HEMATOPOIETIC TISSUES

DEVELOPMENT OF BONE MARROW IN ADULT ANIMALS. B. Steinberg and V. Hufford. From Toledo Hospital Institute of Medical Research. Arch. Path. 117: 117-125, 1947.

Previous studies of marrow regeneration by other investigators have centered around hypoplastic marrows induced by chemicals, starvation, or disease. In the present article, regeneration of the complete marrow was studied following its removal mechanically. The latter was accomplished by forcing sterile liquid petrolatum and saline through rabbit tibiae after holes had been drilled at appropriate locations. Forty-four rabbits were treated in this manner and one or more of the animals were killed at intervals of 1 to 60 days. Regeneration was initiated during the first 9 days by the endosteum sending out sheets of primitive reticular cells. Bony trabeculae were also laid down. Fat spaces were formed by the coalescence of vacuoles in two or more adjacent reticular cells. Between 12 and 17 days islands of myeloid cells were seen throughout the re-forming marrow. By the twenty-first day the marrow cavity was unevenly filled and the bony trabeculae had disappeared. These studies indicate that regeneration of all myeloid elements starts from a primitive reticular cell.

O. P. J.

ERYTHROCYTES AND ERYTHROCYTIC DISEASE

COMPARISON OF THE EFFECTS OF MASSIVE BLOOD TRANSFUSIONS AND OF LIVER EXTRACT IN PERNICIOUS ANEMIA. C. S. Davidson, J. C. Murphy, R. J. Watson, and W. B. Castle. From the Thorndike Memorial Laboratory, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass. J. Clin. Investigation 25: 858-869, 1946.

The authors describe the clinical and hematologic responses obtained in patients with typical Addisonian pernicious anemia who received liver extract after the anemia had been partially or completely corrected by means of whole blood or red cell transfusions. It was found that very little symptomatic improvement was effected by transfusion, excepting for the relief of those symptoms specifically attributable to hemoglobin deficiency; anorexia, apathy, and digestive symptoms persisted until liver therapy was instituted. Leukopenia and thrombopenia were completely unaffected, regardless of the amount of blood given or the level of hemoglobin concentration attained. Following the subsequent course of liver injections, however, the white cell and platelet counts promptly returned to normal. Reticulocytosis, in response to liver extract, was reduced or absent in these transfused patients, depending upon the presence and degree of the anemia existing at the time liver therapy was instituted. Transfusions alone did not stimulate a reticulocyte response. Serial examinations of the bone marrow of these patients indicated that megaloblastic proliferation was promptly reduced as a result of artificial blood replacement. When complete correction of the anemia had been accomplished by transfusion, the appearance of the marrow was relatively normal. Later, as the donor red cells were eliminated and anemia recurred, the marrow again assumed a megaloblastic character.

The megaloblastosis of uncompensated pernicious anemia is the expression of a specific deficiency.
state, and can be eliminated by administration of the maturation factor, or factors, present in liver extract. It now appears that the phenomenon requires, in addition, the erythropoietic stimulus of bone marrow hypoxia, a product of the anemia. Alleviating this hypoxia, by artificially increasing the concentration of circulating red cells, caused a reduction of megaloblasts, although the fundamental deficiency remained uncorrected. The data presented are, moreover, adequate to refute the hypothesis (Clinics 7: 708-726, 1946) that the neutropenia and thrombopenia, characteristic of pernicious anemia in relapse, are on a myelophthisic basis, attributable to megaloblastic proliferation in the marrow. On the contrary, it may justifiably be assumed that the normal development and survival of granulocytes and platelets, as well as of red cells, are dependent upon a common nutrient factor which is supplied in liver extract.

C. P. E.

Relative Clinical and Hematologic Effects of Concentrated Liver Extract, Synthetic Folic Acid and Synthetic 5-Methyl Uracil in the Treatment of Macrocytic Anemias in Relapse.


The authors report the results of studying 100 patients treated with concentrated liver extract, 14 patients treated with synthetic folic acid, and 14 patients treated with synthetic 5-methyl uracil. Each of these three substances caused a remission. Although the clinical and hematologic response to folic acid paralleled that following concentrated liver extract therapy, the latter produced a greater rate of regeneration. Synthetic 5-methyl uracil was the least effective of the three substances.

O. P. J.

Folic Acid in Pernicious Anemia. Failure to Prevent Neurologic Relapse. R. W. Heine and A. D. Welch. From the Departments of Medicine and Pharmacology, Western Reserve University College of Medicine, and the Lakeside Hospital, Cleveland. J. A. M. A. 133: 739-741, 1947.

The substitution of folic acid for liver extract in the therapy of pernicious anemia has awaited evaluation of the status of neurologic changes under the new form of treatment. Reports are now forthcoming which suggest that folic acid does not necessarily prevent neurologic progress in pernicious anemia, and make the routine use of this substance alone at present undesirable.

Heine and Welch report that of 47 patients with pernicious anemia treated with folic acid, 3 had neurologic relapses (6.4 per cent). Two relapses were mild and responded readily to treatment with liver extract. The third patient, who forms the basis for the present report, developed an "explosive" neurologic relapse three months after the initiation of folic acid therapy, at a time when the blood status was normal. Response to further treatment did not occur for one month after intensive therapy with crude and refined liver extract and vitamin B was started.

The exact nature of the neurologic lesion described is not clear. It is certainly not the characteristic posterolateral sclerosis of pernicious anemia, but resembles rather a peripheral neuropathy. It began suddenly with numbness in the hands and was followed by numbness in the forearms and, later, feet, legs, and hips. All the deep tendon reflexes were absent; there was no vibratory sensation below the ribs (before therapy, this was normal); and there were no pathologic reflexes. Improvement was delayed and slow. That this could be peripheral neuropathy due to pernicious anemia is certainly possible.

This patient, as well as the other 2 with neurologic relapse, had very poor dietary intake. The authors speculate upon the relationship of this malnutrition to the occurrence of the relapses. The question as to neuropathy due to other causes (e.g., avitaminosis B) is not discussed. The authors believe that, in certain instances, folic acid may perhaps not only allow but even precipitate neurologic relapse in pernicious anemia. At any rate, liver extract remains the treatment of choice in pernicious anemia at this time.

S. E.

The Anti-Anemic Properties of Pteroylglutamyl Glutamic Acid. T. D. Spies, R. E. Stone, and R. Lopez Toca. From the Department of Medicine, University of Cincinnati College of Medicine, and the Hillman Hospital, Birmingham, Ala. South M. J. 40: 175-176, 1947.

Folic acid is pteroylglutamic acid and has one glutamic acid residue. A related compound, synthetic
pteroylglutamyl glutamic acid—containing two glutamic acid residues instead of one—was successfully utilized by the authors in treating 3 cases of macrocytic anemia (2 of pernicious anemia, 1 of nutritional macrocytic anemia). In a patient with pernicious anemia, an oral dose of 10 milligrams of this new substance daily for ten days resulted in a reticulocytosis of 25.1 per cent on the eighth day; an increase in red count from 1.4 M. to 2.18 M. and in hemoglobin from 5.2 grams to 6.7 grams by the tenth day; and clinical improvement.

Other synthetic products chemically related to folic acid may be expected to have similar effect in pernicious and related anemias. Evaluation of their efficiency and correlation of changes in chemical structure with degree of response may in time lead to better therapies and more fundamental knowledge of the nature of pernicious anemia. This report merely demonstrates the efficacy of the first such chemical modification of folic acid.

S. E.

**The Anemia of Infection. V. Fate of Injected Radioactive Iron in the Presence of Inflammation.**


The experiments reported in this communication were designed to ascertain the mechanism by which iron metabolism is altered in the presence of inflammatory lesions, as manifested by the occurrence of hypoferremia and the development of hypochromic anemia. As described elsewhere (J. Clin. Investigation 25: 65, 1946; 26: 114, 1947) these authors had determined that, whereas iron absorption is adequate in patients with chronic infection and anemia, the utilization of iron for hemoglobin production is sharply reduced, depending on the severity of infection. Iron administered by injection rapidly disappeared from the plasma. This diversion could not be attributed to excretory loss and was clearly not the result of erythropoietic activity, relatively little being incorporated into hemoglobin until the infection had been relieved.

The present report described experiments in which a radioactive isotope of iron (Fe**+)** was administered parenterally into normal rats, and rats with acute inflammatory lesions produced by the intramuscular injection of turpentine or bacterial cultures. The animals were subsequently sacrificed and radioactivity measurements carried out on isolated tissues. It was found that, in the presence of inflammation, the major accumulation of iron was in the liver, normally the chief storage site for this element; a relatively lower proportion of the material had been incorporated into red cells in comparison with the control animals. Most of the infected Fe**+** could be accounted for in the liver and blood, very little being detected elsewhere, including the inflamed tissues.

A preferential diversion of iron to the storage depot, mainly the liver, may therefore be responsible for the hypoferremia associated with infection. The relationship of this phenomenon to the development of anemia is, however, still obscure, for the failure of iron utilization, in the face of ample stores of potentially available iron, remains to be explained. Other metabolic faults, as indicated by the authors, may be implicated, for example a disturbance of protein metabolism involving the protein moiety of hemoglobin.

C. P. E.


The authors present a very interesting case which may represent either a new syndrome or an unusual response to some stimulus. The peripheral blood contained both spherocytes and target cells, so that lysis of red cells was just appreciable in 0.6 per cent saline, half complete in 0.355 per cent saline, and incomplete in distilled water. Studies of bone marrow preparations revealed many cytologic abnormalities. Granulocytic precursors showed a nucleic acid starvation and the formation of tetraploid giant stabs. Among the erythroblasts there was a breakdown of normal spindle development and a replacement by abnormal multipolar spindles. During anaphase there was an incomplete separation. Some cells contained micronuclei derived from chromosomes dissociated from spindles which failed to reconstruct daughter nuclei. Hypoploid mitoses with as few as a dozen chromosomes were present and some
of these were in tripolar mitosis. The marrow differed from pernicious anemia in that it was normoblastic. Anatomic diagnosis at autopsy was: pneumonia (virus type), cortical necrosis of kidney, hyperplasia of bone marrow with myeloid metaplasia in liver, spleen, and renal pelvic fat.

O. P. J.

WEBB AND CONTRACTING BANDS IN THE UPPER ESOPHAGUS (SIDEROBLIC DYSPHAGIA). M. A. Thomas.


Four cases of dysphagia due to upper esophageal lesions are reported. In 3, there were thin membranes just below the level of the cricoid cartilage, and in the fourth, an esophageal stricture. The authors point out that the lesion is frequently missed because of its high location. Capsules filled with barium were swallowed and became lodged just above the membrane. The bands were cut with an esophagoscope with relief of symptoms. Three patients had a significant degree of anemia. The lesions were similar in appearance and location to those reported in a more extensive article by Waldenstrom and Kyellberg. Both authors felt that the lesion was a manifestation of iron deficiency and provided the anatomic explanation for the dysphagia of the Plummer-Vinson syndrome.

C. A. F.

SUR UN CARACTÈRE ESSENTIEL DE L'ANÉMIE PERNICIEUSE (ON AN ESSENTIAL FEATURE OF Pernicious Anemia). M. Loureau.

From the Institut de Biologic physicochimique, Paris. Le sang. 6: 142-146, 1946.

TITRAGE DU FACTEUR ANTIPERNICIEUX PAR UNE MÉTHODE BIOLOGIQUE (TITRATION OF THE ANTI-PERNICIOUS FACTOR BY A BIOLOGICAL METHOD). M. Loureau.

Le sang. 6: 365-375, 1946.

SUR LA DISPARITION DU FACTEUR ANTIPERNICIEUX DANS LE SATURNISME EXPERIMENTAL (ON THE DISAPPEARANCE OF THE ANTIPERNICIOUS FACTOR IN EXPERIMENTAL SATURNISM). M. Loureau.

Le sang. 8: 517-523, 1946.

We have collected these three articles concerning a study of the relations between experimental saturnine anemia of the rabbit and human pernicious anemia. According to the author, anemia is easily obtained by intravenous injection of a water solution of neutral lead acetate at a concentration 3.63 Gm. per liter, this anemia has the following features: first hypochromic anemia, then hyperchromic anemia, the globular value being increased; the bone marrow shows a normoblastic activity. Even when the anemia is cured, the high hemoglobin concentration persists for some time. Oral administration of lead was found to be more effective than injections, and the author gave 1 cc. of a 6.5 per cent solution every other day during 15 days. When liver extract was given to these anemic animals, there was a fall of the corpuscular volume, the intensity and the speed of which was quite specific. In the titration of liver extract one attempts to find the threshold of activity, and thus to determine the minimum dose which is active. This was the same for all the animals, was independent of the experimental conditions, and was called the "rabbit unit." The most important fact was the sudden fall of the globular value (in the hypochromic anemias as well as in the other types of anemia). This was more striking when the globular value was very high, but it was always present when the globular value was above 0.14 per cent (mean value is from 0.16 to 0.44 per cent, and it was far higher than any spontaneous fall observed). Each extract ought to be titrated on at least 3 rabbits. The antipernicious titration of untreated rabbit's liver is quite constant, provided that the antipernicious activity is related to 1 gram of fresh liver extract (the global concentration varying with the liver weight). The saturnine intoxication is associated with a complete disappearance of the antipernicious factor which is persistent if not permanent.

Thus, a new biologic titration method of the antipernicious liver extract is proposed. Although the data concerning the titration of the hemoglobin are somewhat inadequate and although this experimental anemia is normoblastic and not megaloblastic as in man, the importance of any new method of titration is worth verification by more extended investigations (M. C. V., M. C. H., M. C. H. C., which are more precise than the globular value).

J. P. S.

ÉTUDES SUR L'ANÉMIE EXPÉRIMENTALE PAR INANITION PROTÉIQUE CHEZ LE RAT, LES ALTÉRATIONS DU SANG DE LA MOELLE OSEUSE ET DE LA RATE, LES RÉLATIONS AVEC LE CYCLE OESTRAL (Study on the Experimental Anemia Produced by Protein Inanition in Rats. Blood, Bone Marrow and Spleen Modifications and Their Relation to the Evolution of the Estrous Cycle). A. Ascbkenaty.

From the Institut de physiologie générale des Facultés de Strasbourg et de Lyon. Le sang. 17: 54-61, 1946.
Ten white rats were fed a protein-free diet; they showed the following symptoms: a fall of the hemoglobin beginning on the 21st day; a severe anemia by the 38th day, after a decrease of 34 per cent in weight, a few normoblasts at first and then more numerous normoblasts in very anemic rats, a leukopenia, with neutropenia, and an alteration in the lymphocytes.

There was a normoblastic hyperplasia of the bone marrow, and a splenic atrophy, which was much more frequent than liver atrophy (65.5 per cent). There was some alteration of the estrous cycle (irregularity, then interruption) earlier than the blood injury.

There are 60 bibliographic references.

J. P. S.

**LA MÉTHIONINE DANS LE TRAITEMENT DES ANÉMIÉS (METHIONINE IN THE TREATMENT OF ANEMIAS).**


The author begins with an historical review of methionine, its activity and its metabolism. He made the following experiments: Every day for 17 days carbon-tetrachloride was injected subcutaneously into 9 rats; the dose was increased from 0.05 cc. to 0.9 cc. and the rats were fed only on wheat. Three of these rats were kept as controls; the others were injected with 15 to 30 mg. of methionine each day. In spite of the well-known activity of methionine, the rats did not appear to be protected against liver injury: they became icteric about the fourth or fifth day. The histological examination showed a marked fatty degeneration of the liver, the same as in the controls, and an identical amount of lipids in the liver.

On the other hand, erythropoiesis was quite different in the two series: the control rats had a marked anemia, but there was no anemia in the rats treated with methionine. Another experiment (8 rats) gave the same results. In a third experiment, 10 rats were given a cirrhogenic diet rich in lipids and low in proteins, plus 100 mg. of l-cystine a day. In this experiment the protective activity of methionine on the liver was evident, the activity on erythropoiesis still frank; only the controls were anemic after the third month. In man, the author gave 1 mg. of methionine each day for 2 to 4 weeks to 10 cases of anemia of the following types: 4 severe macrocytic anemias, 2 pernicious anemias, 4 normochromic normocytic anemias. The results were as follows: no improvement in the pernicious anemias; but in 7 out of the 8 other cases there was a notable or striking improvement: a moderate increase of the reticulocytes about the fifth day (4 to 8 per cent), an average gain of 1,100,000 red cells in two weeks. This red cell increase was accompanied with an abatement of the serum iron and serum copper.

J. P. S.

**APPLICATION OF THE RADIOACTIVE RED CELL METHOD FOR DETERMINATION OF BLOOD VOLUME IN HUMANS.**


In addition to other uses, radioactive iron promises to provide a direct method of measuring the volume of the blood, in contrast to the present dye methods, all of which are indirect. The method depends upon the injection of a known amount of radioactivity, and the subsequent determination (a few minutes later) of the distribution of the radioactivity in the blood of the recipient. Since all the radioactive iron is lodged within red cells, the mass of red cells can thus be calculated directly, and no correction for a 'mixing phase' is necessary.

The authors gave Fe<sup>59</sup> to volunteer, recently phlebotomized normal individuals, until their blood had a radioactivity of 1000 counts per minute per ml. of blood. This level was maintained by booster doses as required. Freshly drawn citrated radioactive blood was then injected into patients whose blood volume was to be determined; and, for purposes of comparison, Evans blue was simultaneously injected into the same individuals. After 15 minutes to allow for mixing, successive samples of blood were drawn for determination of the concentration of the dye (serum) and for determination of radioactivity (whole blood). The usual method of Gibson and Evans was used to determine plasma volume and, by means of hematocrit, corresponding whole blood volume. Aliquot of the red cell samples were treated for determination of radioactivity, and the red cell mass thus determined; the hematocrit was then used to determine the total blood volume.

It was found that the blood volume as determined by the direct radioactivity method was 81 per cent, on the average, of that by the Evans blue method. The direct value was presumably the more accurate.
result, since an error of unknown magnitude is introduced during the mixing phase of the Evans blue by phagocytosis of the dye by reticulo-endothelial cells.

This paper confirms the existence of the discrepancy between the two types of determination of blood volume. The authors justifiably recommend caution in the use of indirect methods for this determination.

S. E.

HEMOGLOBIN, HEMOGLOBINURIA, AND BLOOD PIGMENT METABOLISM


This paper and the following two papers are concerned with studies on dogs with "double depletion" (anemia and hypoproteinemia) produced by blood removal and a low or nonprotein diet plus abundant iron. Blood protein output and urinary nitrogen balance were measured in such dogs after feeding standard growth mixtures of essential amino acids and mixtures lacking one of the essential amino acids. It was found that tryptophane and to a less extent phenylalanine and threonine when returned to the amino acid mixture were associated with a preponderance of plasma protein output, while arginine, lysine, and histidine were associated with a preponderance of hemoglobin output.

The average figure for production ratio (protein output to intake) was 25 per cent when an essential amino acid was deleted from the complete mixture, 19 per cent when the complete amino acid mixture was administered, and 15 per cent when a good diet protein was fed. It is suggested that, when given whole protein, the severely depleted dog demonstrates a flow of protein-forming materials to organ tissues to replace these stores of protein before the production of new hemoglobin and plasma protein begins. It is further suggested that from tissue protein lost on feeding amino acid mixtures come materials which accelerate production of hemoglobin and plasma protein in depleted dogs. The amino acid mixtures are conserved and the urinary nitrogen shows a positive balance. Some of this amino acid material probably goes into new-formed blood proteins, and "raiding" of body protein stores probably comes into this reaction as the intake of protein or amino acid decreases.

L. E. Y.


The authors showed that in doubly depleted dogs good food proteins in adequate amounts maintain body weight, a strongly positive nitrogen balance, and produce considerable amounts of new hemoglobin and plasma protein. Under comparable conditions mixtures of the pure amino acids essential for growth produce large amounts of new hemoglobin and plasma protein and a positive nitrogen balance but do not maintain body weight. It is concluded that some unidentified substance or compound present in certain proteins but absent in mixtures of essential amino acids may be responsible for the differences in the response of the doubly depleted dog.

L. E. Y.


In this portion of the study on doubly depleted dogs the authors report a blood protein production of from 50 to 140 grams for every kilogram of weight loss. Body and tissue protein are raided to fill the demand for new hemoglobin and plasma protein—an illustration of the ebb and flow or dynamic equilibrium between organ or tissue protein and blood proteins, with the latter having priority. The largest blood protein output is observed when weight loss is most rapid. A premortal rise in urinary nitrogen was
not observed in these studies. It is suggested that this phenomenon, which has been reported in long-term fasting experiments by other investigators, may be due to terminal infection.

L. E. Y.


It is generally stated that no treatment exists for the paroxysmal hemoglobinuria associated with tertiary syphilis, but that treatment of the syphilis may be beneficial. The effects of such therapy remain rather dubious. In the present note, the author reports the use of penicillin for this purpose.

The patient was a 26 year old soldier who had 100 episodes of chills, fever, abdominal pain, headache, and dark urine—always after exposure to cold—in one year. There were no history or physical findings of syphilis, but the Wassermann and Kahn tests were positive, and a Donath-Landsteiner hemolysin was demonstrated in the serum. Immersion of hands or feet into cool water invariably produced hemoglobinuria.

Since treatment with bismuth had already been employed without effect, penicillin was tried, 3.6 million units being given in ten days. During the following month, there were only two paroxysms, and these were mild and not associated with systemic symptoms. This was an unusually small number of episodes for the patient. Cooling of the extremities, however, still resulted in hemoglobinuria, although without constitutional symptoms.

As the author points out, no definite conclusions can be drawn from this incomplete case. It is probably doubtful if the fundamental serum abnormality can be affected by antibiotic therapy.

S. E.


This paper would appear to explain the disagreement over the methylene blue test. In alkaline solutions, bilirubin was found to react one equivalent of bilirubin to two equivalents of methylene blue to form a green compound, the spectral characteristics of which resemble closely the mixture of the reacting pigments. However, the pH of urine is seldom alkaline enough to bring about this reaction. The authors concluded that the methylene blue test for bilirubin in the urine depended primarily on color blending.

C. A. F.

BLOOD GROUPS, THE Rh FACTOR BLOOD TRANSFUSION

This paper, which is written in English, reviews briefly the contributions of Levine, Landsteiner, and Weiner in initiating study of the Rh blood groups and then concerns itself with the details of R. A. Fisher's theory of the composition of the Rh-chromosome and the inheritance of the Rh-genes. Fisher's theory postulates three loci on the Rh chromosome, each locus having two allelomorphs. The nomenclature and its equivalent in the usual American terminology are as follows:

\[
\begin{align*}
Rh_0 &= D; \text{allelomorph is } Hr_0 = d \\
Rh' &= C; \text{allelomorph is } Hr' = c \\
Rh'' &= E; \text{allelomorph is } Hr'' = e
\end{align*}
\]

Two chromosomes, each with its three loci, determine the Rh status (genotype) of an individual. Any individual's Rh status, correspondingly, can (and must) be represented by six allelomorphic genes. For example, an Rh0Rh individual is represented by cDe/cde; an Rh0Rh' individual is represented by cDe/Cde; etc. Within the gene, Rh and Hr are completely reciprocal, and at each locus one or the other (but not both) is present. [i.e., an Rh gene consists of De or Hr; Rh0Hr', and reacts with antiRh serum, antiHr serum, and antiHr' serum.] In actual practice, of course, the formula of the genotype (i.e., of the two chromosomes) is not always subject to discovery with the tools at hand today.

Fisher's theory allows easy comprehension of two recent subgroups of the Rh factor. The first, labeled C\*, is a subgroup of C (Rh\*) and occurs instead of C or c at the same chromosome locus. The second, called D\*, is a subgroup of D (Rh0) and occurs at the D-d locus instead of the more usual D or d. Both
these subgroups have recently been discovered in England, and the irregular reactions provoked by their presence in certain individuals have been made comprehensible by Fisher's simple picture of the Rh chromosome.

This short article by Dr. Race summarizes excellently the fundamentals of Rh knowledge as they are known today. The reasonableness of Fisher's postulates is confirmed by the statistical data presented. The use of the Fisher terminology commendably simplifies the discussion of the "Rh" problem.

S. E.

SUBSTITUTION TRANSFUSION: A NEW TREATMENT FOR SEVERE ERYTHROBLASTOSIS FETALIS. H. Wallerstein.

From the Department of Hematology, Jewish Memorial Hospital, New York City, and the Laboratories of the Queens General Hospital, Jamaica, N. Y. Am. J. Dis. Child. 75: 19-33, 1947.

The procedure described is that of removing the infant's blood from the longitudinal sinus through the anterior fontanel and replacing it with Rh negative blood given through a cannula inserted in a superficial vein of the arm. After about 50 to 60 cc. of blood have been removed by syringe, an equal quantity of Rh negative blood is administered. When this type of exchange has been repeated at least five times, the needle is removed from the fontanel and the infusion in the arm is continued until about 75 to 100 cc. of blood are given in excess of the amount removed. At the end of this procedure it can be shown by differential agglutination that only 20 to 25 per cent of the infant's original Rh positive cells remain.

The objectives of substitution transfusions are to remove the products of hemolysis and to prevent their formation in excessive amounts by the removal of the Rh positive erythrocytes before they are destroyed in large numbers by the maternal antibody. In this way it is hoped that the incidence of hepatic damage and kernicterus can be minimized. Seven of the 9 patients cited in this report responded satisfactorily, and it is the author's opinion that the 9 infants who died might have recovered if treatment could have been instituted during the first 24 hours of life.

Substitution transfusion is recommended chiefly as a prophylactic procedure to be applied during the subicteric period immediately after birth. History of erythroblastosis in a previous infant is emphasized as the principal indication for its use, but due consideration is also given to serologic data, especially a rising titer of maternal antibody.

The results of substitution transfusion thus far reported by a number of investigators are encouraging, but there is an obvious need for further critical evaluation of the efficacy of and indications for this procedure. The technic described by the author is relatively simple and, in experienced hands, this form of therapy should be safe.

L. E. Y.


The technic described involves injection of the donor's Rh negative blood into the saphenous vein at the ankle, withdrawal of the infant's blood through the radial artery at the wrist, and the use of heparin to prevent clotting of the infant's blood. The transfusion is kept about 60 to 75 cc. ahead of the bleeding in order to allow a margin of safety, but the total amount injected is not allowed to exceed by more than 50 cc. the quantity of blood withdrawn. The modified technic recommended also calls for replacement of one half the donor's plasma with saline in order to minimize "conglutination" of the Rh positive cells remaining in the infant's circulation.

Of a total of 17 infants treated by this method, many of them critically ill, all but 1 made a prompt recovery. Details are given concerning 2 cases, in both of which a 90 per cent replacement was effected. In 1 case the maternal serum contained univalent Rh antibodies in moderate titer, and in the other bivalent antibodies were present in high titer. In the former case Rh positive cells were absent in the infant's circulation from the 7th to the 34th days, and in the latter from the 5th to the 15th days. The authors explain the shorter period of "ineffectual regeneration" of erythrocytes in the second case on the hypothesis that bivalent antibodies enter the infant's circulation mainly during labor and are largely removed by exchange transfusion. Univalent antibodies, on the other hand, are thought to enter the infant's circulation continuously during the latter part of pregnancy and to permeate tissue fluids in such

The author studied 125 gestations in 50 families; each case is illustrated by a chart. The statistical results are the following: 30 per cent of the children were uninjured (first-born or born of a heterozygous father). Of the 70 per cent injured: 10 per cent anemic, 40 per cent icterus gravis, 50 per cent born dead or abortive. Of those born dead, 41 per cent showed hydrops foetalis. Of those with icterus gravis, 13 per cent showed evidence of nuclear icterus. When the first-born child was affected, one could almost always find a previous sensitization of the mother by blood transfusion or heterohemotherapy. The study of the hypothesis can be substantiated by further observations following exchange transfusions. It will be of interest to see if this way that they are not readily removed by exchange transfusion. It will be of interest to see if this hypothesis can be substantiated by further observations following exchange transfusions.

L. E. Y.


The author makes the following statements on the basis of his own experiments and publications on the subject. The antigen O is not specifically human but is heterogenic. It bears no relation to the O (recessive) gene. It is diversely distributed in the various red cells O, A1, A2, A, AB, and A0B. The differentiation between homo- and heterozygous A or B is still impossible. The anti-O agglutinins cannot appear in human plasma except in very rare circumstances. Practically, the study of antigen O has opened new possibilities for a better diagnosis of the subgroups A and for the control of universal donors. It is also useful for the study of some transfusion accidents and has some medicolegal applications. For all these reasons the antigen O is not without theoretical and practical interest.

J. P. S.


By questionnaire, a survey was made of 1762 patients with hepatitis in sixty-four general army hospitals. Five hundred of these patients had received either blood or plasma at the time of their battle injury. In the nontransfused patients, the interval between injury and development of hepatitis showed a flat line with no peak incidence. Those transfused, however, showed a clear-cut peak at ten to fourteen weeks after injury (when presumably the blood was given). From the data presented, one might estimate that in about two thirds to three fourths of the transfused patients, the hepatitis could be ascribed to heterogenic materials, presumably blood, received at the time of injury. This is further evidence of the importance of blood products as a cause of hepatitis.

C. A. F.
ABSTRACTS

LEUKEMIA AND LYMPHOMA


The author presents an excellent appraisal of current knowledge of lymphomas and leukemias, with particular reference to diagnosis, prognosis, therapy, and relationship to the general problem of malignant diseases. It is emphasized that tumors of the lymphatics and blood-forming organs are important because (1) they are collectively responsible for over 6 per cent of all deaths from malignancy, (2) they strike the younger elements of the population, (3) their range of morbidity brings them within the scope of every kind of practitioner, and (4) they lend themselves well to clinical investigation of cancer and trial of new therapeutic methods. The author stresses the fact that proper therapy may be not only palliative but also life-prolonging, and he sees some promise of curability in certain types of Hodgkin's disease and lymphosarcoma.

L. E. Y.


After first redefining the myeloblast and myelocyte A as seen in supravital preparations, Schwind very carefully studied the changes in leukemic blood from 2 patients following various transfusions. Fresh normal blood plasma produced a partial maturing effect on the myeloblasts. The causative substance was not present in gamma globulin or in dried plasma.

O. P. J.

EFFECTS OF RADIOACTIVE PHOSPHORUS (32P) ON NORMAL TISSUES. W. R. Platt. From the Department of Pathology, Washington University School of Medicine, St. Louis. Arch. Path. 43: 1-14, 1947.

Changes produced by the radioactive isotope of phosphorus (32P) were studied in tissues from 43 cases, the diagnoses of which included acute leukemia, chronic leukemia, leukosarcoma, aleukemic leukemia, Hodgkin's disease, multiple myeloma, lymphosarcoma, melanoma, and Ewing's sarcoma. Radioactivity of bone marrow, liver, spleen, kidney, muscle, and lymph nodes was determined. Tissues which utilize phosphorus rapidly have a high content and take up higher concentrations of radioactive phosphorus. Normal as well as diseased tissues are affected. Radiophosphorus has a marked sclerosing effect on the bone marrow. Of the various immature marrow cells, megakaryocytes were the most sensitive—to the extent that they were either degenerated or completely absent.

O. P. J.


In recent years there has been a tendency to modify the concept of myeloma. Three clinical subtypes of this disease have been suggested. The classical type is a multicentric tumor involving the red marrow of flat bones. The other types have either a single focus which eventually becomes multiple or a diffuse involvement simultaneously of all red marrow. The present authors recognize two cytomorphic types of myeloma: one the plasma cell type and the other a myeloid type. The origin of these tumor cells may be from the reticulo-endothelial system. In 5 of the 13 cases, aspirated sternal marrow was examined. In 3 cases no myeloma cells were encountered. In the other cases tumor plasma cells were present, even though 2 cases were diagnosed on sectioned tissue as the myeloid type and 2 as the plasma cell type.

O. P. J.


Data on 4 cases are presented to show the interrelationship between primary "systematized" amyloidosis and plasmacytoma with Benc-Jones proteinuria. The patients had symptoms of muscle pain, dyspnea, weakness, and in 3 out of 4 there was macroglossia. Three cases gave a positive Congo red test.
intradermally. In 3 patients there were atypical plasma cells in the marrow and Bence-Jones protein in the urine. X-rays, however, showed no bone lesion. In 2 autopsied cases there was distribution of amyloid as described in primary amyloidosis. The authors discuss the coincidence of primary amyloidosis and myeloma.

C. A. F.


Sarcoma of the stomach is a rare tumor, comprising some 1 per cent of all gastric tumors (Ewing, 1940). The association of a macrocytic hyperchromic anemia with sarcoma is an even rarer occurrence. It is a coincidence that two reports of this combination should be published within a few months. The first was that of Schindler et al. (Surg., Gynec., & Obst. 82: 139-52, 1946), in which 1 patient with leiomyosarcoma of the stomach was first seen because of a typical picture of pernicious anemia, even including reticulocytosis on liver extract therapy. These authors wondered whether, in this case, pernicious anemia had antedated and led to sarcoma.

In the present paper, another instance of gastric sarcoma and "pernicious anemia" is reported. A woman aged 34 was found to have a tender tumor in the left mid-abdomen, which was thought to be spleen. Laboratory studies demonstrated a macrocytic hyperchromic anemia typical of pernicious anemia; gastric achlorhydria; and an increased number of megaloblasts in the bone marrow. There was, however, no response to liver therapy. At operation and subsequent autopsy, the tumor was found to be a spindle-cell sarcoma involving the stomach, omentum, mesentery, and peritoneum, and apparently primary in the stomach. The spleen was normal.

The relationship between carcinoma of the stomach and pernicious anemia is well known. Carcinoma is prone to develop in a patient with pernicious anemia and, conversely, a macrocytic hyperchromic anemia may be the presenting complaint in carcinoma of the stomach. The common denominator is considered to be the atrophic gastric mucosa, a "premalignant" lesion. Since sarcoma of the stomach is a subepithelial lesion, and therefore not based upon the atrophic gastric mucosa, a relationship to macrocytic hyperchromic anemia would not be expected to occur. It is possible that some other type of mechanism must be postulated for this combination; or, perhaps, that the accepted mechanism for carcinoma needs modification. There is also the possibility that this combination is merely coincidental.

S. E.


Methyl bis beta-chloroethylamine hydrochloride was given in dosage of 0.1 mg. per kilo daily for four-day periods to 23 patients. These included 15 cases of Hodgkin's disease, 1 case of lymphosarcoma, 1 case of chronic myelogenous and 1 of chronic lymphatic leukemia, 1 reticulum cell sarcoma, and 1 carcinoma in the lung. The only condition that responded satisfactorily was Hodgkin's disease. There were no serious complications of therapy. The average duration of remission appeared to be about two months. In this report there is nothing to suggest any superiority of this form of treatment over the expected response to x-ray.

C. A. F.


This report concerns the case of an infant with a fatal illness which was manifested by the progressive development of weight loss, fever, hepatosplenomegaly, lymphadenopathy, leukopenia, and a hypochromic, macrocytic anemia. A clinical diagnosis was established at age 7 months by the demonstration, in a bone marrow biopsy specimen, of encapsulated inclusion bodies, 1-5 microns in diameter, each with a central dark chromatin mass. A few extracellular forms were discovered, but most were contained in mature neutrophiles, eosinophiles, monocytes, and megakaryocytes. These findings are well illustrated by means of color plates. The fungus Histoplasma capsulatum was subsequently cultivated from the peripheral blood, duodenal aspirations, and stools, cultures being prepared on hormone blood agar plates containing added streptomycin.
ABSTRACTS

Histoplasmosis, the authors emphasize, deserves serious consideration as a diagnostic possibility in cases with obscure fever and features suggesting a lymphoblastomatous disease.

C. P. E.

AGRAULOCYTOSIS

AGRAULOCYTOSIS IN CHILDHOOD. REPORT OF A CASE WITH SERIAL BONE MARROW STUDIES. E. Bruck. From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio. Am. J. Dis. Child. 75:186-194, 1947.

A well-studied case of agranulocytosis of unknown etiology in a 2-year-old girl is presented. The child recovered despite the fact that the number of granulocytes in the blood varied between 0 and 84 per cu. mm. for 11 days and the illness was complicated by pneumonia and severe stomatitis. At the height of the disease, hypoplastic bone marrow with lymphocytic reaction was found. Although penicillin, blood transfusions, crude liver extract, and pentasaccharide were used in this case, the author stresses the now accepted fact that prevention and treatment of infection are of paramount importance in the management of agranulocytosis.

This is the second case of acute or Schultz type agranulocytosis in a child reported since 1937. All other cases in children reported during the past ten years were due either to sulfonamide compounds or to severe and protracted purulent infections. There were no children in Plum's series of 88 cases and he accepted only 9 cases of agranulocytosis in children reported in the literature up to 1937.

L. E. Y.

BLOOD COAGULATION AND HEMORRHAGIC DISEASES


A material suitable for intravenous injection was prepared by heating a fraction of normal human plasma (Fraction I), in which the clotting factors are mainly concentrated. The resulting product, tested in vitro and in vivo, was found to have lost none of the antihemophilic potency characterizing Fraction I when unheated. Inasmuch as fibrinogen, prothrombin and all formed elements, including platelets, were completely removed by the heating process, further confirmation was obtained of the fact that these substances are not responsible for the clot-promoting properties of normal plasma when the latter is added to hemophiliac blood, or when administered to patients with hemophilia. From the viewpoint of practical therapeutics, it is reasonable to infer that an improved substitution therapy for this disease may be in prospect, one safer, more convenient and efficient than whole blood or plasma transfusion.

C. P. E.


The author presents a well-illustrated, expository review and a coherent working concept of the mechanism of hemostasis. The extravascular, vascular, and intravascular factors concerned in checking blood loss are discussed concisely. A list is given of the probable order of importance of the components of hemostasis in different vessels, vascular contraction being rated most important in checking blood loss from arteries and arterioles, external compression in capillaries and venules, and platelet massing in veins. General deductions are that (a) the nature of the defect in hemostasis largely determines what vessels will be affected, (b) failure of spontaneous hemostasis may not necessarily follow a deficiency of one or two factors provided stresses are moderate and exerted chiefly on vessels not wholly dependent on those factors to check hemorrhage, and (c) most methods of arresting blood loss are attempts to duplicate the steps of the natural mechanism of hemostasis.

L. E. Y.
TREATMENT OF TWO REACTIONS DUE TO GOLD. RESPONSE OF THROMBOCYTOPENIC PURPURA AND GRANULOCYTOPENIA TO BAL THERAPY. L. M. Lockie, B. M. Norcross, and C. W. George. From the University of Buffalo School of Medicine, and Buffalo General Hospital. J. A. M. A. 133: 754-755, 1947.

BAL (British Anti-Lewisite; 2,3 dimercaptopropanol) has recently been widely used in the treatment of toxic reactions caused by arsenic and mercury, with excellent results. The trial of this substance in poisoning due to other metallic substances was therefore to be expected. Apparently, the toxicity of these elements depends upon their inactivation of sulfhydryl systems, and the efficacy of BAL is believed to be due to its ability to reactivate these systems.

In the present report the authors discuss 2 patients with rheumatoid arthritis who developed hematologic abnormalities during gold therapy. The first patient showed thrombocytopenia with bleeding into the skin, gums, and brain. After unsuccessful use of transfusions, liver extract, folic acid, ascorbic acid, and vitamin K, therapy with BAL was instituted, with a prompt remission of the thrombocytopenia and subsequent complete recovery. In the second patient, granulocytopenia developed during gold therapy, and responded to treatment with BAL.

The same issue of the J. A. M. A. contains two other reports of the use of BAL to counteract various toxic gold reactions, chiefly dermatitides (pp. 749-752; 751-755). In one of these reports it was found that an increased excretion of gold was present during therapy with BAL, and the suggestion was made that BAL removes the gold which is inactivating sulfhydryl systems and allows its excretion from the body. With reactivation of these systems, toxic reactions disappear. It is of interest that the same physiologic abnormality seems to produce various types of toxic reaction, including disappearance of megakaryocytes and granulocytes in the bone marrow.

S. E.


In 1945, Seegers, Loomis, and Vendenbelt isolated prothrombin and demonstrated that it was a homogeneous protein (Arch. Biochem. 6: 85-95, 1945). After detailed investigations, they were unable to find two separate prothrombin factors. The substance which they isolated was, in itself, both chemically and physiologically complete. They were at a loss, therefore, to understand the occurrence of two separable components, prothrombin A and prothrombin B, as postulated by Quick; although they were able to confirm his results when using his own methods. In an attempt to determine wherein the error in interpretation might lie, further experiments with plasmas were undertaken.

The present report, which details some of these investigations, demonstrates that "prothrombin A" is in reality fibrinogen, and that "prothrombin B" corresponds to pure prothrombin, which is a single compound and not a mixture of two complexes. There were three critical experiments:

(1) Stored beef plasma retained its prothrombin potency when measured by the two-stage test of Warner, Brinkhous, and Smith (Am. J. Physiol. 113: 667, 1940), but seemed to lose it within a week when measured by the Quick test. Apparently, then, the amount of prothrombin was constant; but its activity diminished with time.

(2) When prothrombin was quantitatively inactivated in plasma which was then allowed to stand, the prothrombin content increased to a normal value in eight days by the two-stage measurement, but remained absent by the Quick test. The addition of fresh prothrombin-free plasma did not affect the two-stage assay, but changed the Quick value to 100 per cent. Again, the interpretation seemed reasonable that fresh plasma added something needed to activate prothrombin already present; and that the Quick determination measured, not the amount of prothrombin present, but the rate of its conversion into thrombin.

(3) The addition of fibrinogen in the latter experiment, in place of prothrombin-free fresh plasma, had an effect similar to that of the fresh plasma.

The conclusions are reached that, in Quick's assay method, fibrinogen ("prothrombin A") and not true prothrombin ("prothrombin B") was the compound denatured during refrigerator storage, and that the postulate that prothrombin is a union of two complexes, each of which, in itself, is inactive, is invalid. The authors discuss in detail the reasons for Quick's arrival at this conclusion, and comment on
deductions since published on the basis of the concept that prothrombin is a complex substance. Their demonstration of the unitary nature of prothrombin is completely convincing.

S. E.


In 15 patients suffering from coronary occlusion the authors found no constant changes in blood volume, circulation time, coagulation time, prothrombin concentration, or coagulability of the blood as measured by a modified Waugh-Ruddick test. Plasma proteins were within normal limits in all cases, but 6 of 15 patients showed significant hemoconcentration on admission.

It is unfortunate that the series reported is too small to justify definite conclusions.

L. E. Y.