ERYTHROCYTES AND ERYTHROCYTIC DISEASE

THE TREATMENT OF MACROCYTIC ANEMIA WITH LACTOBACILLUS CASEI FACTOR (PteroYlglutamic Acid).

Careful clinical and hematologic studies were made on a series of 15 patients with various types of anemia who were treated with L. casei factor (pteroylglutamic acid, folic acid).

Three cases of pernicious anemia showed clinical and hematologic improvement following oral or parenteral treatment with L. casei factor. Improvement was of a degree comparable to that which would have been observed following liver extract therapy, although the reticulocyte responses were not as great following L. casei factor therapy.

One patient with definite signs of subacute combined degeneration of the spinal cord showed marked improvement following L. casei factor therapy. Complete clinical and hematologic remission was maintained for a period of six months in 1 patient on 15 mg. of L. casei factor daily. Four patients with nutritional macrocytic anemia responded satisfactorily to L. casei factor treatment. Two cases of sprue with macrocytic anemia improved clinically with decrease in fatty diarrhea and gain in weight when given L. casei factor, but showed no significant improvement in anemia.

One case of celiac disease showed improvement in clinical condition and slight improvement in anemia. No improvement followed L. casei factor therapy in 2 patients with aplastic anemia, 1 case of unexplained macrocytic anemia with hyperplastic bone marrow, 1 case of myxedema with macrocytic anemia, and 1 case of regional ileitis with anemia.

J. F. R.


It has been shown that rats deprived of pantothenic acid develop anemia and granulocytopenia, and that pantothenic acid prevents the production of these abnormalities. In cases in which the granulocytopenia developed without concurrent anemia, L. casei factor (folic acid) was able to correct the neutropenia without the use of pantothenic acid.

Daft and Sebrell gave rats a pantothenic-acid-deficient diet identical with the one used in the above experiments, except that it contained folic acid in amounts of 4 micrograms per gram of food. Rats on this diet developed both anemia and granulocytopenia. When this condition occurred, treatment with whole dried liver was more effective than treatment with pantothenic acid alone. It was therefore concluded that there is probably in liver an additional factor, neither folic acid nor pantothenic acid, which prevents anemia and granulocytopenia due to dietary deficiency.

S. E.


According to this report, there are some 51 cases in the literature of macrocytic anemia in association with intestinal strictures and anastomoses. Richardson finds that these cases can be explained by the postulate that pernicious anemia probably results from the lack of a hemopoietic principle whose function it is to maintain the integrity of the intestinal mucosa. Lack of this factor, he states, allows the absorption of "toxins" which result in the various changes of pernicious anemia. Other causes of damage to the
Neither type of cell showed any change in fragility.

An increase in erythropoiesis produced as a result of diffuse liver damage. Abnormal plasma constituent acting directly on the erythrocytes, but reflect a more fundamental disturbance in bile pigment concentration of the plasma.

During the icteric phase of the disease, but this decreased erythrocyte fragility was not a function of the bile pigment concentration. Icteric indices and the susceptibility of the erythrocytes to hemolysis in hypotonic salt solutions ("erythrocyte fragility") were determined in 47 soldiers with acute infectious hepatitis during brief periods of observation. Definite decrease in erythrocyte fragility (increased resistance) was observed during the icteric phase of the disease, but this decreased erythrocyte fragility was not a function of the bile pigment concentration of the plasma.

One in vivo experiment is reported in which normal erythrocytes were incubated with icteric serum and erythrocytes from a jaundiced patient (with increased fragility) were incubated in normal serum. Neither type of cell showed any change in fragility.

The author proposes the hypothesis that the observed fragility changes are not due to the effect of some abnormal plasma constituent acting directly on the erythrocytes, but reflect a more fundamental disturbance in erythropoiesis produced as a result of diffuse liver damage.
ABSTRACTS

CHRONIC HAEMOLYTIC ICTERUS RESEMBLING ACUTE ICTERUS OCCURRING IN AN AFRICAN NATIVE.

A 55 year old Msutu male from Northern Transvaal was studied because of persistent pain in both legs. He was found to have old healed scars on the legs, tenderness to pressure over both tibiae, motled pigmentation of the tongue, and a spleen palpable two fingers' breadth below the costal margin. The icterus index was never higher than 18. Spherocytosis and increased osmotic fragility of the red cells were demonstrated repeatedly. The red cell count fell only to 3,390,000 during an acute febrile period at which time both liver and spleen became larger. Bone marrow puncture revealed marked erythroid hyperplasia, but x-rays of the tibiae and skull were normal. Although hemolysins could not be demonstrated, cold hemagglutinins were present in low titer. Splenectomy was refused by the patient. Other members of the family could not be examined; both parents had died of unknown cause.

Merskey and Baskind state that this is the first case of chronic hemolytic icterus to be reported in an African native. Wintrobe (Textbook of Clinical Hematology) has, however, encountered congenital hemolytic jaundice in a Negro of mixed blood, and Scherer and Ceci (J. Lab. & Clin. Med. 35: 244-246, 1945) have reported another case in a Negro in whose family miscegenation could not be excluded.

Although this case conforms to the usual pattern of congenital hemolytic icterus, the authors prefer to leave open the question as to whether the disease in this patient was congenital or acquired. The possible role of malignant tertian malaria is also considered since the patient lived in a malarious area and rings were found in a blood smear on one occasion. The conservatism of the authors with regard to exact diagnosis is probably justified in view of current uncertainties in the classification of hemolytic disorders.

L. E. Y.


A group A, Rh positive infant with erythroblastosis fetalis (mother group O, Rh negative, father group A, Rh positive) accidentally received a transfusion of 400 cc. of group A, Rh negative blood. The infant’s condition remained satisfactory following transfusion; icterus of the skin was not noted.

Whereas erythrocytes of the cord blood had reacted weakly with anti-Rh serum, the infant’s red cells 9 days after the massive transfusion reacted strongly. The author therefore postulates that the infant received an “anti-Rh antigen-antibody reaction factor” in the transfused blood which permitted his own Rh positive cells to survive. Blossom is of the opinion that Rh negative persons may have in their blood a suppressing (or anti-Rh antigen-antibody reaction) factor which “cushions” the antigen-antibody reaction. He therefore suggests that use be made of this inhibitory substance by giving to erythroblastotic infants larger transfusions of Rh negative blood than are customary (although not as large as given accidentally in this case).

There is some evidence in the literature that substances capable of inhibiting hemolysis and hemagglutination are present in both normal and pathologic human sera. It is unfortunate, however, that the speculations advanced in this paper are not supported by more detailed information on the case reported. No mention is made of blocking or “developing” antibodies, as contrasted with agglutinating antibodies, in the serum of either the mother or child.

L. E. Y.


This report concerns a 37 year old woman with a five year history of fatigue, dyspnea, blue spots on the face and legs, and ulcers of the lower legs. Physical examination revealed cyanosis, hepatosplenomegaly, and several small ulcers of the lower third of both legs. The blood counts were as follows: RBC 6.5 M., HGB 140 per cent., WBC 9,200 (P6o, L3o, M4, E4), platelets 95,000. The serum bilirubin was 1.6 mg., indirect, and the reticuloocytes numbered 3. The blood smear showed spherocytosis, and in hypotonic solutions hemolysis began at 0.55 per cent sodium chloride and was complete at 0.33 per cent. The bone marrow was hypercellular and showed marked normoblastic hyperplasia, with 5.6 per cent of the red cells in mitosis. The ratio of normoblasts to granulocytes was 3:1.

To the authors this case is easily explained. They consider the underlying disease to be a hemolytic process. Most cases of hemolysis are accompanied by anemia, but in this individual, they state, hyper-
compensation by the bone marrow resulted in the development of erythrocytosis. Certainly such an event is rare. It is difficult to see why there is not a total bone marrow reaction, for the white and platelet counts are not elevated; but, on the other hand, this is not the typical picture of polycythemia vera with hemolytic jaundice, for the same reason (i.e., the reaction is purely erythrocytic). The possibility that this is an example of asymmetrical hemolytic anemia in association with polycythemia vera, however, cannot be ruled out, for a certain number of polycythemia cases do not show leukocytosis and thrombocytosis. The occurrence of leg ulcers, seen in other chronic hemolytic processes, is of interest. The case is presented as a curiosity of obscure pathogenesis.

S. E.


Callender summarizes her observations on the length of survival of transfused erythrocytes in the circulation of normal male and female subjects as determined with the Ashby technic. In male subjects the average life of the transfused red cells was 60 days and the rate of destruction was 0.83 per cent of the initial amount per day. This indicated that the red blood cells live nearly a constant time—120 days from their birth. The average life after transfusion is half this—60 days, since the transfused cells are of all ages and have already lived 60 days on the average. In females menstrual loss produced different types of survival curves, although the life of cells was 120 days, just as in males.

Loutit discusses the survival of erythrocytes transfused into patients with various hematologic abnormalities, survival being determined by the Ashby technic. Normal cells transfused into patients with hypochromic anemia had a life span of 100-105 days.

Normal erythrocytes transfused into patients with pernicious anemia showed an average survival of 40.3 days (in contrast to the average survival of 60 days in normal recipients), a low value which probably is attributable to the fact that the transfused blood had been stored for 5-14 days. Transfusion of blood from pernicious anemia patients into normal subjects was followed by rapid disappearance of the transfused cells from the recipient’s circulation. Fifty per cent survival occurred at the 10th and 11th days. These observations suggest that the cells of patients with pernicious anemia are destroyed a great deal more rapidly than normal.

Transfusion of normal cells into patients with familial hemolytic anemia was followed by a normal survival curve (maximum 120 days). In marked contrast when normal cells were transfused into cases of acquired hemolytic jaundice, they were destroyed very rapidly, the mean 50 per cent survival being 5 days (in contrast to 54 days in familial hemolytic anemia).

When cells from patients with familial hemolytic anemia were transfused into normal subjects they were rapidly destroyed, 50 per cent survival being noted between the 4th and 15th days. Cells of acquired hemolytic anemia transfused into normal recipients survived normally (50 per cent survival in excess of 50 days).

These observations are interpreted as indicating that the cells of familial hemolytic anemia are abnormal due to an inborn defect of the cell, while in acquired hemolytic anemia the cells are “sensitized” by some circulating hemolysin.

J. F. R.


Jope studied spectrophotometrically the disappearance of methemoglobin (MHB) and sulphhemoglobin (SHb) from the circulating blood of 7 TNT workers after their withdrawal from contact with TNT. The plots of SHb levels against time after removal from contact with TNT were well fitted by a straight line indicating complete disappearance of SHb at 116 (±5) days. This was considered a valid estimate of the life span of red cells containing SHb, upon the assumptions that (1) the intact red cell has no means of transforming SHb and the body has no means of removing it other than by removal of the red cells which contain it, (2) no significant SHb formation continues after removal from TNT, and (3) neither SHb nor the heme portion of its molecule is incorporated into new cells. Jope points out that in relating the destruction of red cells containing SHb to that of normal cells it must also be assumed that (4) SHb is formed at random in cells of all ages, and (5) formation of SHb within the cell neither

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prolongs nor shortens its life. All of these assumptions seem reasonable to the author except that some formation of SHb may continue for a few days after removal of the toxic agent.

Conclusions as to average life span of erythrocytes containing SHb and the linear decay curve agree well with the results obtained by differential agglutination (Ashby) studies and N\textsuperscript{5} isotope methods. SHb and N\textsuperscript{5} isotope methods have the advantage of permitting studies on the longevity of the subject's own cells.

In contrast to SHb, MHb disappeared from circulating blood within 2 to 3 days after removal of the causative agent. Other aspects of Jope's work have been published in the Brit. J. Indust. Med. 3:136, 1946 (see following abstract).

L. E. Y.


Methemoglobin and sulfhemoglobin were found in the blood of TNT workers. After removing the patients from all further occupational exposure, the disappearance rate of these two pigments from the circulating blood was determined spectrophotometrically. Methemoglobin was gone in less than a week. However, in seven workers with an original amount of over 4 per cent sulfhemoglobin, there was a straight line disappearance curve of the latter pigment, extending over 110 to 130 days. This disappearance curve corresponds to the survival of a mixed age population of erythrocytes studied by the agglutination technics. It was concluded that once formed in the cell, sulfhemoglobin remained there until the cell was destroyed. The abnormal pigment formation did not affect the viability of the erythrocytes.

C. A. F.


Investigations of the life span of the red cells have come into prominence in recent years. The usual methods of study have been based upon the study of transfused red cells by the Ashby technic. In the present note, the authors have approached the problem from a different point of view. They have found that feeding glycine labeled with an isotope of nitrogen, N\textsuperscript{5}, results in the production of a heme most of whose nitrogen is of this isotopic form. Quantitative studies led to the conclusion that glycine is the nitrogen precursor of the protoporphyrin of hemoglobin; various other materials (proline, leucine, glutamic acid, ammonium citrate) did not substitute for glycine in heme formation. These workers, accordingly, could follow the concentration of the isotope in the red cells for months after labeling with N\textsuperscript{5}; and they found that the average life of the red cell, by this technic, was about 115 days. This result correlates well with those obtained by the transfusion-Ashby technic.

S. E.

**IRON AND BLOOD PIGMENT METABOLISM**


The appearance of injected radioactive iron in circulating hemoglobin, in the excreta, and in various tissues was studied in normal human subjects, patients with various types of anemia, and in dogs rendered anemic by hemorrhage and by the administration of phenylhydrazine. In normal human subjects the injected iron appeared in the circulating hemoglobin with great rapidity, more than 60 per cent being present in the circulating red cells seven days after the injection. Eventually 80 to 110 per cent of the injected dose was reported as appearing in the circulating red blood cells. The authors' values for the percentage utilization of the iron may be criticized since these values are derived from an assumed blood and cell volume. The blood volume was arbitrarily assumed to be 80 cc per kilogram body weight, and the red blood cell mass presumably was calculated from this value and the venous hematocrit without further correction.

It is rather generally recognized that blood volume may vary widely from these arbitrary figures from
one normal individual to another, and that in anemic states marked variations occur. This criticism is recognized by the authors, but its importance is deprecated. Furthermore, it is also probable that the actual circulating erythrocyte mass is considerably less than the values calculated from the assumed blood volume and the venous hematocrit. These considerations would suggest that the amount of iron actually appearing in the circulating cell mass might be considerably less than the values given by the authors.

Normal dogs utilized injected iron less rapidly and less completely than the normal human subjects. The difference in total utilization conceivably might be related to errors introduced by assuming a constant 80 cc. blood volume for both human and animal subjects.

Tissue analyses were made to determine the distribution of radioactive iron in two dogs. Seventy-two and 78 per cent of the injected material was accounted for, most of it being present in circulating hemoglobin, bone marrow, and liver.

Utilization of iron was more rapid and more complete in iron-deficient human patients and dogs. Utilization was very slight in patients with hypoplastic anemia. In pernicious anemia utilization was slight during relapse, but was increased following injection of liver extract, indicating that some of the iron had temporarily been deposited in storage depots.

In hemolytic anemias utilization was less than normal and there was apparent rapid fluctuation in radio iron concentration in the circulating cell mass, fluctuations attributed by the authors to rapid hemolysis of the subjects' erythrocytes. Part of the hemoglobin iron released from hemolyzed erythrocytes was rapidly reutilized for formation of new hemoglobin.

The authors present a justified criticism of the use of the appearance of orally administered radioactive iron in circulating erythrocyte hemoglobin as an indication of iron absorption. They point out that appearance of iron in the circulating erythrocytes is determined by rate of erythrocyte formation as well as by the amount of iron absorbed from the bowel.

J. F. R.


The authors describe improved technics for determination of total hemoglobin, active hemoglobin, and inactive hemoglobin by CO capacity procedures. The accuracy of the methods in their hands was considered to be for total hemoglobin ±0.26 per cent, active hemoglobin ±0.38, and inactive hemoglobin ±0.41 (probable error calculated as 0.674 X standard deviation).

In human blood the mean inactive hemoglobin by the CO method was 1.3 per cent ±0.35 per cent of total hemoglobin when the analysis was performed immediately after drawing blood. This fell to 0.56 per cent ±0.23 per cent in 2-4 hours. Mean methemoglobin by the spectrophotometric method of Horecker and Brackett was only 0.04 per cent of total hemoglobin and there was no change over 2-4 hours in this value.

The results presented a problem. It appeared that 1 per cent of total hemoglobin (as measured by the Na2S2O5-CO method) existed in an inactive form, resembling methemoglobin in its ability to bind CO only after reduction of Fe++ to Fe++, but differing from methemoglobin in not showing the methemoglobin color reaction with HCN, and in rapidly acquiring ability to combine with CO as blood stood in vitro.

C. A. F.

LEUKEMIA AND LYMPHOMA


The authors report an analysis of the white blood count in a series of 888 cases of brucellosis seen in Mexico. In most of the cases the causative organism was Brucella melitensis. The infection was acute in half the cases (present for less than three months), and chronic in the other half (present for three to twelve or more months). A single white and differential count taken from each patient was the basis for the study.

In 30 per cent of the cases leukopenia was present (5,500 to 5,500 white blood cells per cu. mm.) In 32 per cent of the cases the white count ranged from 6,500 to 9,500; and in the remaining 18 per cent the white count was between 10,500 and 20,000. In the cases with leukopenia there was relative lymphocyto-
sis and therefore neutropenia. In the cases with normal or high white counts, the percentage of lymphocytes was correspondingly high, so that absolute lymphocytosis was present in most of these cases. Neutropenia occurred in the cases with low and normal white counts, but when the counts became high, absolute polymorphonuclear leukocytosis was also present.

As a result of their data (many of which do not appear in the published report), the authors conclude that the usual concept that brucellosis is commonly associated with leukopenia is at fault. Brucellosis, rather, is a lymphocytogenic disorder, and is usually associated with a normal or high white count with absolute lymphocytosis. In the cases in which neutropenia does occur, the authors believe that it is probably the result of inhibition of the bone marrow by some material produced in a damaged spleen. Critical evaluation of these conclusions is not possible from the data presented. The choice of normal values by the authors is somewhat unorthodox: they consider a white count of 3,500 as leukopenia, and 6,000 questionable normal. The normal lymphocyte count is considered to be 2,800, whereas a range of 1,500 to 3,000 is more commonly maintained. What data are given, however, suggest that in fully 20 per cent of their cases there is a definite leukocytosis, a fact at variance with the commonly accepted data.

S. E.


Four cases of infectious mononucleosis are reported in which there was clinical or electrocardiographic evidence of involvement of the heart. The prominent electrocardiographic change was flattening and inversion of the T-waves. In 2 cases a friction rub was audible over the heart. All cases showed return toward normal after subsidence of the infection, although alterations in the T-waves often persisted for a time after the patient was clinically well.

The authors believe that the cardiac changes were indicative of pericardial rather than myocardial involvement. The incidence of these changes in the authors' series was approximately 4 per cent.

S. E.


The author reports a 14 year old boy with infectious mononucleosis whose electrocardiogram showed marked changes in the Q- and T-waves during the height of the disease, with a gradual return to normal after subsidence. He gathers six other reports of cardiac involvement in infectious mononucleosis from the literature, including prolongation of the PR-interval, alterations of the T-wave, and occurrence of premature ventricular contractions. In one other case the diagnosis of mitral stenosis was made on clinical grounds, and in yet another a rheumatic valvular lesion was found at autopsy.

Geraghty considers the disorder to be an acute granulomatous process with reticulo-endothelial proliferation, mononuclear infiltration, and necrosis. Involvements of the central nervous system, kidneys, lymph nodes, gastrointestinal system, and skin are well recognized in the disorder. Involvement of the heart may correspondingly be expected to occur, and usually, he believes, consists of myocardial changes which show up on the electrocardiogram as similar to those usually associated with various acute infections.

S. E.


A case of hepatosplenomegaly and leukopenia is presented. Despite the reduced numbers of granulocytes in the circulating blood, the bone marrow showed active granulopoiesis. The fact that the patient showed polynuclear changes suggestive of rheumatoid arthritis makes it likely that the disorder was an example of Felty's syndrome (rheumatoid arthritis with splenomegaly and leukopenia), rather than truly primary splenic neutropenia.

The author draws attention to the fact that splenomegaly may be associated not only with neutropenia but also with lymphocytopenia. In this instance, of a total of 900 to 1,750 white cells per cu. mm., only 80 were granulocytes (normal over 3,000) and 500 to 1,000 were lymphocytes (normal over 1,500). The occurrence of lymphocytopenia in such instances suggests a relationship between the enlarged spleen and the lymphocytes or their sites of production in the body, similar to the postulated relationship between the spleen and granulocytes or bone marrow.

No splenectomy was done in this case. Pyridoxine had no effect on the blood counts.

S. E.
ABSTRACTS


The authors describe 2 cases of lymphoblastic leukemia in children in which the presenting complaints were bone or joint pains. In the first case migratory polyosalgia was associated with fever, night sweats, increased sedimentation rate, and a leukocytosis but with a normal differential count. In the second case polyarthralgia and actual objective joint changes were present, and the blood count showed absolute lymphocytosis. In both instances the bone marrow was infiltrated with blast forms, and the diagnosis of lymphoblastic leukemia was confirmed at autopsy.

X-ray examination of the bones in both patients showed changes which were considered diagnostic of leukemia. According to the authors, these changes are as follows: (1) patchy destruction of bone; (2) expansion of the marrow cavity, with resultant atrophy of the cortex; (3) elevation of the periosteum by leukemic infiltration, with formation of new bone in lamellae parallel to the shaft of the bone; and (4) demineralization. Pathologically, these changes are found to be due largely to infiltration of bone marrow, cortex, and periosteum with leukemic tissue.

These x-ray changes are not specific for leukemia, and in most cases the diagnosis is made independently of x-ray examinations. The authors suggest, however, that the persistence of bone or joint pain in a child, which does not respond to the usual treatment with salicylates, sulfonamides, and penicillin, should call for x-ray examination of all the bones (especially the long bones), and consideration of the possibility of leukemia.

S. E.


This paper reports a patient with chronic leukemia in whom the outstanding circulating white blood cell was the basophil. The patient’s initial complaint was enlargement of the abdomen, which was found to be the result of massive splenomegaly. Treatment with x-irradiation resulted in moderate improvement and some reduction of the white blood count. Four months before death the white count was 50,400, and the blood smear showed adult neutrophils, basophils, and eosinophils, as well as neutrophilic, eosinophilic, and basophilic myelocytes. Granulocytes totaled 95 per cent of the circulating white cells, of which only 8 per cent were basophilic. A few days before death the white count was 16,600; there were 86 per cent granulocytes of all types; and there were 6 per cent basophilic myelocytes and 66 per cent adult basophils in the circulating blood. Postmortem examination showed leukemic infiltration, mostly with myeloblasts, of spleen, liver, pancreas, bone marrow, lungs, heart, kidneys, and stomach.

The authors find nine reports in the literature of true leukemia confirmed by autopsy, in which a basophilia of over 25 per cent was noted. In most of these cases the data were obtained only terminally. The authors suggest that basophilic leukemia is not a disease entity unto itself, rather, that the basic disorder is myelogenous leukemia, and that the basophilia is merely an unexplained terminal event in certain rare instances of chronic myelogenous leukemia.

S. E.


Records of 500 patients with malignant lymphomas were reviewed. Only those patients were considered whose lesion was localized and whose treatment was limited to x-ray. Fifteen cases were found whose diagnosis was established by biopsy who were alive and apparently free of the disease five years later. The cases included, according to the classifications of Gall and Mallory (Am. J. Pathol. 18: 381-439, 1942), two stem-cell, one clastomatocytic, three lymphocytic and one Hodgkin’s lymphoma, one Hodgkin’s sarcoma, and one follicular lymphoma. X-ray dosage was from 1000 to over 1500 r.

According to Gall and Mallory, about 10 per cent of lymphomas are localized at autopsy. Gall (Ann. Surg. 118: 1064, 1943) reported a group of about 16 patients, if the same criteria are used, who were alive and free from their disease after surgical excision. Both studies provide valuable data relating to the prognosis of localized lymphoma, with these different forms of treatment.

C. A. F.