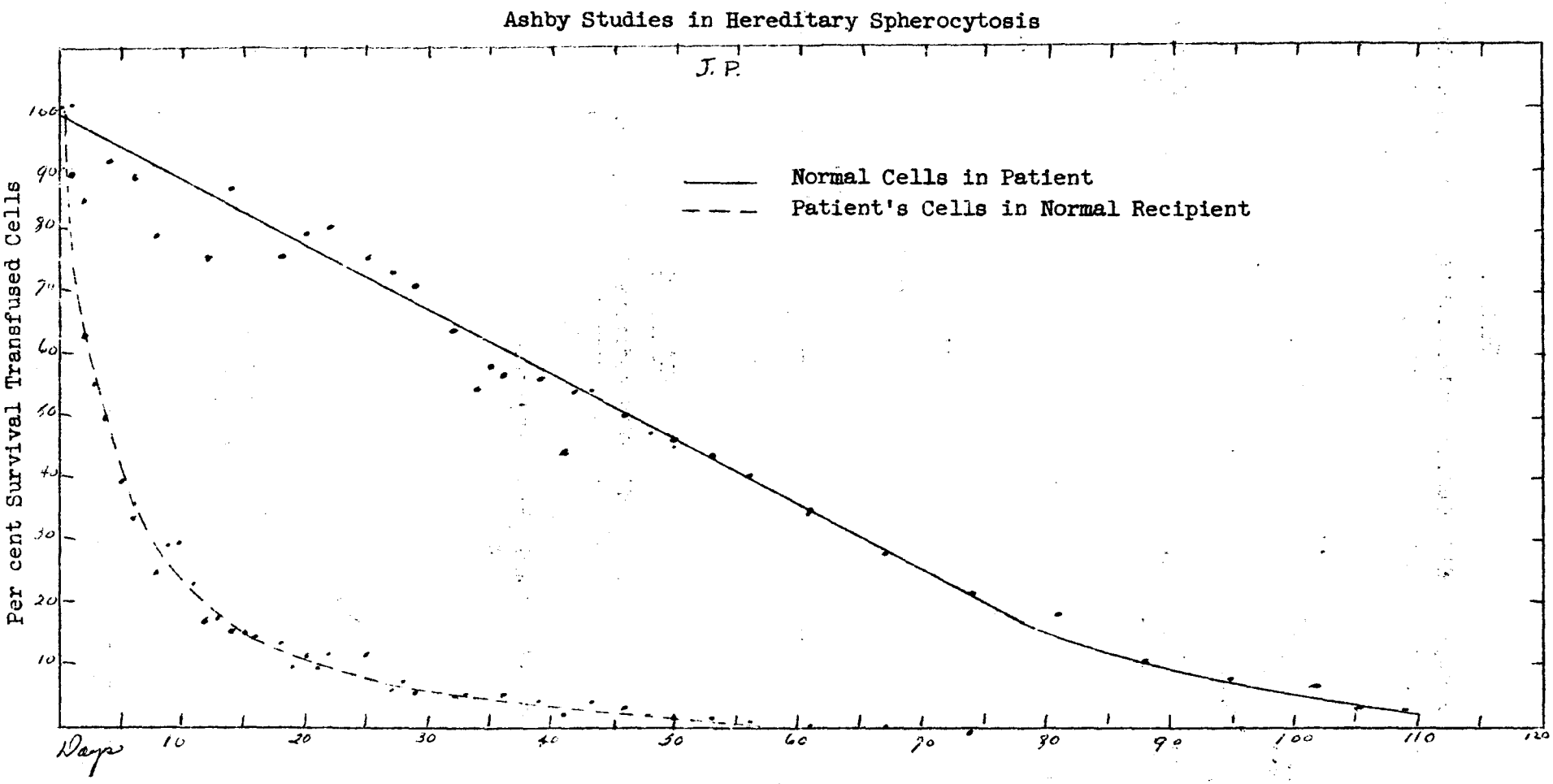


Figure 3


Ashby Studies in Hereditary Spherocytosis
J. P.
Normal Cells in Patient
Patient's Cells in Normal Recipient
Per cent Survival Transfused Cells
Days
10
20
30
40
50
60
70
80
90
100
110
120

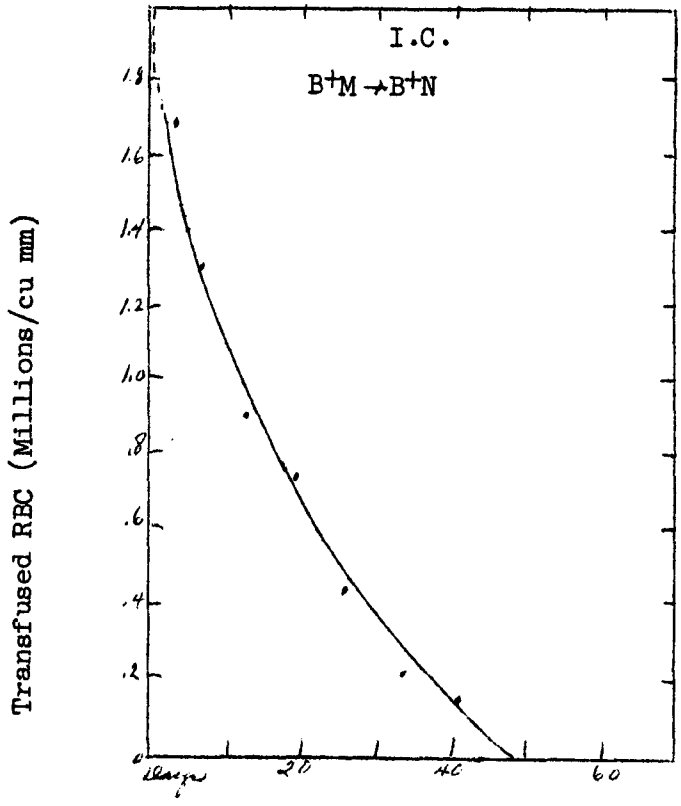


Figure 4

Idiopathic Acquired Hem. Anemia

Figure 5

Idiopathic Acquired Hemolytic Anemia

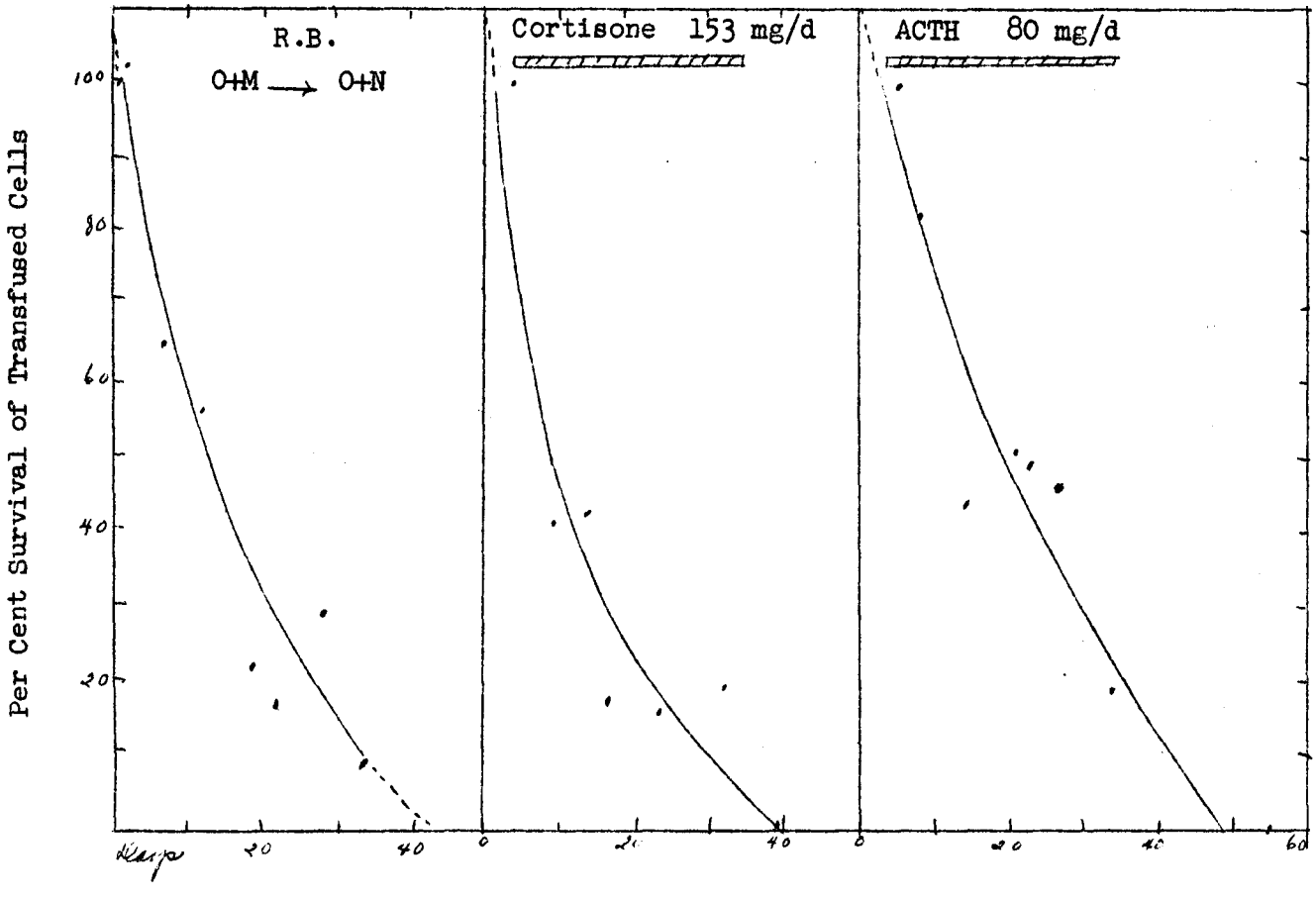


Figure 6

Hemolytic Anemia with Hodgkin's Disease

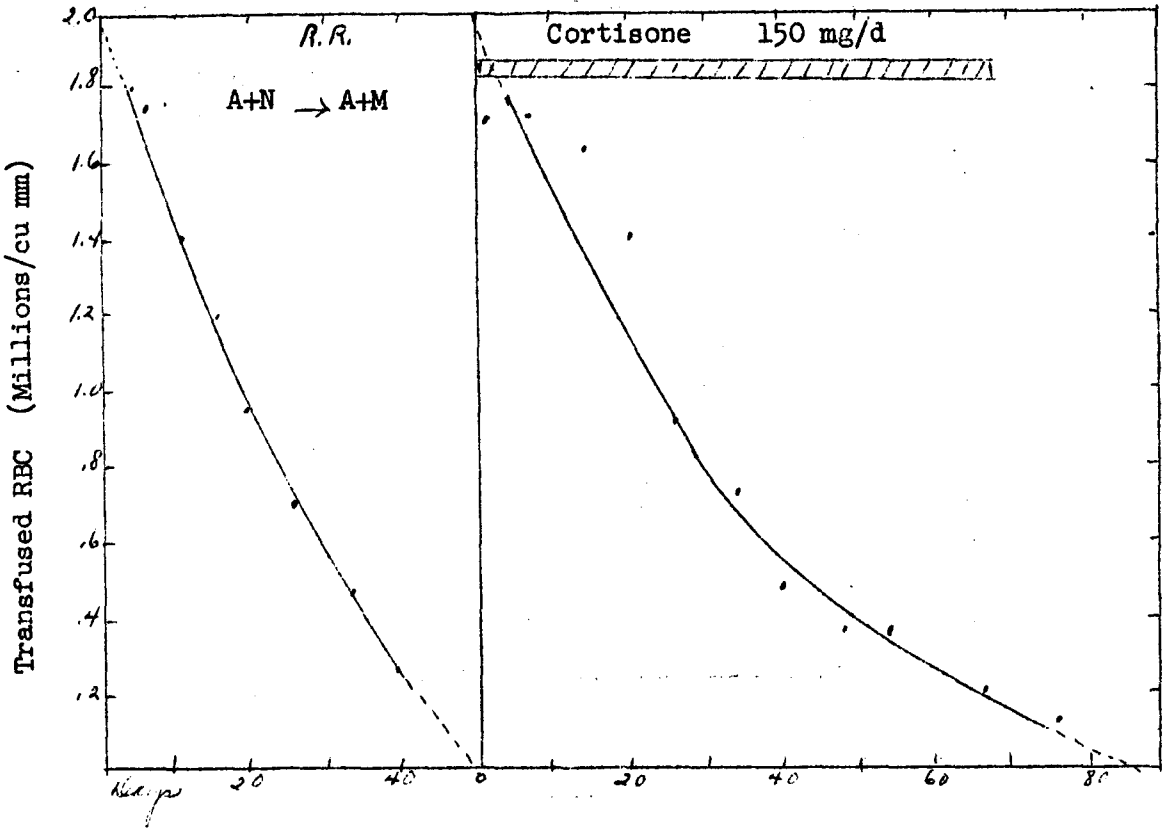


Table I

Survival of Transfused Red Cells in Leukemia and Hodgkin's Disease

Pt.	Diagnosis	Hb gm/100 ml	Retic %	Coomb's test Dir	Coomb's test Ind	Trypsinated cell test	F.U. mg/d	"Apparent" Hb wastage %	Average survival transfused cells, days***
	CML	5.3	0.1	0	0	0	758	7.4	17****
	CML	10.5	7.4	+	+		322	1.5	38
*	CML	8.4	0.6	0	0	0	117	0.6	48
	LRE	8.4	0.1	+	0		Aureomycin		29
	CLL	8.0	0.0	+	+	+	Aureomycin		17
*	CLL	7.8	0.5	0	0	0	135**	0.9	33
	Hodg.	10.1	8.5	0	0	0	897	4.1	24

CML = Chronic myelocytic leukemia
LRE = Leukemic reticulo-endotheliosis
CLL = Chronic lymphocytic leukemia

* Post splenectomy
** Aureomycin 7 weeks previously
*** Normal = 50 to 60 days calculated by the area method
**** During cortisone administration

Blood, 6, 1284, 1951
7. Mollison, P. L.
Blood Transfusion in Clinical Medicine.
Chas. C. Thomas, Springfield, 1951.
8. Sheets, R. F., Janney, C. D., Hamilton, H. E. and De Gowin, E. L.
J.Clin.Invest.,30:1272:1951.
9. Evans, R. L., Amatuzio, D. S., and Ebert, R. V.
Science, 115:572:1952.
10. Jope, E. M.
Brit.J.Indust.Med.,3:136:1946.
11. Brown, Ivan, personal communication.
12. Dod, K. S., Bierman, H. R., and Shimkin, M. B.
J.Natl.Cancer Inst., 11:1093:1951.
13. Ashby, W.
Blood, 3:486:1948.
14. Brown, G. M., Hayward, O., Powell, E. O. and Witts, L. J.
J.Path.Bact., 56:81:1944.
15. Callender, S. T. E., Powell, E. O., and Witts, L. J.
J.Path. Bact., 57:129:1945.
16. Callender, S.T.E., Powell, E.O., and Witts, L. J.
J.Path.Bact.,59:519:1947.
17. Shemin, D. and Rittenberg, D.
J.Biol.Chem.,166:627:1946
18. London, I. M., Shemin, D., West, R., and Rittenberg, D.
J.Biol. Chem.179:463:1949.
19. Finch, C. A., Wolff, J. A., Rath, C. E., and Fluharty, R. G.
J.Lab.Clin.Med.,34:1480:1949.
20. Schiødt, E.
Acta med. Scand., 95:49:1938.
21. Watson, C. J., Outlines of Int.Med., 7th ed., 1952, Wm. C. Brown, Dubuque, Iowa.
22. Drabkin, D. L.
Physiol. Rev., 31:345:1951
23. Rous, P.,
Physiol.Rev.,3:75:1923.
24. Dacie, J. V. and Mollison, P. L.
Lancet, 1:550:1943.
25. Loutit, J. F. and Mollison, P. L.
J.Path.Bact.,58:711:1946.
26. Owren, P. A.
Blood, 3:231:1948.
27. Wright, C. S., Bouroncle, B. A., Bubis, S. R. and Doan, C. A.
J.Lab.Clin.Med.,36:1006:1950.
28. Schrumpf, C. A. A.,
Proc.Third Intl.Cong.Intl.Soc. Hematology, P.94, C.V.Moore, ed., Grune and Stratton, N.Y., 1951.
29. Kaplan, E. and Zuelzer, W. W.
J.Lab.Clin.Med.,36:511:1950.
30. Dacie, J. V. and Mollison, P. L.
Lancet, 1:390:1949.
31. Singer, K., Robin, S., King, J. C., and Jefferson, R. N.
J.Lab.Clin.Med.,33:975:1948.
32. Callender, S. T. E., Nickel, J. F., and Moore, C. V.
J.Lab.Clin.Med., 34:90:1949.
33. Kaplan, E. and Zuelzer, W. W.
J.Lab.Clin.Med.,36:517:1950.
34. Kaplan, E. and Zuelzer, W. W.
J.Lab.Clin.Med.,36:524:1950.
35. Crosby, W. H.
Blood, 5:233:1950.
36. Hedenstedt, S. and Vahlquist, B.
Acta Paed., 35:355:1948.
37. Loutit, J. F.
Proc.Roy.Soc.Med.,39:757:1946.
38. Singer, K., King, J. C., and Robin, S.
J.Lab.Clin.Med.,33:1068:1948.
39. Hamilton, H. E., Sheets, R. F., and Janney, C. D.
Program Am.Soc.Clin.Invest., Atlantic City, 1952:p.27.
40. Grinstein, M.
J.Biol.Chem.,167:515:1947.
41. Watson, C. J.
J.Biol.Chem.,105:469:1934.
42. Preparation and Measurement of Isotopic Tracers, A Symposium:
Wilson, D. W. and Nier, A. O. C., Chairmen:
J.W.Edwards, Ann Arbor, Mich.,1947.
43. Gibson, J. G., 2nd, and Evans, W. A. Jr.,
J.Clin.Invest.,16:317:1937.
44. Schwartz, S., Sborov, V., and Watson, C. J.
Am.J.Clin.Path.,14:598:1944.
45. Watson, C. J.
Handbook of Hematology, ed. H.Downey, P.B.Hoeber, Inc., N.Y., p.2506:1938.
46. Evans, R. L.
Personal Communication.
47. Emerson, C. P., Jr., Shen, S. C., Ham, T. H. and Castle, W. B.
J.Clin.Invest.,26:1180:1947.
48. Young, L. E., Platzer, R. F., Ervin, D. M. and Izzo, M. J.
Blood, 6:1099:1951.
49. A Syllabus of Laboratory Examinations, Ed.T.H.Ham, Harvard University Press, Cambridge, 1950.
50. Dacie, J. V. and Firth, D.
Brit.Med. J., 1:626:1943.

51. Mollison, P. L.
Clin.Sci.,6:137:1947.
52. Dacie, J. V.
Clin.Sci.,7:65:1948.
53. Evans, R. S. and Duane, R. T.
Calif.Med.,70:244:1949.
54. Owren, P. A.
Scand.J.Clin.Lab.Invest., 1:41:1949.
55. Selwyn, J. G. and Hackett, W. E. R.
J.Clin.Path.,2:114:1949.
56. Dameshek, W., Rosenthal, M. C., and Schwartz, L. I.
New Eng.J.Med.,244:117:1951.
57. Gardner, F.
Blood, 5:791:1950.
58. Clearkin, K. P.
Lancet, 1:183:1952.
59. Berlin, R.
Acta med. Scandinav.,139:Suppl. 252; 1951.
60. Ross, J. F., Crockett, C. L., Jr., and Emerson, C. P.
Prog.Am.Soc.Clin.Invest.,Atlantic City, p.47 (April) 1951.
61. Brown, G. M., Elliot, S. M., Young, W. A.
J.Clin.Invest.,30:130:1951.
62. Berlin, N. I., Lawrence, J. H., and Lee, H. C.
Science, 114:385:1951.
63. Watson, C. J.
Ann.Int.Med.,12:1782:1939.
64. Wintrobe, M.M.
Clinical Hematology, 3rd ed., Lea and Febiger, Phila., 1951.
65. Gibson, J. G., 2nd, and Evelyn, K. A.
J.Clin.Invest., 17:153:1938.

II. MEDICAL SCHOOL NEWS

Coming Event

June 23-28 Continuation Course in Otolaryngology for Specialists.

* * *

Minnesota State Medical Association Meeting

Several members of the Medical School faculty participated in the scientific sessions of the recent meeting of the Minnesota State Medical Association. Dr. Ivan D. Baronofsky, Associate Professor, Department of Surgery, discussed "Shock in Trauma," and Dr. Leo G. Rigler, Professor and Head, Department of Radiology and Physical Medicine, talked on "Roentgen Observations on Vascular Lesions of the Lung." Dr. William T. Peyton, Professor and Director, Division of Neurosurgery, spoke on "The Surgical Treatment of Intractable Pain." The Minnesota Medical Foundation Lecture was presented by Dr. Carleton B. Chapman, Associate Professor, Department of Medicine. The subject of his lecture was, "Some Recent Advances in the Management of Hypertension." In a lecture sponsored by the Northwestern Pediatric Society Dr. Lewis Thomas spoke on "Recent Advances in Research on Rheumatic Fever." Dr. Thomas also took part in a round table luncheon which was devoted to the consideration of the effects of cortisone and ACTH on infection.

* * *

Senior Students Honored

Special awards were recently presented to three outstanding members of our graduating senior class by Dean Harold S. Diehl. Jerome J. DeCosse received the $500 Borden Award for undergraduate research on home accidents while Roger Murray was awarded the Rollin E. Cutts prize for research on pulmonary tumors. John A. Higgins was given the Southern Minnesota Medical Association prize of $100.

On Monday evening, June 2, 20 members of the senior class were initiated into the Alpha Omega Alpha honorary medical fraternity. The students selected for membership included: Herman D. Bentz, Jerome J. DeCosse, Robert E. Doan, Russell J. Eilers, Vernon D. Erickson, Mrs. A. Sigrid Gilbertsen, Marvin E. Goldberg, Charles L. Harris, John A. Higgins, Edward G. Hustad, John A. Johnson, Donald W. Klass, Richard C. Kogl, Lyle V. Kragh, Douglass E. Perkins, Donald E. Roach, Paul C. Royce, Charles M. Samet, Mrs. Mildred J. Schaffhausen, and Benjamin Wittels. The faculty and student body extend congratulations and best wishes to these students. The members of the Alpha Omega Alpha were also privileged to initiate, as honorary members, two distinguished members of our faculty, Dr. John L. McKelvey, Professor and Head, Department of Obstetrics and Gynecology, and Dr. Wesley W. Spink, Professor, Department of Medicine.

* * *

Dr. Huseby to Accept Denver Post

Congratulations are in order to Dr. Robert Huseby, Assistant Professor, Department of Pathology, and Research Associate, Department of Surgery, who has accepted a position as Associate Professor of Surgery (Research) at the University of Colorado in Denver. His appointment will be effective July 1. Dr. Huseby has been a member of our faculty for six years and has done outstanding work in the field of cancer biology. In recent years he has been especially interested in the effects of

estrogenic and androgenic hormones on metastatic breast tumors. Our best wishes go with him for a successful and productive career in his new position.

* * *

Continuation Course in Otolaryngology for Specialists

The University of Minnesota will present a course in Otolaryngology for Specialists at the Center for Continuation Study on June 23 through 27. Dr. Lawrence R. Boies, Professor and Head, Department of Ophthalmology and Otolaryngology, and Director, Division of Otolaryngology, has planned an outstanding program for physicians who specialize in diseases of the ear, nose, and throat. The faculty for the course will include several distinguished visiting physicians: Dr. Louis Clerf, Professor, Department of Laryngology and Broncho-Esophagology, Jefferson Medical College, Philadelphia; Dr. Leland Hunnicutt, Clinical Instructor, Department of Otolargynology, University of Southern California, Pasadena; Dr. William J. McNally, Professor, Department of Otolaryngology, McGill University, Montreal, Canada, and Dr. W. Wallace Morrison, Professor, Department of Otolaryngology, New York Polyclinic Medical School, and Associate Clinical Professor, Department of Otolaryngology, New York University Medical College Graduate School, New York. The remainder of the faculty will include clinical and full-time members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

* * *

Faculty News

Dr. Berry Campbell, Associate Professor of Anatomy, has been appointed Visiting Professor of Neurology at the College of Physicians and Surgeons, Columbia University, New York City, for the summer of 1952.

Dr. Davitt Felder, Clinical Instructor, Department of Surgery, was a guest speaker at the Ontario Medical Association meeting in Hamilton, Ontario, on Wednesday, May 21. Dr. Felder discussed "Raynaud's Syndrome."

Dr. Edmund B. Flink, Associate Professor of Medicine, took part in the recent spring clinics presented by the Wisconsin State Medical Society in Racine, Sheboygan, and Marinette. He discussed hyperthyroidism and electrolyte disturbances. Dr. Flink also spoke on "Clinical Studies on Eosinophile Rhythm" at the meeting of the Endocrine Society in Chicago on Thursday, June 5.

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III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

June 9 - 14, 1952

Monday, June 9

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom, Todd Amphitheater, U. H.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Pediatric Seminar; Cerebral Palsy; James Dugger; Sixth Floor West, U.H.

4:30 - Public Health Seminar; 15 Owre Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

7:30 - Fracture Grand Rounds; Dr. Zierold; Sta. A.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Ancker Hospital

8:30 - 10:00 Chest Disease Conference.

1:00 - 2:00 Medical Grand Rounds.

Monday, June 9 (Cont.)

Veterans Administration Hospital

8:00 - 9:00 Neuroradiology Conference; B. J. O'Loughlin, R. C. Gray; 2nd Floor Annex.

9:00 - G.I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; B. J. O'Loughlin; Conference Room, Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; C. K. Aldrich; Bldg. I.

Tuesday, June 10

Medical School and University Hospitals

8:30 - Conference on Diet Endocrines and Cancer; M. B. Visscher; 116 Millard Hall.

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Mt. Sinai Hospital; Dr. Friedman; Eustis Amphitheater, U. H.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

8:30 - 9:30 Medical-Roentgenology Conference; Auditorium.

1:00 - 2:30 X-ray - Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

12:30 - Neuroroentgenology Conference; O.Lipschultz, J. C. Michael, and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Tuesday, June 10 (Cont.)

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; L. J. Hay, B. J. O'Loughlin; Conference Room, Bldg. I.

1:00 - Surgery Chest Conference; T. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason; Conference Room, Bldg. I.

Wednesday, June 11

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Norman Jacob and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Pediatrics Case; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:30 Permeability and Metabolism Seminar; Nathan Lifson; 129 Millard Hall.

1:30 - Conference on Circulatory and Renal System Problems; M. B. Visscher; 116 Millard Hall.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

2:00 - 4:00 Medical Ward Rounds;

3:30 - 4:30 Journal Club; Surgery Office.

Wednesday, June 11 (Cont.)

Minneapolis General Hospital

8:00 - Pediatric Allergy Rounds; Lloyd Nelson; 4th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

1:30 - Pediatric Rounds; E. J. Huenekens and Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, June 12

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

3:30 - Medicine-Pediatric Infectious Disease Conference; Heart Hospital Auditorium.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 Radiology Seminar; Fibrosis of the Lung; Leo Blank; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

4:00 - Medical Pathological Conference; Auditorium.

Thursday, June 12 (Cont.)

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

8:30 - Neurology Rounds; William Heilig; 4th Floor.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; B. J. O'Loughlin; Conference Room, Bldg.I.

Friday, June 13

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Coin Lesions of the Lung; Daniel L. Fink and Joseph J. Asta; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

11:00 - Pediatric-Surgery Conference; Dr. Wyatt, Forrest Adams; Classroom, Sta. I.

12:00 - Surgery-Pathology Conference; Dr. Zierold; Dr. Coe; Classroom.

Friday, June 13 (Cont.)

Minneapolis General Hospital (Cont.)

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

1:30 - Chest Conference; Wm. Tucker and J. A. Meyers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

Saturday, June 14

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; George Lund; 5th Floor.

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

11:00 - Pediatric Clinic; C. D. May and Floyd Denny; Classroom, 4th Floor.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Hagen, Goldish, and Aufderheide

11:15 - 12:00 --Morphology . . . . . Dr. Aufderheide.