ABSTRACTS OF SPECIAL INTEREST


By indirect immunofluorescence, antibody to gastric parietal cells was found in 42 of 220 relatives of patients with pernicious anemia and in only 5 per cent of a control group. In 20 asymptomatic relatives with parietal cell antibodies, achlorhydria was found in 11 and 6 of the 11 had an abnormal Schilling test. Sixteen of the 20 showed varying degrees of gastric atrophy and cellular infiltration on specimens obtained by biopsy of the gastric fundus. The authors considered the parietal cell antibody a convenient method for selecting those asymptomatic relatives of patients with pernicious anemia who are particularly prone to develop the disease. Positive tests should be followed by a Schilling test. If positive, in the opinion of the authors, treatment with B12 prophylactically should be instituted even in nonanemic subjects.—H. H. F.


A follow-up study was made of 1222 polycythemia patients seen between 1937 and 1953 in respect to their risk of developing acute leukemia. Acute leukemia developed terminally in about 10 per cent of patients treated with P32 and/or x-rays, compared with 1 per cent in the control patients. The length of survival did not seem to play a major role in the development of acute leukemia. (Abstractor's note: E. E. Osgood (Lancet 2:967, 1964) has commented on this paper. He remarks that: 1. ionising radiation does increase the frequency of acute leukemia, but that it also prolongs life in polycythemia more effectively than any other method of treatment, 2. the frequency of acute leukemia decreases rather than increases with time at risk after radiation therapy is started and 3. the apparent increase with dose is related to the fact that dose increases with survival time.) —P. B.


During the past 18 years, there were 303 cases of leukemia in Hiroshima and 190 of these occurred in people who were within 5000 meters
from the epicenter of the atomic bomb. Total incidence of leukemia per 100,000 per year was 4.79, whereas that of exposed cases was 10.84. Total death rate of leukemia was 4.22, whereas that of exposed cases was 9.98. As the mean death rate from leukemia in all Japan was 2.03, the death rate from leukemia in Hiroshima was about 2.1 times higher and the rate among exposed cases was about 4.8 times higher. There has been a gradual decline in the incidence and death rate of leukemia among the survivors in recent years. A higher incidence of chronic types (most were chronic myeloid) was one of the important features of the leukemia in exposed cases. Among persons who entered Hiroshima within 2 weeks after the explosion, 41 cases of leukemia were observed and 28 cases occurred in persons who entered the city within 3 days. Most of the cases among early entrants were of the chronic myeloid type. There have been some reports of severe anemia which took a fatal course. These cases were complicated by abnormal manifestations not only in erythrocytes, but also in the thrombocyte and granulocyte series. The development of aplastic anemia with aplasia of bone marrow as a delayed manifestation of radiation injury was unexpected. Only a few reports have dealt with the question of a hemorhagic diathesis as a delayed effect. Cataracts have been important manifestations of delayed injuries. According to the report from Masuda (1950), the incidence of cataract among Hiroshima survivors exposed within 2000 meters from epicenter was 48.5 per cent, but a marked decrease in incidence was noted among survivors exposed at a distance greater than 2200 meters. Harada et al. (1960) surveyed the incidence of tumors among survivors living in Hiroshima. The incidence of malignant tumors in persons exposed within 1000 meters from epicenter was about 4 times that of nonexposed cases. Specifically, the incidence of malignant tumors of stomach, lung, breast and ovary among persons exposed within 1500 meters was statistically significantly greater.

Socolow et al. (1962) and Shimizu (1962) reported a marked increase in thyroid carcinoma. Yamamoto and Anderson (1963) reported 12 cases of myelofibrosis of which 10 came from exposed cases. There was a correlation between the incidence of myelofibrosis and the distance from the epicenter; the incidence in exposed persons was approximately 5 times greater than in nonexposed persons, and 18 times more frequent than the mean value for all Japan.—K. F.

HEMOSTASIS


Blood samples, obtained from 18 medical students (nonsmokers) before and 5 minutes after smoking, showed a significant increase in platelet adhesiveness.—H. H. F.


Platelet clumping induced by ADP was strongly inhibited by substituted α-amino-acids, such as arginine methyl ester. Arginyl esters in which the α-amino group was also blocked (benzoyl arginine methyl ester, benzoxy arginine ethyl ester and tosyl arginine methyl ester) were also effective. The inhibition appeared to be competitive. The results were consistent with the hypothesis that an enzymatic reaction is involved in aggregation of platelets by ADP. The postulated enzyme did not appear to be 'von Willebrand factor'.—P. B.


Addition of a highly encephalitogenic factor derived from human brain to plasma of patients in an acute phase of multiple sclerosis caused increased stickiness of their platelets. This phenomenon was not observed in the plasma of normal people or of those with general paralysis of the insane, but was pronounced in the plasma of cirrhotics.—P. B.


Eighteen of 19 patients with hereditary hemorrhagic telangiectasia and hemorrhagic manifestations showed unusually low in vivo platelet adhesiveness levels. These low levels appeared to be correlated with the severity of the bleeding tendency.—P. B.

Lipoprotein-Lipase Levels and Platelet Stickiness in Patients with Ischaemic Heart Disease and in Controls, Distinguishing Those with a First Degree Relative. J.
Lipoprotein lipase activity was significantly lower and increased platelet stickiness. The relation between decreasing plasma lipoprotein lipase activity and increased platelet stickiness is well documented. In patients with ischemic heart disease and in normals, there was a significant correlation between the two factors. In controls with an affected first degree relative, the correlation was also significant.

-P. B.


Autopsy of a 38-year-old woman suffering from vascular pseudohomophilia of albinos (a syndrome characterized by the presence of pigmentophages in bone marrow) revealed generalized cedoid pigmentation, particularly in the reticuloendothelial system, proximal renal tubules and vascular intima. Ciliary cells were transformed into pigmentophages at some sites. The first anatomic confirmation of this peculiar syndrome was compared with data reported in the literature. Related features have been found in Chédki-Higashi syndrome, but the granulocytes were normal. Pathogenetically, both syndromes involve impaired phosphatidic metabolism which is connected in an obscure manner with albinism.—L. D.


The authors presented clinical data on 5 patients with the Aldrich syndrome from 3 unrelated families. In the course of the study, 3 more cases were detected and historically, 19 other boys were probably affected. No relationship to the family described by Aldrich in 1954 was found. Three of 5 proven carriers had definite thrombocytopenia.

—E. A. L.


Increased activities of anti-Willebrand factor and of factor VIII (AHF) were found in plasma of patients with atherosclerosis. The activity of anti-Willebrand factor could be determined indirectly by measuring platelet adhesiveness. The increased platelet adhesiveness in atherosclerosis, diabetes and hypercholesterolemia was reduced to normal after oral administration of linolenic acid. Linoleic and the pentanoic and hexanoic unsaturated fatty acids were ineffective. The authors suggested that the thrombotic complications of atherosclerosis may be related to a dietary lack of linolenic acid.—P. B.


In a previous study, the authors had observed glomerular lesions after intravascular coagulation. The present study was conducted to determine whether coagulation plays any part in glomerulonephritis caused by the injection of anti-kidney serum. The first stage, a mild glomerulitis with proteinuria, could not be prevented by the administration of warfarin sodium, although the changes were less marked. The second stage which was associated with marked deposition of fibrinogen, fibrin and fibrinoid in the glomerular tuft and endothelial cells was almost completely abolished and there appeared to be much less damage to the glomerulus. Unfortunately, the difficulties of warfarin therapy in rabbits seem to be very great and one could wish that more than 8 of 34 treated rabbits had survived. If these findings are confirmed with larger numbers of anticoagulant-treated animals and with more manageable drugs, they will underscore the importance of coagulation factors and mechanisms in an inherently immunologic disease.—C. R. M.

WARFARIN AND DIET-INDUCED LIPIDOSIS IN RATS. J. W. Woods and G. D. Penick. From University of North Carolina School of Medicine, Chapel Hill, N. C. Arch. Path. 78:234-244, 1964.

This study was prompted by an earlier observation that phenindione, in doses producing no detectable effect on coagulation factors, could prevent the usual consequences of a thrombogenic diet in rats. In the present study, warfarin was used instead. Although the dosage used caused considerable depression of factors II, IX and X,
ABSTRACTS

there was no reduction in the frequency of thromboses. There was also no reduction in the serum lipid levels caused by the special diet.—C. R. M.


The author reported on 82 patients with abruptio placenta: 18 mildly, 44 moderately and 20 severely affected. Only 1 patient died. Clinical features, hemostatic disturbances, infant mortality, and pathogenetic aspects were dealt with in detail. Treatment was conservative, except with a living child when caesarian section was performed. In severe cases, blood transfusion of at least 1500 ml. was necessary. Intravenous fibrinogen administration was seldom called for. Effective uterine contraction after delivery was considered to be the principal factor in hemostasis, even with a severe coagulation defect.—E. A. L.


Euglobulin lysis time was examined in 55 cases of infectious hepatitis, 65 cases of chronic infections of hepatic parenchyma, 22 cases of biliary disorders, 7 cases of biliary cirrhosis and 8 cases of hepatic malignancy. No characteristic changes were found in infectious hepatitis. In chronic parenchymatous diseases of the liver, lower values were found, corresponding approximately to the decrease in the functional capacity of the liver parenchyma. In biliary disorders, normal or elevated euglobulin lysis times were noted, the elevations being most pronounced in inflammatory disorders of lesser bile ducts and in tumors. Hepatoma in a cirrhotic liver or some other neoplasm accompanying cirrhosis was characterized by distinctly prolonged euglobulin lysis time. This finding may be of diagnostic importance.—L. D.


Patients with cirrhosis of the liver showed a striking decrease in serum inhibitors of fibrinolysis when compared with controls. This finding would explain the increased fibrinolytic activity in hepatic cirrhosis.—P. B.


The author formulated the conditions under which Michaelis-Menton kinetics can be applied to quantitation of the interaction of clotting factors involved in the one-stage prothrombin time assay. First, clotting factors VII, X, V, II (and I) have to react in a chain of proteolytic interactions in which substrates are converted into enzymes in sequence. Second, coagulation time is regarded as inversely proportional to coagulation velocity. Third, in the case of varying amounts of only one coagulation factor, the rate of the coagulation process should be directly proportional to the concentration of coagulation factor. Finally, the limited amount of substrates must be considered and corrected. Clotting times found in the one-stage Factor II assay, after correction for the residual amount of prothrombin present in the reagent, fit a straight line in the Lineweaver-Burk plot. This finding speaks in favor of the applicability of Michaelis-Menton kinetics to the field of blood coagulation. Preliminary evidence is given that the method can be applied to one-stage Factor VII and Factor V assays.—E. A. L.


The authors compared methods of controlling prothrombin estimations using commercial lyophilized plasma, 2 normal donors, random presumably normal donors and random diabetic patients. No significant differences were found between the last 3 groups and all were included in the analysis of 44 plasma samples versus lyophilized. Even though pooled thromboplastin batches were used in 4 hospitals, significant differences could not be entirely eliminated. Conclusions: lyophilized and fresh plasma were equally acceptable for controls, if used within 90 minutes of reconstitution or venepuncture, respectively. While the lyophilized plasma was somewhat more variable than the fresh, it had other advantages. Dilution curves in saline were comparable at the

Fifteen different snake venoms from three basic zoologic groups were investigated: Viperidae: V. russelli, V. berus, V. amadus, V. lebetina, Bitis gabonica, Echis carinata; Crotalidae: C. anthrox, C. terrificus, C. viridis, Agkistr. piscivorus, A. constrictor, B. jararaca; Elapidae: Naja naja. A thromboplastic component corresponding to incomplete thromboplastin was present in all toxins. It was thermostable and its effect depended upon the presence of cephalin or another phospholipid and calcium. In Saw-scaled viper venom, the effect was due to a component which converted prothrombin directly and did not require the presence of phospholipids and calcium. Three venoms (B. alternatus, B. jaraaca and C. terrificus) effected a direct conversion of fibrinogen.

In nine toxins with an inhibitory effect, fibrinolytic activity was noted. All anticoagulant venoms, with the exception of cobra toxin, inhibited the conversion of prothrombin into thrombin to various degrees, probably by direct action on prothrombin.—L. D.

LEUKOCYTES


A microculture medium for the culture of leukocytes is described in which dextran-glucose has been substituted successfully for plasma enrichment. The use of dextran-glucose results in a more standardized medium and one which might be useful for the study of the influence of various plasma constituents on cell growth in tissue culture.—T. E. B.


A detailed description of a method for chromosome counts and karyotype determination. The advantages are that, instead of 10 ml of whole blood normally used, as little as 1 ml of plasma can be utilized. The equipment is disposable and inexpensive.—C. R. M.


A large population of nondividing or slowly dividing leukemic cells was found in the bone marrow of a patient with acute leukemia. Thus, morphologically uniform malignant cell populations may not be uniform in proliferative activity.—P. B.

Electron microscopic observations have been made on the mechanisms underlying degranulation of neutrophils and eosinophils during phagocytosis. The content of the granules is released into the phagocytic vacuole when their membranes fuse with the membrane lining the vacuole. As a result of such fusion, the hydrolytic enzymes of the granules are prevented from gaining access to the cytoplasm proper. How membrane fusion is actually accomplished remains unknown.—T. E. B.


A modified skin window procedure was used in dogs to investigate the pattern of cellular response elicited by introducing a fibrin network into an inflammatory site. Morphologic evidence was provided that exudative neutrophils engaged in either fibrin dissolution or in incorporating products of extracellular fibrin lysis. Fibrin ingestion by neutrophils was mediated by pseudopods which formed hooks engulfing small fibrin masses and ultimately isolating them. Exudative neutrophils in contact with fibrin showed a striking loss of specific granules and of vesicles of the endoplasmic reticulum. Exudative neutrophils were considered to be important cellular agents for the removal of fibrin from inflammatory sites.—T. E. B.


It has been shown that the phagocytic activity of leukocytes is stimulated more by an inflammatory exudate than by blood serum or transudate, the latter being the least effective. Anti-histaminic substances were found to inhibit the phagocytosis-promoting effect of exudates. Histamine and serotonin enhanced phagocytic activity. Protein hydrolysaties (Dekansky), leukotaxin and exudin isolated from exudates, according to Menkin, greatly increased phagocytic activity in vitro. Menkin's leukocytosis promoting factor (LPF) stimulated leukocytic activity both in vivo and in vitro. The peak of the effect coincided with the peak of the leukocytosis produced. Leukopenin and the leukopenic factor (Menkin) prepared from older acidotic exudates reduced the number of leukocytes and diminished the phagocytic activity of the cells. The phagocytic activity of leukocytes incubated with necrosis obtained from exudates decreased. Fractions obtained from serum or transudates by methods similar to those used for isolating the secondary inflammatory stimulants of Menkin were ineffective. Leukocytic bacterial phagocytosis was enhanced by sodium ribo- and deoxyribonuclease, hyaluronidase and bradykinin. On the basis of these results, the phagocytosis-promoting effect of exudates was thought to result from the interaction of several factors. Various biological substances are involved. These exert local effects and have distant actions which start from the area of inflammation. All this proves once again that a close interaction exists between the organism as a whole and the area of inflammation which is demarcated more or less by the inflammatory barrier.—S. R. H.


A total of 189 hematologically interesting autopsy cases (including atypical aplastic anemia and myeloid leukemia, myeloid leukemia with a so-called preleukemic phase and examples of difficult differential diagnosis between leukemia and anemia) were collected from medical schools and leading hospitals in Japan. The following 3 points were stressed. The clinical features of so-called preleukemia were (a) pancytopenia similar to aplastic anemia, and (b) abnormality in the erythrocytic series. Through retrospective review of clinical data, including reexamination of blood smears, immature granulocytes, although very small in number, were found in peripheral blood or bone marrow smears of most cases, even in the so-called preleukemic phase. This fact suggested that latent, true leukemia had already developed. The authors believe that the so-called preleukemic phase was not a stage prior to occurrence of leukemia, but was early leukemia which may be very difficult to diagnose. In some cases of aplastic anemia, immature cell proliferation was revealed in the granulocytic or erythrocytic series. To determine the nature of these cells, electron microscopy was found quite useful. Even with material
fixed in formalin solution for moderately long periods, specific granules could be demonstrated in many immature granulocytes. No cases showed definite transition from aplastic anemia to myeloid leukemia or erythroleukemia. Some cases of leukemia modified by therapy were difficult to diagnose because they had become severely aplastic. Sometimes, hematological data obtained clinically were the only proof for leukemia. The following changes in leukemic bone marrows caused by various treatments were noted: (1) severe desolation because fat tissue, (2) regenerative changes in leukemic bone marrows caused by various treatments were noted: (1) severe desolation because fat tissue, (2) replacement by fat tissue, (3) regeneration, (4) fibrosis.

The histochemical dithizone method was used to evaluate the zinc content of peripheral blood granulocytes. All of 50 patients with neoplastic disease studied were found to have an abnormally low granulocyte zinc content, while none of 50 control patients with various non-neoplastic diseases had a low granulocyte zinc. —T. E. B.


Acid phosphatase, G-6-P dehydrogenase and Gal-1-P uridyl transferase activities were all present in large amounts in the leukocytes of patients with Down’s syndrome when compared with control subjects. The finding of increased activity of a particular enzyme in a trisomic condition cannot, in itself, be used as evidence of gene location. —P. B.


There are indications of a relationship between, or even identity of, transplantation and leukocyte antigens. A method is described for the partial purification of leukocyte group substance from placental tissue. The active principle is probably a lipoprotein and seems to originate from the cytoplasmic membranes of cells. —T. E. B.


To examine the immunohistochemical nature of cellular antibody, the reaction of antigenic cells with sensitized lymphocytes was studied quantitatively and cytologically in vitro. Cytotoxic activity was determined with an extract of membranous components of sensitized lymphocytes. SCI cells (cultured lymphatic leukemia cells originally derived from S mouse) and lymph node cells (sensitized lymphocytes) were incubated together. Sensitized lymphocytes inhibited proliferation of SCI cells in the absence of complement. Proliferation of SCI cells was inhibited only by lymphocytes of A mice sensitized by syngeneic cells of S mice, but not by lymphocytes sensitized by allogamous cells obtained from 129, BALB/c, and C3H mice. Sensitized lymphocytes inhibited proliferation of SCI cells by specifically conjugating with SCI cells. Such findings raised the possibility that cellular antibody might be bound to the membranes of sensitized lymphocytes. The membranous components of these sensitized lymphocytes were isolated and SII (microsomal-like) and M (cellular membrane and swollen or disrupted mitochondria) components were extracted with deoxycholate. Extracts from both components showed cytotoxic activity against antigenic SCI cells in the presence of complement, but similar extracts of normal lymphocytes did not. Cytotoxic activity was dependent on the concentration of SII extract and had strain specificity. The cytotoxic activity of SII extract was sensitive to mercaptoethanol and was found in the y fraction on agar electrophoresis and in the 19S fraction of a sucrose density gradient. These results suggested that the cellular antibody bound to cellular membranes of sensitized lymphocytes was different from cytophilic antibody (y2-globulin), as described by Boyden and Sorkin. The present results also suggested that y1M antibody formation was an important function of lympho-reticulum cells. It was not possible to determine if the cellular antibody was similar to serum y1M globulin. —K. F.
ABSTRACTS


Further experimental evidence, thought to be conclusive, is given for the belief that the "graft-versus-host" reaction is the only immunologic component of the normal lymphocyte transfer reaction which is outwardly discernible in the first 3 days.—P. B.


ABO blood group and sex do not affect the reactions obtained in the normal lymphocyte transfer test. A new technic for recording the results was described. The test may indicate degrees of incompatibility between graft recipients and members of a tissue-donor panel.—P. B.


The effect of sera from rabbits with leukopenia and leukocytosis on normal rabbit bone marrow was studied in vitro. The rate of C14-formate incorporation served as a measure of the mitotic rate. Sera collected in the leukopenic phase or in the initial phase of leukocytosis were found to increase C14-formate incorporation into cells significantly. On the other hand, sera collected at the peak of leukocytosis inhibited formate incorporation. Bone marrow from control rabbits incubated with sera from animals with leukopenia or leukocytosis showed characteristic changes in the mitotic rate and in the ratio of myeloid precursors and mature myeloid elements. Kinetics of formate incorporation agreed qualitatively when bone marrow from control or leukopenic rabbits or those with leukocytosis was incubated with the animal’s own serum. It may be assumed that the agents in the sera represent the humoral system maintaining the homeostasis of myeloid elements.—S. R. H.


Hematologic lesions induced by 3 Gm. per day of Metopiron given to 12 patients have been studied. The number of circulating lymphocytes increased, whereas the number of granulocytes diminished significantly. The author suggests that these effects were the consequence of inhibition of polar corticoids and of the predominance of the vago-insular system.—S. R. H.


A 10-year-old boy was found to have had eosinophilia since early childhood. A similar finding was present in several well members of his family. Three generations were affected. An autosomal dominant mode of inheritance was evident. Another 17 families with such “hereditary eosinophilia,” i.e., without allergy or parasitic infestation, were found in a search of the literature.—H. H. F.

ERYTHROCYTES


Data are presented on the incorporation of iron into hemoglobin in a rat marrow cell culture. It was shown that iron was incorporated more efficiently into hemoglobin if it was bound to a homologous iron binding serum protein than if it was bound to calf serum.—A. J. E.

The Fe^{59} uptake by rabbit bone marrow cells was studied in a medium consisting of 20 per cent homologous serum in Tyrode's solution and containing 10^7 nucleated cells/ml. The Fe^{59} activity of the cells was expressed as the ratio of the total counts administered to the activity taken up by the cells, related to the erythroid cell count. It was found that the Fe^{59} uptake depended on the temperature and was influenced by treatment with agents which inhibited fermentation and oxidation (fluoride and dinitrophenol).—S. R. H.


The authors showed that when erythropoietin was added to cultures of human synovial membrane cells and cultures of human monocytic leukemia cells there was stimulation of proliferation, a stimulation which disappeared when sheep erythropoietin had been stored (inactivated?). These results led the authors to suggest that erythropoietin was merely a nonspecific growth factor. (These results are somewhat at variance with findings in vivo which suggest that erythropoietin stimulates only erythropoiesis and with findings which show a lack of stimulation of cultures of human leukocytes (McFarlane and Sohnlein, Proc. Soc. Exper. Biol. Med. 115:563, 1964), long-term cultures of human bone marrow cells and of human fibroblasts. (Erslev, Blood 24:331, 1964).—A. J. E.


Blood volume, hematocrit and hemoglobin concentration were followed in 6 subjects during prolonged acclimatization at varying altitudes up to 19,000 feet. The red cell mass and total hemoglobin mass rose progressively, reaching mean values of 49 per cent above the sea level control values. The hemoglobin concentration rose only by 30 per cent in the first 18 weeks and 8 per cent during the following 9-14 weeks. This discrepancy was explained by the reduction in plasma volume which kept the hemoglobin from going up too far and too fast. Data from 8 Himalay expeditions have revealed that the mean hemoglobin concentrations of acclimatized individuals (20.19 Gm./100 ml.) do not reach the same values (22.9 Gm./100 ml.) as reported in natives living in Peru at about the same altitudes.—A. J. E.


Radiation of an exteriorized kidney in a unilaterally nephrectomized dog resulted, 6 weeks later, in a complete lack of erythropoietic response to a control injection of cobalt. Despite this impairment in erythropoietin production, the dog did not develop any significant anemia. This discrepancy is discussed, but not resolved.—A. J. E.


Further evidence has been provided testifying to the importance of the kidneys in the control of red cell production. Although ureter ligation or ureter implantation into the vena cava results in a quite substantial suppression of erythropoiesis, it does not compare with the suppression found after bilateral nephrectomy. The almost total erythroid aplasia found in dogs as early as 3 days after bilateral nephrectomy are clearly at variance with results from rats, rabbits and, more recently, man (Nathan, Schupak and Merrill, Blood, 22:811, 1963). The authors discuss this interesting species difference.—A. J. E.


The effect of protein starvation on red cell production is receiving much attention (K. R. Reissmann: Blood, 23:137, 146, 1964). In the present study, a reduction in food intake to one-third normal produced a diminution in red cell production and a smaller total red cell mass.
However, body weight and plasma volume were reduced even more, resulting in a relative polycythemia. As the authors point out, these results certainly should be remembered in any study in which animals are maintained on restricted diets.

—A. J. E.

**Stimulation of Erythropoiesis by Whole-Body Irradiation (Spleen Shield)**


It is known that sublethal whole-body irradiation with spleen shielding is followed within a day or so by the development of increased erythropoiesis in the spleen, despite an absence of any known stimulus to erythropoietin production. In the present paper, it was reported that splenic erythropoiesis can be abolished by hypertransfusion and enhanced by the administration of exogenous erythropoietin. Since erythropoietin production is apparently increased in the absence of any known stimulant, the authors suggest that irradiation may be a stimulus to the release of increased amounts of erythropoietin, in addition to the development of increased sensitivity to erythropoietin.—A. J. E.


In a previous study, it was shown that under hypoxic conditions every tissue was able to produce ESF. In the present investigation, the site of action of tissue ESF was studied. Two samples prepared from the same lung homogenate and a saline control were mixed with fresh bone marrow from albino rats. One lung tissue sample was kept under reduced pressure for 3.5 hours, the other from albino rats. One lung tissue sample was kept under reduced pressure for 3.5 hours, the other from albino rats. The results indicated that hemoglobin synthesis in bone marrow was increased by pulmonary ESF which had the same effect as serum ESF. This experimental system was therefore to be suitable for determining different tissue ESFs.—S. R. H.


Lactate dehydrogenase (S.L.D.) and α-hydroxybutyrate dehydrogenase (S.H.B.D.) activities were determined in sera of patients with severe anemia of pregnancy. There was a definite correlation between elevated S.L.D. and S.H.B.D. levels and megaloblastic erythropoiesis. S.H.B.D. activities were more sensitive to marrow changes than were those of S.L.D.—F. B.


Of 78 patients with chronic cor pulmonale due to chronic bronchitis with obstructive emphysema, 6 had erythroblasts in the peripheral blood. The patients were in respiratory acidosis. The more serious the illness the higher was the incidence of erythroblasts and the more immature were the red cells; even macroblasts were found. In a control group consisting of patients with different types of heart disease, erythroblasts were not found.—L. D.


In 35 per cent of cases of cardiac insufficiency, the number of reticulocytes was higher than normal and in 17 per cent the number of normoblasts increased. In cases with normal reticulocyte counts, normoblasts were found in 3 per cent, whereas in cases with increased reticulocyte counts, normoblasts were found in 17–52 per cent. The increase in reticulocyte count and the presence of normoblasts in the blood were temporary phenomena which correlated with the oxygen satura-
tion of arterial blood. The peak incidence of immature cells did not coincide in time with the minimum oxygen saturation. In prolonged hypoxemia, these phenomena were rarely observed. The mortality of patients with cardiac decompensation increased in relation to the degree of reticulocytosis. The presence of normoblasts in the peripheral blood implied a still greater mortality.—S. R. H.


Hemoglobin levels in 126 patients with chronic renal insufficiency, 9 with subacute uremia and 34 with acute uremia were investigated. In chronic renal insufficiency, normal values were found in only 5 cases with nitrogen levels under 60 mg. per cent. In all others, different degrees of anemia developed. There was a significant correlation between the increase in nitrogen level and the decrease in hemoglobin. The type of renal lesion had no significance for the severity of anemia. The lowest level of hemoglobin in chronic uremia was 4 Gm. per cent. In acute uremia, the lowest level was 6.4 Gm. per cent. The decline in hemoglobin in acute uremia reached its nadir during the period of recovery from uremia. The hemoglobin level started to rise during the first week after azotemia disappeared.—L. D.


The changes in iron concentration in the vena portae and the brachial vein of 105 patients were investigated during surgery. The blood in the vessels of the stomach, duodenum, jejunum and ileum had a high iron concentration, indicating that iron absorption from the respective parts of the digestive tract occurred. Administration of 80 mg. of ferrous iron caused no significant rise, but administration of 160 mg. led to an increase in all vessels. Although no marked difference in absorption was observed, iron intake was somewhat less in patients with malignant tumors. Absorption increased proportionally with the dose administered. The increase in iron content was parallel in vessels of the digestive tract and in the brachial vein. In such cases, the increase indicated the rate of absorption. The transferrin content in the brachial vein and in the vena portae remained unchanged during absorption. Iron entering through the intestinal wall was found bound to transferrin.—S. R. H.


Anemia, induced by a milk diet soon after weaning, slows the growth rate of rats. This slowing is due to anemia, since addition of iron and copper to the milk prevented all changes. If such animals are fed the standard laboratory diet at the age of 100 days when they are still growing, the hemoglobin returns to normal parallel with the weight gain. Feeding a standard diet at 170 days of age is not so effective for weight gain, although the level of hemoglobin rapidly returns to normal values.—L. D.


Prolonged anemia induced by feeding a milk diet deficient in iron induces an increase in the size of the heart in rats. The density of capillaries and muscle fibers in these hearts is the same as in normal animals. Following feeding for 90 days (day 180 to 270 postnatally) with the normal laboratory diet, the heart size remains increased, but the level of hemoglobin returns to normal after 10–14 days. The resistance of the myocardium to anoxia has been measured by the contractions after stimulation with suprathreshold rectangular impulses. The right ventricles of anemic rats are more resistant to anoxia in vitro than those from normal rats of the same age.—L. D.

The upper gastrointestinal tract was studied in 2 groups of anemic youngsters. Among those with iron-deficiency anemia, duodenal biopsy revealed shortening and clubbing of the villi and infiltration of the lamina propria with plasma cells, lymphocytes and eosinophils. Deficient or absent gastric acidity, impaired xylose and vitamin A absorption and reduced levels of serum carotene were commonly noted, as was the presence of steatorrhea, melela, hypalbuminemia and circulating milk precipitins. Following iron therapy, the morphologic and functional abnormalities reverted to normal. Except for low serum carotene levels and flat vitamin A tolerance curves, gastrointestinal function and morphology were normal in patients with chronic anemia not due to iron deficiency. The authors suggested that iron deficiency causes impaired epithelial regeneration and function, resulting in an abnormal gastrointestinal mucosa. The mucosal changes lead to impaired function characterized by achylia, steatorrhea, melena, hypalbuminemia and a loss of red cells and plasma proteins.—J. B. S.


In a study of a large random population of males and females aged 40-75 years, no evidence was found of an increased prevalence of anemia or of latent iron deficiency in those with dysphagia. Females with postcricoid webs demonstrated radiologically showed no evidence of iron deficiency. These findings provide no evidence for the existence of a syndrome in which pectricoid dysphagia is associated with iron deficiency.—P. B.


A report of two new cases of thymoma and regenerative anemia and a very useful analysis of the 43 cases previously reported in the literature.—A. J. E.


Thymectomy was performed in an infant with severe autoimmune hemolytic anemia who had failed to respond to both corticosteroids and corticotrophin and who had relapsed shortly after splenectomy. Slow but complete recovery followed the operation.—P. B.


The mean AChE in adults, expressed as units/min./mg. hemoglobin was 153 (S.D. ± 24). In normal full-term infants, the mean activity was 97 (S.D. ± 15). In infants with ABO erythroblastosis, the mean value was 59 (S.D. ± 18). Among infants with Rh hemolytic disease, AChE activity was the same as in normal infants. In several infants with ABO disease, the low AChE levels persisted through the first month. Attempts to produce alterations in red cell AChE by direct action of anti-A and anti-B antigens were unsuccessful. Exposure of red cells to bromelin, papain and trypsin resulted in a marked decrease in AChE activity.—J. B. S.


In 1 female and 4 male subjects, the hemoglobin destruction rate was increased by re-injecting autogenous erythrocytes which had been treated with N-ethylmaleimide. In all subjects, the rate of CO production increased after the injection of the cells. The amount of this increase corresponded to the formation of an average of 0.97 ± 0.06 mole CO for each mole of heme destroyed.—H. H. F.


Six Dutch families with 145 members displaying elliptocytosis were investigated. Hemolysis was generally well compensated. No abnormality in
phospholipid composition of the erythrocyte membrane could be demonstrated. Genetic linkage between elliptocytosis and rhesus factors was demonstrated in one family and could be excluded in 3 families. These findings confirmed data in the literature which indicate that at least 2 loci for elliptocytosis exist. Crossing over of the 2 genes in the "linked families" amounted to 3 ± 1.7 per cent. However, as recombination of the elliptocytosis gene with a less privileged rhesus allele probably entails a severe risk of nonviability of the zygote, this figure was too low and suggested too close a linkage. Irregularities in the mode of transmission of rhesus factor and elliptocytosis were dealt with in detail.—E. A. L.


The structure, function and evolution of the hemoglobin molecule and the laboratory methods for the detection of abnormal hemoglobins are discussed. The persistent fetal hemoglobin, sickle cell anemia and thalassemia syndromes are described. Studies concerning the detection of a new hemoglobin M variant (Hb MK₁kuftla) are presented. The absorption spectra of this hemoglobin and of the cyanmethemoglobin form differ from those of other hemoglobin M variants, though they are very similar to those of hemoglobin Mnzs. Hb MK₁kuftla is an alpha-chain anomaly. A peptide can be detected which is absent from fingerprints obtained from hemoglobin A.—S. R. H.


Cyanosis in 1 patient was due to the presence of hemoglobin M₁Boston, an α-chain variant. Hemoglobin M₁sakatoon, a β-chain variant, was found in the other patient.—P. B.


A patient with well compensated congenital non-spherocytic hemolytic anemia was found to possess an abnormal hemoglobin, (Hb Köln), as a minor component. Hb Köln was heat unstable and tended to form excessive amounts of methemoglobin on storage. Hemolysis was associated with the passage of dark urine containing an abnormal pigment of dipyrrolic type which was presumed to be a breakdown product of the abnormal hemoglobin. Nine other members of the family which has remote German ancestry had the abnormal hemoglobin. Heinz bodies regularly appeared after splenectomy, but were more difficult or impossible to demonstrate in un-splenectomized individuals.—P. B.


This hemoglobin variant was found in a survey of 1971 unrelated out-patients in Oxford and Peterborough. The new hemoglobin was found in 8 members of a family which came from Gloucestershire and which also had some Irish ancestry. The affected members were clinically and hematologically normal. The new variant was named Hb Ja Oxford because it had the electrophoretic properties of Hb J and was shown, by hybridization experiments, to have an abnormality in the α-chain. The abnormal hemoglobin comprised 20 per cent of the total.—P. B.


Hemoglobin E and G-6-PD deficiency had frequencies of 27.7 and 17 per cent respectively. There seemed to be a correlation between the frequencies of these abnormalities.—P. B.


Evidence is provided that in patients heterozygous or homozygous for the thalassemia gene there is a marked selective decrease in hemoglobin A formation. This defect in Hb-A syn-
ABSTRACTS

Assay of peroxidase activity was used to determine plasma hemoglobin levels, instead of the more usual benzidine method. Benzidine is unstable, but the peroxidase method suffers from the fact that plasma contains a peroxidase inhibitor. The authors believe they have overcome this difficulty by the use of known increments of hemoglobin as a step in the assay procedure. They claim the resulting technic is more reliable, reproducible and convenient than the benzidine technic for plasma hemoglobin assay and clearance studies.—C. R. M.

MISCELLANEOUS


Anatomic lesions in porphyric diseases were investigated in 22 autopsies and 84 needle biopsies of the liver. Red fluorescence of liver tissue under Wood’s light and the presence of porphyrin crystals in renal tubules represented the most constant and the only pathognomonic finding in porphyria cutanea tarda. Focal pink or red fluorescence of the periosteam was found to be less frequent. There was a conspicuously high incidence of hepatic cirrhosis: 5 instances in 6 cases of the latent form and 7 in 10 patients suffering from the manifest form. Completely normal liver tissue was seen in only one case of manifest porphyria cutanea tarda; in all others, there was some degree of hepatic cirrhosis. There was an unusually high incidence of hepatocellular carcinoma (9 of 12 cases of hepatic cirrhosis). Grossly, the organs were not pathologically colored, except in cases accompanied by hemosiderosis in which the liver and spleen had a rusty brown hue. Generalized hemosiderosis was noted microscopically in only 3 cases. By comparing autopsy findings with those made on biopsy material, it was concluded that hepatic cirrhosis was not the cause of the late form of porphyria, but that it developed after the onset of the porphyric disease. The hepatic cirrhosis which accompanied the porphyric disease was a pigment cirrhosis similar to that seen in hemochromatosis.—L. D.

The ribonucleic acid (RNA) of plasma cells was labeled by giving tritiated cytidine to rats during the proliferative phase of a secondary immune response. Autoradiography of smears of the popliteal nodes taken as long as 30 days after the last dose of tritiated cytidine showed the presence of stable RNA in both plasma cell cytoplasm and nuclei. It was not possible to state in which fraction of RNA the label had persisted. Restimulation with specific and nonspecific antigens had no apparent effect on the number of labeled plasma cells or on their stable persistent RNA. The experiments reported add information on the basically stable end cell nature of plasma cells and suggest that a single molecule of messenger RNA may serve repeatedly as a template for a large number of molecules of the specifically coded antibody protein.—T. E. B.


By means of an immunoelectrophoretic method, the Gc types in the sera of 228 blood donors of Czechoslovakian nationality were determined. The results were: Gc 1-1 46.49 per cent, Gc 2-1 43.85 per cent, Gc 2-2 9.46 per cent. The frequency rate of the allele for the fast moving component (Gc1) was 0.684 and for the slow component (Gc2) was 0.136.—L. D.


The tolerant state of rabbits tolerant to BSA was terminated following the injection of arsnil-sulfanil-BSA and native HSA. The injection of heat-aggregated BGG failed either to terminate tolerance to BGG or to elicit antibody production to aggregated BGG. Apparently, mere alteration of the physical properties of BGG was not sufficient to render it antigenic in BGG-tolerant rabbits. The termination of tolerance to BSA following injection of related antigens was interfered with by simultaneous injections of either large or small doses of soluble BSA.—H. H. F.


One-half to 2/3 of rabbit 7S γ-globulin can be dissociated after reduction of one very labile disulfide bond. Dissociation of the remainder of the γ-globulin requires the reduction of more than one disulfide bond. Presumably, the bond joins two "A" chains.—H. H. F.


Autoradiography of immunoelectrophoretic patterns of tissue culture fluid, containing 2 radioactive aminocids, disclosed the ability of different normal, fetal, and pathologic human tissues to synthesize immunoglobulins in vitro. Normal lymphocytes isolated from blood produced gamma globulins, βγA-globulin, and β2M-globulin. In lymphatic leukemia, the formation of βγA-globulin by peripheral blood lymphocytes was consistently absent and there appeared to be preferential labeling of the medium to high speed fraction of gamma globulin. Lymphocytes from patients with infectious mononucleosis and rubeola showed increased synthesis of β2M-globulin during the first 10 days of illness, possibly as the result of primary antigenic stimulation. Lymphocytes and bone marrow samples from patients with an agammaglobulinemia synthesized no or only a minimal amount of immunoglobulins. Normal human thymus cells appeared to synthesize only gamma globulin and βγA-globulin, whereas thymus cells from 2 patients with an autoimmune disease induced appearance of radioactive β2M-globulin. Fetal thymus cells did not synthesize immunoglobulin. Fetal spleen older than 20 weeks, however, appeared to produce gamma globulin and β2M-globulin. In vitro synthesis of paraproteins was observed in bone marrow biopsy material from patients with multiple myeloma and Waldenström's macroglobulinemia. By means of the immuno-
fluorescent staining technic, the site of immunoglobulin and paraprotein synthesis in the cells was determined. Medium size and large lymphocytes, and plasma cells, could produce 1 of the 3 immunoglobulins. In general, fair agreement was found between the pattern of synthesized immunoglobulins and the immunofluorescent staining of the samples. The weakly positive fluorescence of normal circulating small lymphocytes was postulated to represent the initial synthesis of β-M-globulin when engaged in a primary immunologic response.—E. A. L.

THE DEVELOPMENT OF THE IMMUNE RESPONSE.


Most infants responded to immunization with Salmonella flagellar antigen by 2 weeks of age. The appearance of agglutinins followed a consistent pattern. The first response was the appearance of a gamma-1-macroglobulin (17 to 20S). Not until the second month was there any significant production of 7S gamma-2-globulin. An agglutinin with an intermediate sedimentation rate and the electrophoretic mobility of a gamma-2-globulin appeared after the macroglobulin and before the 7S antibody. In the adult, macroglobulin agglutinins appeared 4 to 5 days after immunization, followed in 3 or 4 days by the appearance of 7S agglutinins. Where the infants received maternal flagellar agglutinins transiently there was an inhibition of immunologic response to the homologous flagellar antigen.—J. B. S.

SUPPRESSION OF ANTIBODY SYNTHESIS AND PROLON GATION OF HOMOGR AFT SURVIVAL BY CHLORAMPHENICOL. A. S. Weisberger, T. M. Daniel and A. Hoffman. From School of Medicine, Western Reserve University, Cleveland, Ohio. J. Exper. Med. 120:183–196, 1964.

Chloramphenicol suppresses primary antibody synthesis in vivo without affecting the ability to develop a normal anamnestic response and prolongs homograft survival in rabbits. The mechanism of action of chloramphenicol differs markedly from that of other immunosuppressive drugs thus far studied. Purine, pyrimidine and folic acid analogs, actinomycin and nitrogen mustard all inhibit cell growth and suppress antibody formation by interfering with nucleic acid synthesis. Chloramphenicol suppresses antibody synthesis by interfering with the function of messenger RNA. —H. H. F.


Detailed clinical reports on bone marrow aplasia in 7 patients treated with chloramphenicol. The total dose in 6 was more than 20 Gm. Five of these patients died as a consequence of leukopenia or thrombocytopenia.—E. A. L.


The influence on the serum properdin level of thymectomy and/or adrenocortical hormones was investigated in 111 male Wistar rats weighing an average of 60 Gm. The sera were tested for properdin activity by the zymosan test of Cseh and Szabó on the 25th day following thymectomy or sham-operation. As compared with the control value (17.9 U/ml.), the prop:rdin level was found to be significantly increased after thymectomy (31.2 U/ml.). In thymectomized animals, zymosan did not increase the serum properdin level. In thymectomized rats, hydrocortisone (5 mg./day for 8 days) significantly increased the serum properdin level to 33.9 U/ml., whereas desoxy-corticosterone acetate (1 mg./day for 8 days) decreased it to 10.5 U/ml. In the controls, hydrocortisone caused a slight rise and DOCA no change.—S. R. H.


Infants with ABO erythroblastosis requiring exchange transfusion were treated with either group O blood having iso-agglutinin titers of less than 1:100 or with washed group O red cells resus-
ABSTRACTS

Pended in AB plasma. No significant difference in the number of exchange transfusions required or the course of post-transfusion bilirubin levels was observed.—J. B. S.


Routine investigation indicated the presence of a defective blood group O. More detailed serologic investigation revealed that the bearer of this group was a secretor of B, H and Le* Anti-B antibody could be obtained by the elution test, thus proving that B substance was present in an extremely small amount in the erythrocytes. Results of serologic reactions provided evidence that this variant was most probably similar to the variant reported in the literature under the symbol B+.—L. D.


The specificity of 9 eluates from red cells of acquired auto-immune hemolytic anemia was studied using normal red cells, partially deleted (D-/D-) red cells and red cells of a Negro woman (Nou.) in which no antigen corresponding to the Ee locus could be detected. The autoantibody corresponded to an antigen produced by the Ee locus.—H. H. F.


The authors found that the incidence of carcinoma in those who secrete blood-group substances was about the same as in those who did not. There was, however, a significant excess of secretors in those with distant metastases, or, conversely, nonsecretors had fewer distant metastases.—C. R. M.