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HEMOSTASIS

The mechanisms by which pulmonary thromboemboli produce pulmonary hypertension, increased airway resistance, pulmonary edema and sudden death have not been explained satisfactorily solely by mechanical obstruction of the pulmonary vasculature. Previous studies in dogs revealed that release of autologous stasis thrombi to the lung and platelet microemboli formed by the administration of bacterial endotoxin induced rapid development of airway constriction. In both experimental conditions, the acute physiologic responses to emboli were prevented by prior administration of heparin. Airway constriction was also inhibited by a serotonin antagonist, suggesting that in dogs the release of serotonin from platelets was responsible for its production. The purpose of this study was to compare, by light and electron microscopy, thromboemboli recovered from the lungs of untreated and heparin-treated rabbits. Serum-induced stasis thrombi were formed in the jugular veins of rabbits. In one group, thrombi were released to the lungs from their site of formation and were recovered at autopsy approximately 8 minutes after release. In another group, the identical procedure was followed, except that heparin was administered intravenously before thrombi were released. A fine granular eosinophilic rim was observed around the emboli from nonheparinized animals, but was absent in those from heparinized animals and from the neck vein thrombus itself. Electron microscopy demonstrated that the eosinophilic rim consisted of platelets, most of which had undergone some degree of metamorphosis. Only occasional platelets were seen to adhere to emboli from heparinized animals. Since thrombin appeared to be the only substance which produced platelet aggregation and which was inhibited by heparin, it was postulated that platelet aggregations on the surface of the fresh thromboemboli were caused by traces of thrombin on the fresh thromboemboli which had not been destroyed by antithrombin. These observations were considered to provide a morphologic basis for the occurrence of thrombin-induced amine release from platelets in pulmonary embolism and its prevention by heparin.—R. G.


Evidence of recurrent pulmonary embolism after ligation of the inferior vena cava was found in
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9 patients in 2½ years, representing a 20 per cent recurrence rate. Three deaths were ascribed to recurrent emboli. The presence of large collateral veins was demonstrated in 7 patients, and their development over a period of months appeared to undermine the protective effect of a caval tie. Such collaterals could provide adequate pathways for the passage of emboli of medium to large size. They may also undergo thrombosis and provide additional sources for emboli. Venous thrombosis may result from the simultaneous combination of altered coagulability of the blood and local stasis. Ligation alone ignores the problem of "hypercoagulability" and tends to compound venous stasis and, although it may be immediately life-saving, may not suffice for long term protection against recurrent pulmonary embolism.—R. G.

WHEEZING DUE TO PULMONARY EMBOLISM:

Three patients were observed to have wheezing as a prominent feature of the presenting syndrome of pulmonary embolism. The mechanism of the broncho-constriction in such patients has been postulated to be the release of serotonin from platelets which adhere to the thrombus presumably induced by the action of thrombin. Since this action of thrombin on platelets can be prevented by heparin, this agent should be useful in the treatment of broncho-constriction which occurs with pulmonary emboli. In the three cases reported, it was difficult to evaluate the role heparin therapy played in the relief of the wheezing. —R. G.


Prophylactic treatment for 3 months in 4 adult hemophilia A patients with EACA in daily doses of 3, 10, 15 and 20 Gm., respectively, was without effect. Therapeutic doses of 0.4–0.5 Gm/Kg/day per os seemed to have a hemostatic effect in hematuria and in bleeding from the oral mucosa, irrespective of the type of hemophilia. The biologic T1/2 of Factor VIII was not altered during administration of EACA. Slight gastric intolerance and nausea were noted as side effects.—E. A. L.


AHF activity of plasma was found to be enhanced by dialysis against MnCl₂. Thrombic destruction of AHF was prevented by prior dialysis of plasma against MnCl₂. Manganese was found to be the most effective cation tested and 0.02M was the optimal concentration. Manganese did not protect AHF by destroying thrombin or by altering the thrombin-destroying properties of antithrombin. The protective action of MnCl₂ may be related to changes induced in the AHF molecule. The AHF activity observed in vitro could also be observed in vivo, normal dogs circulating somewhat more and hemophilic dogs somewhat less AHF than expected from the amounts infused. —R. G.


A review of the literature with discussion of the methods, clinical observations (hemorrhagic patterns, diagnosis, prognosis, therapy) and of the findings of the authors was presented.—P. d. N.


A Kasabach-Merritt syndrome occurred in a new born male infant with a platelet count 15,000/mm³ and an extremely low fibrinogen level, as assessed by biological methods. Coagulation times were reported to be normal, so more than traces of fibrinogen must have been present. Immunochemically, the fibrinogen content was ¼ of normal. The patient died from uncontrollable epistaxis. Histologically, the hemangioma was benign and only a few platelet thrombi were seen.—E. A. L.

LETHAL ANAPHYLACTIC SHOCK DURING TRANSFUSION OF A PLATELET CONCENTRATE. R. Flury and F. Reutter. From Kantospital, St. Gallen,

A 56 year old woman with idiopathic thrombocytopenia died suddenly of anaphylactic shock during transfusion of platelets freshly prepared from 10 donors by the buffy coat method. The patient, mother of 4 children, had received 6 blood transfusions 2 3/4 years before. Since red cell incompatibility, as well as bacterial contamination, could be ruled out and hypersensitivity to plasma seemed unlikely, the deadly anaphylactic reaction most probably was caused by antileukocyte or antithrombocyte antibodies. Unfortunately, neither the amount of white cells in the platelet concentrate nor the antileukocyte antibody titer in the patient's serum were assessed.—E. A. L.


The cases were observed after splenectomy and were associated with erythrocyte abnormalities which could be ascribed to the "Mediterranean trait" (decreased osmotic fragility, marked poikilocytosis). In some relatives of the patients, there was an increase in Hgb A2, and in morphologic abnormalities of erythrocytes. Thromboplastin generation tests with platelets were abnormal with the concentration of platelets equivalent to that in the patient's blood. The role of the concomitant anemia which was not improved by splenectomy was considered from the pathogenetic point of view.—F. d. N.


The distribution of human platelets in the body was studied with Cr51-labeled platelets, external scintillation scanning, epinephrine stimulation and platelet counts on the blood of surgically removed spleens. The findings presented were consistent with the interpretation that normally about 1/5 of the total platelet mass is concentrated in the spleen and exchanges with the remaining 4/5 which is evenly distributed throughout the rest of the vascular system. Pulmonary or marginal pools of platelets did not seem to make up a significant portion of the platelet mass. In splenomegaly, the splenic platelet pool may be increased to 50–90 per cent of the total platelet mass. This redistribution of cells from the peripheral circulation to the spleen could produce thrombocytopenia, despite normal platelet production, normal total platelet mass and normal platelet lifespan. The prolonged thrombocytosis which usually follows splenectomy may be due to the removal of the splenic platelet pool. It was also postulated that platelet production is governed by the rate of platelet destruction, rather than by the platelet concentration.—R. G.


Visible light produces toxic effects in many biological systems exposed to a variety of organic dyes. Some of the initial effects of photodynamic action on whole animals have been attributed to release of histamine, and rat mast cells treated with hematoporphyrin and light appear to be depleted of histamine. Since serotonin, a closely related amine, is present in high concentration in human platelets, the effects of hematoporphyrin and light on these cells have been studied. The release of serotonin and the depletion of ATP from irradiated platelets apparently reflects alteration in the membrane. Platelets exposed to hematoporphyrin and light are no longer aggregated by thrombin and calcium. These results indicate that aggregation is a more complicated process than simple proteolysis of clottable protein.—O. P. J.


The authors correlated the effects of photodynamic action on human platelets with the uptake by the cells of the photosensitizing substance, hematoporphyrin. Similar studies, employing other drugs which alter the physical, chemical or functional state of the platelet, may give additional information about the structure and metabolism of the cell.—O. P. J.
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THROMBOCYTE ISO-ANTIBODIES IN THE BOVINE.


Using a simple method of complement deviation, the author found that some platelet iso-antibodies were genetically transmitted. These antibodies, located in bovine iso-antisera, were specifically adsorbed by thrombocytes.—J. C.

SYNTHESIS OF CLOTTING FACTORS BY THE ISOLATED PERFUSED RAT LIVER.


The role of the liver in the synthesis of coagulation factors was studied with the technic of isolated, intact rat liver perfusion. Evidence for synthesis of prothrombin, Factors V, VII and X was obtained. Inhibition of synthesis of prothrombin, VII and X by Coumadin and reversal of inhibition by vitamin K₁ were demonstrated. No effect of Coumadin and vitamin K₁ on Factor V synthesis was demonstrated. Further evidence for hepatic synthesis of prothrombin and Factors V and X was obtained with puromycin as an inhibitor of protein synthesis. Studies of puromycin in combination with Coumadin and vitamin K suggested that the latter two agents acted between ribosomal synthesis and the appearance of active prothrombin, VII and X.—R. G.

LEUKOCYTES

CYTOCHEMICAL STUDY OF STEM CELLS DURING ACUTE PHASES OF CHRONIC MYELOID LEUKEMIA.


This study included 28 cases of chronic myeloid leukemia during acute transformation and involved examination of smears and bone marrows stained by the May Grunwald Giemsa method, by the Gomori method for peroxidases, by the MacManus method modified by Hayhoe for P.A.S., the alkaline phosphatase reaction according to Kaplow and chromosome studies with the Tijo and Whang technic in 15 patients. A great polymorphism among leukoblasts was observed: typical myeloblasts (10 cases), cells with azurophilic granules without peroxidase but P.A.S. positive, lymphoblasts (7 cases), and small blasts, unclassified (5 cases). In 18 cases, the erythroblasts had P.A.S. positive material. Karyotype study in 12 cases showed the presence of the Philadelphia chromosome. This latter fact suggested that all the blasts, even with a different appearance, belonged to the myeloid series. The acute transformation of the leukemia usually differed from the common acute myeloblastic leukemia. The criteria for the cytolologic diagnosis of acute lymphoblastic leukemia appeared to be inadequate.—J. C.

CLINICAL CONTRIBUTION TO THE STUDY OF ELECTROPHORETIC PROTEIN PATTERNS IN ACUTE LEUKEMIAS AND IN CHRONIC MYELOGENOUS AND LYMPHATIC LEUKEMIAS.


Thirty-seven cases of acute, 10 cases of chronic myelogenous and 26 cases of chronic lymphatic leukemia were studied. In most cases of acute leukemia, an increase in the alpha-1, alpha-2 and gamma globulins was observed. In some cases, gamma globulins also were increased. Total proteins and albumin were subnormal in almost all cases. No significant modifications were found in chronic myelogenous leukemia, except for hypergammaglobulinemia in one. In chronic lymphatic leukemia, a decrease in gamma globulins was found in 46 per cent.—P. d. N.

FIRST OBSERVATIONS ON THE THERAPEUTIC EFFECTS OF 6-(1-METHYL-4)NITRO-5-IMIDAZOQUINOLINOTHIO-PURINE (IMURAN) IN LEUKEMIAS, ESPECIALLY IN THE ACUTE FORM.


The drug was always well tolerated in 21 cases, most of whom had acute leukemia. With large doses (not less than 7 or 8 mg/Kg), good results were obtained. Small doses (1 to 3 mg/Kg) were not as satisfactory. According to the authors, the drug could be used in patients with thrombocytopenia or anemia.—P. d. N.

PATTERNS OF GLYCOPROTEINS IN ACUTE LEUKEMIAS.

Thirty-five cases were studied. The most marked changes were observed in histiocytic leukemias and, to a lesser degree, in hemocytomyeloblastic forms. In lymphatic forms, the modifications were less pronounced. They were similar to, but more marked than those already described in chronic forms.—P. d. N.


This type of leukemia was considered to be the rarest and most severe and was characterized by marked hemorrhagic manifestations. A rapidly fatal course, invasion of atypical promyelocytes into the bone marrow and peripheral blood, a complex clotting disorder with deficiencies in Factors I, V and VII and platelets and alterations in thromboplastin generation. The authors assumed that the clotting disorder might be due to excess consumption of coagulation factors.—P. d. N.


A murine leukemia virus was capable of inducing leukemias in rats of the Wistar/Furth, Fisher/Furth and Sprague-Dawley strains and in F-hybrids of the first two strains. All leukemias induced in intact rats with the rat-adapted Cross passage A virus were lymphoid and thymic in origin. Electron microscopy revealed a greater abundance of virus particles in the thymus than in any other organ examined. Thymectomy one month after virus infection lowered the induction rate of lymphoid leukemia from 97 to 49 per cent and raised that of myeloid leukemia from 0 to 15 per cent. Neonatal thymectomy followed by virus infection reduced the induction rate from 74 to 13 per cent in one experiment and from 93 to 19 in another. Intercurrent infections, mostly pneumonia, seemed to be responsible for a reduced induction rate of both thymic and non-thymic types. Grafts of neonatal thymus in the thymectomized virus infected rats restored susceptibility. Multiple thymus grafts were much more effective than single ones. Transplantation assays for genetic and histocompatibility factors following thymus grafts suggested that the induced lymphoma cells were of three types: 1) Some possessed the transplantation pattern of the host, 2) some that of the donor cells, and 3) some were immunologically altered. An attempt to demonstrate a co-leukemogenic thymic humoral factor was inconclusive. Grafts of cultured epithelial-reticulum cells of the thymus seemed to be capable of restoring the sensitivity of thymectomized rats. Parallel observations were made on the role of the thymus in leukemogenesis, lymphopoiesis and immunocompetence. There appeared to be some parallelism in behavior of the three presumably hormone-like factors of the thymus, but there also was marked divergence, indicating basic differences.—K. F.


Mice infected with the Rauscher virus developed prominent splenomegaly with erythroblastosis in the peripheral blood and about 50 per cent of infected mice died during the early phase of the disease from intraperitoneal hemorrhage due to splenic rupture. Lymphoid leukemia was not observed among mice who escaped splenic rupture. Early mortality due to splenic rupture could be prevented by splenectomy prior to virus inoculation, but the eventual development of the disease could not be prevented, indicating the presence of susceptible cells in other sites, such as bone marrow or liver. Thymectomy did not modify the course of the disease. Transplantation studies demonstrated that the proliferating cells in various tissues possessed the characteristics of the neoplastic cells. It was suggested that the disease elicited by infection with Rauscher virus was comparable to erythroleukemia in man and erythroblastosis in birds. Various types of leukemia, including thymic and non-thymic lymphoid leukemia and erythroleukemia, developed among W/Fu rats infected at birth with Rauscher virus. Host factors played an important role in the determination of the type of leukemia induced by the leukemogenic viruses.—K. F.


A comprehensive study which included an analysis of the incidence of the different forms, their relationship with age, sex and blood groups, the familial occurrence, the incidence of the most im-
important signs and symptoms, and the modifications in some relevant laboratory data. Criteria for the early detection and differential diagnosis of these diseases were presented.—P. d. N.


Absolute neutropenia, toxic granulation of the neutrophils and Döhle bodies were found in the great majority of a series of carefully studied patients with infectious mononucleosis.—T. E. B.


Exudate leukocytes lost approximately 30 per cent of their original intracellular ascorbic acid content during 2 hours of incubation in a glucose medium. The same loss was observed for cells initially containing both high and low levels of ascorbic acid. High concentrations of ascorbic acid in the incubation medium depressed lactic acid production and increased oxygen uptake by the cells. Iodoacetate and fluoride at low concentrations decreased ascorbic acid loss from cells during incubation; at high concentrations, they increased loss. Ascorbic acid uptake from the medium was inhibited by iodoacetate but was stimulated by fluoride. The results indicated that the guinea pig exudate leukocyte may be useful as an experimental tool in studies of ascorbic acid metabolism.—O. P. J.


The pathogenesis of Brucella abortus in cattle has two phases. In the first, organisms are taken up by phagocytic cells in which some survive and multiply and are transported to lymphoid tissue. In the second phase in the pregnant female, susceptible tissues, such as the fetal placenta and fluids, are involved. An explanation for the second phase is the occurrence of erythritol, a growth stimulant for Brucella. There is no complete explanation for the first phase. The object of the present investigation was to obtain large quantities of bovine phagocytes relatively free from other cells so that extracts of these cells could be examined for their growth stimulating effect on virulent and avirulent strains of the organism. Simple techniques were developed for the separation of bovine buffy coat from erythrocytes by flotation on “dense plasma” and for the separation of the phagocytes from the lymphocytes by a settling procedure. The effects of extracts of the purified phagocyte and lymphocyte fractions on the growth of Br. abortus suggested that the growth stimulant present in bovine buffy coat was concentrated in the lymphocytes, rather than in the phagocytes. The factor, therefore, is unlikely to be of importance in the growth of virulent strains, rather than avirulent strains, within bovine phagocytes.—O. P. J.


The osmotic resistance of leukocytes was investigated after 30, 60, 120 and 180 minutes of exposure to hypotonic 0.2 per cent sodium chloride solution. Mouse leukocytes displayed the greatest resistance, followed in decreasing order by: the dog, rabbit, white rat and guinea pig. The resistance of leukocytes from adult humans was lower than that of mouse leukocytes, and corresponded approximately to the values for dog leukocytes. The leukocytes of newborn infants showed a much lower resistance than those of adult humans.—L. D.

Erythrocytes


In this carefully controlled double blind study, an examination was made of the frequency of toxic erythropoietic changes occurring in patients with chronic renal or hepatic disease during the course of chloramphenicol therapy in comparison with the changes caused by another broad spectrum
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antibiotic, tetracycline. Twenty-two patients were given 3 Cm. daily of either antibiotic for 21 days. Tetracycline did not produce significant hematopoietic changes, while chloramphenicol led to reversible erythroid depression in 5 of 10 patients treated. Reticulocytopenia, a drop in hemoglobin, a rise in serum iron, cytoplasmic vacuolization of early erythroid forms, normoblastopenia and complete recovery after withdrawal of the drug occurred. This study reemphasized the considerable hematopoietic toxicity of chloramphenicol. —A. J. E.


In 4 of 8 cases, after gastric resection for peptic ulcer, abnormal utilization of tryptophan during a loading test was found. A latent deficiency of vitamin B₆ was postulated. The administration of pyridoxine alone or with niacin normalized the metabolic pattern. The concomitant anemia improved after treatment. The pathogenesis of this anemia was considered to be a consequence of alterations in pyridoxine-dependent enzymes. —P. d. N.


First report of a case suffering from hemolytic anemia with hepatic damage caused by neo-salvarsan. The patient, a 29 year old African Rhodesian, had G-6-PD deficiency in the erythroctes. —E. A. L.


The primary structure of the hemoglobin and myoglobins is, to the surprise of all, extraordinarily variable. In none of the investigated proteins are there so many and so diverse insights as there are for the hemoglobin and myoglobins. All possess the same physiologic function, but only about 6 per cent of the primary structure is constant. This paper provides a general view of how the structure varies and which modifications have been detected.—O. P. T.


The study of ontogenesis of erythrocytes has provided descriptions of the morphology of erythrocyte precursors, of the kinetics of their proliferation and of the modifications which may involve the hematopoietic cells during physiologic or pathologic events. In a review of these observations, it seemed convenient to dissect the overall problem of the control of hemoglobin formation into several less complex aspects, since the genetic and cellular control of hemoglobin synthesis may be studied at different levels of biological organization and by widely different experimental approaches.—O. F. J.


Precision scale models of sickle cell hemoglobin molecules indicate that the genetic substitution of valine for glutamic acid at the sixth position in the two β chains allows an intramolecular hydrophobic bond to form. This alteration changes the conformation to allow molecular stacking. Results of studies subjecting Hgb S solutions to temperature changes and to propane are consistent with the presence of such a bond. Examinations of sickled erythrocytes in a magnetic field and in polarized light indicate that the Hgb S molecules are aligned in situ. Filaments interpreted as hollow cables of six Hgb S monofilaments have been demonstrated by electron microscopy.—H. H. F.


Three offspring of Swiss parents, natives of Graubünden, aged 21, 23 and 25, had marked cyanosis without any related laboratory or clinical
pathology, except for slight erythrocytosis in one son (Hgb 18.1 Gm. per cent, erythrocytes 6.1 \( \times 10^6/\text{mm}^3 \)). The parents were not cyanotic. Consanguinity could not be demonstrated. Homozygous methemoglobinemia in the children was diagnosed with a methemoglobin reduction test using lactate, whereas heterozygosity in the parents could be demonstrated spectrophotometrically. The father and mother had 48 and 44 units of diaphorase activity, respectively (normal: 60–100). In all three children, glutathione reductase activity appeared to be slightly diminished. In addition, a slight familial elevation of Hgb F, a quite common feature in the Swiss alpine population, was found. Two other unrelated Swiss families with the same enzyme deficiency have been described previously.

—E. A. L.


These two reviews present up to date descriptions of the many hypothetical feedback controls which maintain a steady level of circulating blood cells and which provide compensatory changes when needed.—A. J. E.


In this careful and interesting paper, a number of physiologic parameters were systematically measured in a human subject exposed for four days to a simulated altitude of 16,400 ft. The serum erythropoietin became detectable at twelve hours, reached maximum concentration on the third day and fell to low levels on the fourth. The urine erythropoietin reached maximum levels on the second day and showed a fall on the third and fourth days. This fall in erythropoietin was believed to relate to an improved degree of acclimatization with a resulting reduction in functional hypoxia. The plasma iron turnover and hemoglobin synthesis followed a similar pattern, although elevated rates persisted for a considerable length of time after return to sea level pressure. This observation was quite definite and difficult to explain. Platelet counts and leukocyte counts became elevated shortly after the onset of hypoxic exposure. These elevations were similar to those found in a human subject given large amounts of crude human erythropoietin. It was speculated that erythropoietin in high concentrations possibly had some general bone marrow stimulating property. Other studies showed that the rise and fall in erythropoietin and red cell production correlated with changes in cardiac and pulmonary function, with changes in serum protein bound iodine and with urinary excretion of adrenal corticosteroids.—A. J. E.


Permanent catheters were placed in the renal vein and the carotid arteries of dogs so that blood samples could be obtained without using anesthesia. The renal production of erythropoietin was studied during acute hypoxia or after experimental renal infarction produced by injection of plastic microspheres. The erythropoietin assays were done in fasted rats or hypoxia-induced polychromatophilic mice. The results indicated that significant AV erythropoietin differences existed after two hours of hypoxia or after micro infarcts. Histologic changes suggested that it is the renal cortex, rather than the medulla, which is the site of erythropoietin production.—A. J. E.


Prolonged starvation induced a profound depression of erythroblast output in 48 hours, probably due to disappearance of endogenous erythropoietin. Protein administration 48 and 72 hours after the beginning of starvation induced only partial recovery of erythropoiesis after 96 hours. Exogenous erythropoietin given after 48 and 72 hours of starvation induced complete recovery of erythropoiesis within 96 hours. Granulocytopenia
and thrombocytopenia showed no changes. Erythropoietin was obtained from urine.—P. d. N.


Dose response curves usually are constructed after administration of sheep erythropoietin dissolved in saline. Since activities of various body fluids are determined from such curves, it is important to know if there is a difference in response if the erythropoietin is present in saline or in serum. The results of this study indicate that erythropoietin dissolved in serum is almost twice as active as erythropoietin dissolved in saline. If erythropoietin is given in fractionated doses, however, the response of a given dose is the same, whether dissolved in serum or in saline. It is suggested that plasma proteins may slow down absorption and give the erythropoietin-sensitive cells a more continuous exposure. As a practical conclusion, it seems to be advantageous to use fractionated doses in order to achieve higher responses with a given dose of erythropoietin and also to eliminate the problems of the character of the solvent.—A. J. E.


These two papers emphasize the not uncommon complication of erythrocytosis in patients with hepatoma. About ten per cent of such cases will have an unusually high hemoglobin level. In the paper from Japan, erythropoietic activity was found in tissue and serum extracts, adding to the general impression that hepatomas may cause inappropriate secretion of erythropoietin.—A. J. E.


Wilm's tumors previously have not been associated with polycythemia, in contradistinction to hypernephromas. In this report of a case of an 18-year-old woman, there was a striking erythrocytosis and a significant elevation of erythropoietin titer which dropped to normal after surgery. The erythropoietin titer did increase one year later when the patient was found to have pulmonary metastasis, but this time no erythrocytosis was found, possibly due to extensive metastatic disease.—A. J. E.


The clinical and ferrokinetic records of 28 patients with myeloid metaplasia and bone marrow myelofibrosis were reviewed. Of these, 21 patients were anemic and received testosterone enanthate, 600 mg. intramuscularly, once a week. Thirteen patients responded, but the number of nonresponders and the complications, such as splenic enlargement, hypermetabolism and hyperuricemia, made therapy quite difficult. The conclusion was that androgens would probably only be effective if there was some active bone marrow left, but that there was enough uncertainty to warrant a trial of therapy in every established case of myelofibrosis and myeloid metaplasia with anemia.—A. J. E.


Studies of the release of Fe59-heme from labeled marrow cells showed that the hemolysis of megaloblastic cells was greater than that of normoblastic cells. The increased hemolysis was reversed by treatment with vitamin B12 of a patient with pernicious anemia but not by the in vitro addition of either vitamin B12 or folic acid to suspensions of megaloblastic cells.—F. A. K.

Abnormal Propionic-Methylmalonic-Succinic Acid Metabolism in Vitamin B12 Deficiency and Its Possible Relationship to the Neuroligic Syndrome of Pernicious Anemia. R. J. Vicacqua, R. M. Myerson, D. J. Prescott and J. L. Rabinowicz. From the Veterans
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Increased urinary excretion of methylmalonic acid (MMA) was found to be present only in patients with deficiency of vitamin B₁₂. The injection of C¹⁴-labeled propionate resulted in the excretion of radioactive MMA in a patient with vitamin B₁₂ deficiency and posterior lateral sclerosis. Autoradiography showed evidence of C¹⁴ labeled material in a nerve biopsied from this patient, but not in a nerve from another patient with vitamin B₁₂ deficiency who had no neurologic symptoms. The authors suggested that altered propionate metabolism may be related etiologically to the neurologic syndrome of vitamin B₁₂ deficiency.—F. A. K.


Six male patients admitted with iron deficiency and megaloblastic changes in the bone marrow were treated with iron while being maintained on a diet which restricted folate intake to less than 8 μg per day. Serum vitamin B₁₂ concentrations were normal. Serum folate levels were subnormal in 2 subjects prior to treatment and became subnormal in 2 additional patients during treatment. Iron replacement was associated with conversion to normoblastic erythropoiesis in all 6 subjects. On the basis of these results and past observations cited from the literature, the authors proposed that iron deficiency plays an important role in the production of secondary folate deficiency.—F. A. K.


The binding of tetracyclines to intact bovine erythrocytes, hemoglobin and stroma was investigated. Erythrocytes had the greatest affinity for oxytetracycline, then for tetracycline and least for chlortetracycline. A considerable portion of the chlortetracycline and, especially, of tetracycline was bound irreversibly by erythrocytes. Oxytetracycline was bound by a labile bond. Chlortetracycline and tetracycline had a greater affinity for stroma, oxytetracycline a somewhat greater affinity for hemoglobin than for stroma.—L. D.


As red cells mature and age, they become more dense. The separation of younger and older red cells according to their density can be achieved by centrifugation or, possibly, by gravity alone, either in media that are less dense than the red cells or in media that are similar in density. The present paper presents modifications and verification of the technic and findings of Leif and Vinograd (1964). The movement of a cohort of Fe⁵⁹-labeled red cells through the various densities of gradient tubes as the cohort ages is shown.—O. P. J.


Although observations on the respiratory activity of avian blood have been made over many years, little information is available on the effect of such factors as individual variation and thermal effects when using whole blood as the tissue.—O. P. J.