LEUKOCYTES


Among 180 patients undergoing by-pass open heart surgery, 30 developed a postoperative syndrome with circulating atypical mononuclear cells and often fever and splenomegaly, but rarely lymphadenopathy, 5 to 60 days after operation. The more severe manifestations had an onset 3 weeks or more post-operatively. Two patients who did not have by-pass operations but were given large transfusions of fresh blood had a similar syndrome. The post-transfusion mononucleosis thus was significantly associated with the giving of large quantities of fresh blood, rather than with the use of a by-pass. Since the atypical cells resembled lymphocytes transformed after PHA stimulation, the suggestion was made that the syndrome was an immunologic phenomenon, possibly a graft rejection directed against viable transfused foreign lymphocytes.—F. W. G.


Four children beginning therapy for acute leukemia developed anorexia, nausea, persistent vomiting, lethargy and extreme weakness; 2 convulsed, 3 became comatose, and all died. Serum uric acid levels ranged between 20 and 55 mg. per 100 ml. The authors believed that the symptomatology was related to the hyperuricemia, inasmuch as a similar clinical picture had been described in patients infused with 20 mg. of uric acid per kg. In two postmortem examinations of the brain, edema was the only prominent abnormality.—J. B. S.


In a man of 37 affected with acute leukemia of the Naegeli type, the onset was marked by cutaneous lesions. A large pericardial effusion (2.3L.) with a massive multinodular attack of myocarditis was noted at autopsy. The latent character of cardiac localization of acute leukemia and the rarity of the “tumor” type were stressed.—J. C.

An 8 month old infant developed the typical physical and laboratory findings of CML. Fetal hemoglobin values were normal and the Philadelphia chromosome was found in peripheral blood and bone marrow preparations. The infant’s course at first was typical of CML, but 6 months after onset “blastic” transformation of the marrow occurred. The picture of the “adult” type of CML occurring at this age was a rarity.—J. B. S.


Hydroxyurea therapy led to many remissions in 26 patients with chronic myeloid leukemia in various stages. The characteristic features of this therapy were: 1) low toxicity, 2) extreme rapidity in obtaining remission, 3) possible effectiveness in cases resistant to other therapy and in acute transformations, and 4) short duration of remissions if long-term therapy was not instituted.—J. C.


The author analyzed the foundations of visual “quantitative” photometry of cytological objects and the causes for possible errors. Simple mathematical analysis was carried out of an error in visual photometry without consideration of the volume of the object. For an example of diploid nuclei, the author presented an estimate of the minimal number of measured nuclei required to obtain the mean DNA value which approached the true value. It was impossible to differentiate nuclei into diploid and tetraploid types with visual photometry. The change in DNA content in acute leukemia caused by frequent aneuploidia proved to be undetectable by visual photometry.—J. K.

LYMPHOGRAPHY IN HEMATOLOGY. R. Bourdon, J. P. Desprez-Curely, V. Bismuth, F. Marko-


In a study of 653 cases, the authors confirmed the diagnostic value of lymphography. Lymphography was indispensable in malignant lymphohemopathy before any treatment, for it showed precisely the degree of spread, its variation in relation to the clinical stage and the localization of supra- or sub-diaphragmatic adenopathy. The authors noted the limitations of lymphography and its "evolutionary value" because node opacification lasted several months.—J. C.


The authors reviewed 107 cases of apparently localized forms of lymphosarcoma and reticulosarcoma of the cervico-facial area treated and observed at the Gustave-Roussy Institute from 1951 to 1964. They studied the distribution by sex, age and histology, the clinical and biological characteristics, the results of treatment and the eventual evolution. Attention was drawn to several points: the particular characteristics of the facial mass, the necessity for systematic lymphography which permitted the diagnosis of the localized form to be made more precisely and the differences, more apparent than real, between cervico-facial tumor and disease located elsewhere.—J. C.


Murine leukemia virus (Rich) was inoculated into one of the 2 thymes of infant mice which were sacrificed 2 months later. The incidence of lymphoma evolving in the inoculated thymus was compared with the incidence in the uninoculated thymus. In 90 per cent of cases in 30 animals suitable for analysis, the tumor arose in the inoculated thymus, supporting the view that the mechanism of viral leukemogenesis was direct.—H. H. F.

A cytopathogenic agent was isolated in cultures of human embryos and on chorio-allantoic membranes of chick embryos from organs of a mouse suffering from spontaneous leukemia. This agent could be passed on cellular cultures and chick embryos.—J. K.


Congenital alymphocytosis in a male infant was diagnosed on the first examination at age 15 days because of a family history. On the 28th day, a graft of thymus was taken from a 6 month old girl, but it was a complete failure. Autopsy revealed the lesions of the syndrome, but the lymphocytic load in the spleen was normal. The patient’s lymphocytes were cultured in the presence of phytagglutinin. The authors analyzed the present status of early diagnosis and reviewed the published cases in regard to thymic grafting. There appeared to be no further interest in persevering with thymic grafting, even from a fetus. Perhaps preferable would be cellular perfusion of thymus, spleen or marrow. The systematic culture of lymphocytes from these patients with a view to studying their karyotypes was of particular interest.—J. C.


The synthesis of RNA and replication of DNA in normal human lymphocytes was studied in an in vitro culture system containing phytohemagglutinin. Addition of prednisolone-21-phosphate to the system effected inhibition of RNA synthesis and DNA replication which was logarithmically dose related. The decline in number of blood lymphocytes after treatment with corticosteroids may have resulted, in part, from a decrease in the replication of lymphocytes. When serum has been added to media used for the investigation of the response of lymphocytes to phytohemagglutinin, the potential effects of any corticosteroid in the serum must be considered.—A. L. B.


An electron microscope study of mouse spleen germinal center reticular remnants 2 days following treatment with actinomycin D and sheep erythrocyte injections was described. Elongated narrow processes of cells in the remnant were found, in some areas, to be connected by desmosomes of the macula adhaerens type. A conspicuous feature of the remnant was the extensive interdigitation of elongated cytoplasmic protrusions forming labyrinths of apposed cell processes. The occurrence of complex junctions (desmosomes) in spleen germinal centers was of interest because of their proposed functional significance in epithelial permeability. Specifically, the involvement of some types of desmosomes as a barrier to permeability and their possible role in the antigen-retaining ability of the reticular network of germinal centers warrants further study.—O. P. J.

**The Synthesis and Storage of Protein by Isolated Lymphoid Cells Examined by Autoradiography with the Electron Microscope. S. L. Clark, Jr.** From Washington University School of Medicine, St. Louis, Mo. Amer. J. Anat. 119:375–403, 1966.

Autoradiography with the E. M. was employed to locate sites of synthesis and storage of newly-formed protein in cells isolated from lymph nodes of immunized rabbits and incubated with tritium-labeled leucine. By making counts of grains over nuclei, Golgi complex and ergastoplasm and relating these to the relative volume of each region, evidence was obtained that, during the latent period of secretion, antibody moved into the Golgi region from its site of synthesis in the ergastoplasm. Statistical analyses supported the biological conclusion that the newly formed antibody migrated to the Golgi region, but the role of the Golgi complex in secretion of antibody remains to be explained. The hypothesis that plasma cells originate by differentiation from large lymphocytes received circumstantial support from the observation that among those cells active in synthesis of protein, a series transitional in structure from large lymphocytes to mature plasma cells could be assembled.—O. P. J.

**Difference Between Medullary and Cortical Thymic Lymphocytes of the Pig in Their Response to Phytohemagglutinin. W. T. Weber.** From School of Veterinary Medicine,
EFFECT OF THYMIC GRAFTS ON LYMPHOPOIESIS

PHA were located predominantly in the medulla of the thymus. Of interest was the peculiar association of PHA-responsive lymphocytes with reticular-epithelial cells in the medulla. Perhaps thymic cortical lymphocytes and, possibly, immigrant cells from the circulation (bone marrow derived?) must reach the medulla before they mature into immuno-competent cells in the special micro-environment of the reticular-epithelial cells. —O. P. J.


The aim of this study was to determine if thymic grafts placed within millipore diffusion chambers in neonatally thymectomized rats could influence the level of circulating lymphocytes or stimulate lymphopoiesis in the spleen and other lymphoid tissues. In spite of the obvious role of the thymus in lymphopoiesis, the possible release of a potent factor affecting lymphoid tissues or circulating lymphocytes was not borne out by this study. —O. P. J.


Until recently, it was accepted that sterile damaged and disintegrating tissues did not attract polymorphs chemotactically. Experiments with an in vitro test system practically identical with that used by Harris (1953) provided results indicating that certain types of damaged tissue regularly were chemotactic to polymorphs. For example, human polymorphs were attracted towards severely damaged tissue from burned rat skin, but not towards tissue from areas of less severe heat injury. Fragments of rat cardiac muscle or liver became chemotactic after incubation in fresh rat serum, but not after a similar period of incubation in saline. Perhaps damaged tissue may interact with serum to produce a factor that is chemotactic to polymorphs. —O. P. J.

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Pig thymus tissue was cultured with organ culture techniques in the presence and absence of phytohemagglutinin (PHA). Morphologic and autoradiographic observations indicated that, in the pig, lymphocytes capable of responding to PHA were located predominantly in the medulla of the thymus. Of interest was the peculiar association of PHA-responsive lymphocytes with reticular-epithelial cells in the medulla. Perhaps thymic cortical lymphocytes and, possibly, immigrant cells from the circulation (bone marrow derived?) must reach the medulla before they mature into immuno-competent cells in the special micro-environment of the reticular-epithelial cells. —O. P. J.


The ability of neutrophil leukocytes to extravasate into the peritoneal cavity in response to an intraperitoneal injection of bacterial endotoxin was studied in mice. The normal response of a marked accumulation of intraperitoneal neutrophils was completely abolished by halothane anesthesia. No other reports of this effect of anesthetics have been found. The phenomenon appeared to be caused either by a change in vascular permeability or by a change in the ability of the leukocytes to escape the vascular confines. The effect of the commonly used, volatile general anesthetics on the microcirculation has not been defined, so the former possibility should be seriously considered. Perhaps, however, the effect was on the neutrophil, rendering it less deformable and less able to undergo trans-vascular diapedesis. —O. P. J.


Bone marrow plasma cell counts were obtained from aspirates of normal infants and children, and from ill children. Values of 1/1000 or less were generally found in infants below the age of 6 months. Thereafter, mean values progressively increased, reaching adult values after 5 years. Increased numbers of plasma cells were present in children with sickle cell anemia and decreased numbers in patients with hypogammaglobulinemia. Normal values were present in iron deficiency and accompanying the Wiskott-Aldrich syndrome. Because of the low values in healthy infants and young children, it was not possible to diagnose immunoglobulin deficiency by counting bone marrow plasma cells in patients younger than 5 years. —J. B. S.


In a γ-A myeloma with hyperlipidemia, the serologic antilipoprotein (anti-Pg) activity was associated with an abnormal γ-A globulin. The whole abnormal globulin was isolated in a complex of γ-lipoprotein with Pg antigen. —J. C.
HEMOSTASIS


The clinical course of ITP in 152 children was reviewed. Although boys and girls were equally affected, the tendency to chronicity, demonstrated in about 8 per cent, was twice as frequent in girls. More than 80 per cent had an acute febrile illness during the 3 weeks prior to onset. The absence of a history of antecedent infection was also associated with a tendency to chronicity. The incidence in Negroes was less than expected, and eosinophilia was universal. The patients were classified as mild, average or severe. The latter term was reserved for children with massive cutaneous purpura, profuse epistaxis and/or retinal hemorrhages and only in this group was steroid therapy routinely administered. In 117 of the mild or average cases, therapy consisted of restriction of activity and occasional transfusions. Twenty-four of the mild and average cases and all 11 of the severe cases were treated with corticosteroids, usually prednisone, 2 to 3 mg./kg./day. Except for one child admitted moribund and in deep coma, no instance of bleeding into the central nervous system was observed. Steroid therapy was not accompanied by more rapid return of platelet counts to normal, even among the mild cases, and chronicity was not significantly different in treated and untreated groups. Nine of 12 patients who developed chronic ITP underwent splenectomy. The only failures occurred in 2 youngsters in whom there had been no response to steroids.—J. B. S.


Studies of platelet adhesiveness were performed on 45 healthy young adults before and after a 50 mile walk. Platelet adhesiveness, measured in the presence of ADP or celite, was significantly reduced after the exercise in a majority of the subjects. There was no definite pattern of change in platelet counts after the exercise, but white cell counts increased to twice the normal value. The fall in platelet adhesiveness was considered to be due to a change in environment, rather than to an alteration in the platelets themselves.—A.L.B.


In von Willebrand's disease, a decrease in platelet adhesiveness has been reported. This observation could not be confirmed in a study of 68 Swedish patients. Adhesiveness was studied in citrated whole blood and in plasma after addition of ADP.—S. A. K.


A patient with Hodgkin's disease who was treated with external irradiation and intralymphatic infusions of colloidal radioactive gold developed aplastic anemia. Thrombocytopenia was alleviated by repeated transfusions of platelet concentrates given over a period of 9 weeks until recovery of bone marrow function occurred 13 weeks after the initial infusion of radioactive gold.—A. L. B.


The rate of release of potassium and acid phosphatase from irradiated platelets was the same at 4°C. as at 37°C. In contrast, the release of serotonin from irradiated platelets was markedly retarded in the cold. Serotonin and acid phosphatase may be associated with different subcellular fractions within the platelet or the affinity of serotonin for its binding site may be greater at 4°C. than that of acid phosphatase for its site.—O. P. J.


The electrophoretic mobility of platelets from two patients with thrombasthenia was studied. In neither case, was there any change in mobility after contact with a non-siliconized glass surface or after incubation with ADP, procedures which alter the electrophoretic mobility of normal platelets. The addition of extra sulfhydryl groups or normal platelet-poor plasma did not correct the
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A study of platelet function in the course of congenital or acquired hemorrhagic diseases permitted the authors to confirm the fact that plasma fibrinogen contributes to platelet aggregation, while anti-hemophilic factors are deprived of any role. Divergent results were found for Hageman factor. Thrombocyte anomalies have been noted rarely in von Willebrand's disease and frequently in cases of isolated prolonged bleeding time. Thrombasthenic platelets were but moderately aggregated by bovine fibrinogen; preincubation with ADP inhibited this effect. In some cases of paraproteinemia, a plasma factor inhibited platelet deaggregation. This activity appeared diminished in the plasma of subjects with chronic myeloid leukemia.—J. C.


In a series of patients with obstetric hypofibrinogenemia, those with abruptio placentae responded well to fibrinogen therapy without relapse and with no evidence of an anticoagulant in the thrombin-fibrinogen reaction. In these cases, fibrinogen depletion was attributed to intrauterine fibrinogen utilization with serum absorption, rather than to fibrinolysis or intravascular coagulation. In patients with proved or possible amniotic fluid embolus, there was evidence of increased clot lysis, an inhibitor of the thrombin-fibrinogen reaction or incomplete response to fibrinogen therapy. Fibrinogenolysis was thought to be a major factor causing the hemostatic defect in this group. Continuing intravascular coagulation was thought to be the cause of fibrinogen deficiency in one case of retained dead fetus. The clinical diagnosis may give a strong lead to the type of hematologic abnormality. This substantial paper contained a detailed discussion of the pathogenesis and diagnosis of obstetric hypofibrinogenemia.—A. L. B.

ERYTHROCYTES


Homotransplantation of the hypophysis was employed in 7 patients with hypoplastic anemia. The hypophysess were preserved by quick freezing at —79 C. Following transplantation, 5 patients showed improvement in their general condition and in their peripheral blood pictures. One patient had improvement of the bone marrow. The positive effect lasted 1.5 to 6 months.—J. K.


The previously described decrease in the clinical severity of hemophilic bleeding following a reversal of behavior from passive, fearful dependence to a state of more aggressive and active independence was confirmed. The best adjusted hemophilic boys came from families in which both parents accepted the diagnosis, understood its complications, exerted a firm disciplinary approach, and permitted and encouraged maximal activity and independence within the bounds of safety. Although seasonal variations in bleeding were not observed, almost all of the 35 patients studied reported cyclic episodes of increased bleeding tendency. Some of these, but not the majority, appeared to be related to stress or to anticipation of some upcoming major event.—J. B. S.
The effect of the source of donor tissue on erythropoiesis in regenerating spleens was studied by the injection of spleen or bone marrow cells into irradiated mice. Erythropoiesis was quantitated by measuring the splenic uptake of iron per unit weight of spleen. In 8-10 week old and 4-6 month old mice, spleens containing colonies derived from bone marrow tissue were found to be more active than those containing colonies derived from splenic tissue. In young mice, the erythropoietic activity of regenerating spleens containing either splenic or bone marrow tissue was greater than that of normal spleen. In older mice, only regenerating spleen containing bone marrow tissue had greater erythropoietic activity than that of normal spleen. The source of the donor hemopoietic tissue, therefore, influenced its subsequent initial activity in the irradiated host.—A. L. B.


In a 16 month old boy with the Imerslund syndrome, gastric juice contained IF and serum contained no IF antibodies. Schilling test without and with IF showed no B₁₂-absorption. Intestinal juice from the duodenum and jejunum (80 cm. distal to the pylorus) obtained during gall bladder operation did not induce absorption of radioactive vitamin B₁₂, but intestinal juice from about 1–1.5 M down the jejunum from two normal persons induced B₁₂-absorption. In this case, the cause of the specific B₁₂-malabsorption was probably lack of "releasing factor".—S. A. K.


Two B₁₂-binding components were separated from hog intrinsic factor concentrate by recycling gel filtration and their molecular size was estimated. The larger component was antigenically similar to a B₁₂-binder in hog bile, while the smaller component resembled human intrinsic factor and reacted with sera from patients treated with hog IF. Only this smaller component had IF activity, as determined by Schilling tests.—S.A.K.


The saliva of 4 healthy controls and 3 patients with pernicious anemia was examined for antibody to intrinsic factor with ammonium sulfate precipitation and a complex of radioactive vitamin B₁₂ and intrinsic factor. Precipitable antibody, found in the saliva of one patient with pernicious anemia, was shown to be IgA. Salivary antibody may neutralize intrinsic factor and thus accelerate the development of overt B₁₂ deficiency.—A.L.B.


Antibodies against B₁₂-binding components in human and hog IF preparations were studied by employing a precipitin reaction combined with autoradiography after diffusion in agar gel. Sera from 78 patients with pernicious anemia (p.a.), 71 patients with other diseases and 116 healthy persons were studied. Antibodies against B₁₂-binders in human gastric juice were found in 9 p.a. sera, but not in other sera. Antibodies against B₁₂-binders in hog IF were found in 19 of 31 p.a. patients treated with hog IF orally, but only in one of 47 patients treated otherwise. Antibodies to hog IF were also found in non-p.a. patients, notably those who had been treated with hog IF, and in 7 of the healthy persons. It was concluded that the antibodies demonstrated were IF antibodies and that hog IF antibodies were to a great extent the result of immunization due to oral hog IF therapy, whereas antibodies against human IF were thought to be autoantibodies.—S. A. K.


Of 24 patients with megaloblastic anemia of pregnancy, 6 had medical disorders predisposing to development of folate or vitamin B₁₂ deficiency and 6 had excessive bleeding associated with thrombocytopenia at the time of parturition. Serum folate concentrations were subnormal in 83 per cent of patients with megaloblastic anemia, as well as in 25 per cent of a group of 50 non-anemic pregnant women. Microbiologic estimates of serum vitamin B₁₂ activity were subnormal in 71 per cent of patients with megaloblastic anemia.
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and in 46 per cent of non-anemic women. The finding that the binding capacity of serum proteins for B₁₂ was increased and that added Co⁺⁺B₁₂ was bound by beta and not alpha-1 globulin in these subjects indicated that actual deficiency of vitamin B₁₂ was rare in pregnancy.—F. A. K.


Following an oral test dose of tritiated folic acid, plasma levels of radioactivity were below normal in a group of 10 alcoholics with recent exposure to alcohol, but were normal in 13 alcoholics who had abstained from alcohol for a week. The 24 hour urinary excretion of radioactivity was within the normal range in both groups. In 4 of 5 normal subjects, the acute ingestion of alcohol did not alter H⁺-PGA absorption. The authors considered that the saturating dose of 30 mg. folic acid given parenterally one-half hour before the absorption study was sufficient to preclude inadequate folate saturation as a cause for the subnormal results in the actively imbining group and proposed that sustained alcohol ingestion resulted in malabsorption of crystalline folic acid.—F. A. K.


A method for determining the cobalt-binding capacity of serum with the aid of gel filtration on Sephadex D-50 resin was described. Cobalt-binding capacity was normal in iron-deficiency anemia and was reduced in infectious-toxic anemias, especially in anemias associated with neoplasms.—J. K.


A potpourri of data was presented to indicate that among females with sickle cell anemia, onset of menarche was delayed, dysmenorrhea was more frequent, fertility was decreased, first pregnancies were delayed, and fetal wastage and premature delivery were greater when compared to non-sicklemic negroes. In addition, low mean values for weight, height, span and ratio of upper to lower body segments were obtained among sicklemic youngsters. Occasional children with this disorder demonstrated hypogonadism or delay in development of secondary sex characteristics. Chemical determinations revealed a tendency to low serum alkaline phosphatase levels, low borderline urinary excretion of 17-ketosteroids and low serum folic acid levels in many of the undersized patients, none of whom demonstrated any hematologic evidence of folate deficiency.—J. B. S.


Observations on over 221 patients with sickle-cell anemia and its variants (SC, SD and S-thalassemia) included the multiple clinical manifestations, the results of laboratory examinations and roentgenotherapy, and the differential diagnosis. Peculiarities in the course of these diseases in patients of different age were described, as well as differences in the clinical picture of sickle-cell anemia according to the date of its description in various countries.—J. K.


Toads have no diaphragm or ribs and depend upon valves in the throat for lung inflation and deflation. The position of toads in the evolutionary scale makes them interesting forms for study of respiratory processes. The effects of three physicochemical factors (temperature, hydrogen ion concentration, partial pressure of oxygen) on the respiratory functions of blood have been studied. These functions conform to the pattern of respiratory mechanisms available for gas exchange between the environment and tissues.—O. P. J.

Serum haptoglobin content was determined in the blood of 31 children, aged 6 months to 14 years, with various forms of hemolytic anemia. The determination of haptoglobin was a sensitive test in the detection of hemolysis of any origin and the efficiency of therapy could be judged by the change in concentration.—J. K.


The incidence of G-6-PD deficiency, HgbS and HgbC was determined in the red cells of 100 Nigerian children suffering from severe falciparum malaria with parasite counts of 100,960 per mm.³ or greater and in 200 control children. A significantly lower proportion of children with malaria had G-6-PD deficiency or HgbS, but the proportion of children with HgbC was similar in both groups. The results supported the hypothesis that inheritance of C-6-PD deficiency or HgbS protected against falciparum malaria, but HgbC offered no such advantage.—A. L. B.


A screening test for G-6-PD deficiency was carried out over a two year period on all severely jaundiced infants in whom there was no serologic evidence of blood group incompatibility. Twenty-two were found to have a deficiency which was confirmed by a number of more quantitative tests. Eight of the infants weighed less than 2,500 Gm. at birth or when first brought to medical attention. Fourteen were colored, 4 were White, 2 were Asiatic and 1 was a Bantu. Blood smears in a number of instances showed reticulocytosis, while polychromatic red cells and normoblasts were also present. The level of unconjugated bilirubin, however, was raised in only 1 instance.—T. H. B.