HEMOSTASIS


Isonicotinic acid hydrazide was shown to inhibit the terminal stage of blood coagulation by inhibiting the enzyme-catalyzed transpeptidation necessary for the cross-linking of fibrin. The drug did not, therefore, interfere with the coagulation time, but rendered the clot soluble in one percent monochloroacetic acid and it was active in vitro in concentrations close to those obtained in plasma during therapeutic administration. Other compounds which resemble functionally the amino or carbonyl side-chains of fibrin have a similar action.—A. L. B.


Intrinsic and extrinsic coagulation are characterized by two features, to some degree related: the speed of coagulation, as measured by the coagulation time, and the consumption of Factor X. Intrinsic coagulation (spontaneous coagulation of shed blood or coagulation of plasma in the partial thromboplastin time) is slow and little Factor X disappears. All factors involved in this system influence the speed of coagulation, but have no effect on Factor X consumption. Conversion of prothrombin to thrombin can occur with little utilization of Factor X, but the reaction is slow. In contrast, extrinsic coagulation in the presence of tissue thromboplastin or Russel viper venom with cephalin is rapid and destroys nearly all the Factor X present. The lack of almost any factor diminishes the speed of the reaction and the utilization of Factor X. Factor X appears to be the clue to the high-speed conversion of
prothrombin to thrombin and to be its main determining factor. Intrinsic coagulation in the guinea pig is more rapid than in man and rapidly consumes Factor X. It is possible to establish a human intrinsic coagulation model resembling intrinsic coagulation in the guinea pig by addition of partly purified Factor VIII to a human system for intrinsic coagulation. Phylogenetic progress may have produced transformation of the quick, high rate of Factor X consuming intrinsic coagulation system to a more delayed, Factor X sparing system in man. The mechanism remains unknown. This adaptation may have been obtained by natural reduction, if not suppression, of the action of Factor X during coagulation.—C.M.


Thrombin inactivation in serum obtained from native and recalcified blood was compared. No differences were found.—M.K.


Hypercoagulability was disclosed in patients with cardiac compensation and in cases with slight decompensation. In several cases, impaired blood clotting was observed during periods of severe circulatory insufficiency, but hypercoagulability reappeared after successful treatment. A discussion of the probable role of blood clotting disturbances in the pathogenic mechanisms of thromboembolic complications in chronic cor pulmonale was included.—M.K.


A patient with pre-eclampsia developed an acute hemolytic anemia with distorted and fragmented red cells and thrombocytopenia. During treatment with heparin, hemolysis and plasma Hb levels decreased, the platelets tended to recover and the blood urea fell. When heparin was stopped, the platelet count fell again and the blood urea rose. The authors reviewed the syndrome of hemolysis in pre-eclampsia and theorized that it may be due to fibrin formation in small blood vessels. Hence, the thrombocytopenia, fragmented damaged red cells and favorable response to heparin.—A. L. B.


The concentration of Cr51-labeled platelets was measured in circulating blood simultaneously with the organ distribution in normal persons and in patients with splenomegaly (69 year old male with Felty syndrome, 53 year old male with fibroadenoma of the spleen, 64 year old male with osteomyelofibrosis). The lifespan of the platelets was normal in the patients, but there was very pronounced storage of platelets in their spleens.—K.B.


Five cases of thrombocytopenia after vaccination against diphtheria, tetanus or abdominal typhus were described. The authors were not able to demonstrate antithrombocyte antibodies in the sera of these cases.—M.K.


Three cases of thrombocytopenia in children with congenital cyanotic heart disease are described. The authors consider thrombocytopenia to be an indication for subjecting such cases to diagnostic and surgical procedures, since thrombocytopenia disappears after successful operations.—M.K.

A CASE OF THE MARTIN DE GIMARD SYNDROME IN AN EIGHT-MONTH OLD CHILD.
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A case of necrotic purpura successfully treated with antibiotics and adrenocortical hormones is described.—M. K.


A newborn infant with Down’s syndrome presented a peripheral leukocyte picture suggesting acute myelogenous leukemia. A Coombs-negative hemolytic anemia also developed. The unusual finding was a platelet count of 1.2 million/mm.3 with many giant platelets noted on the peripheral smears. The bone marrow was essentially normal and by one month the hematologic values were almost normal. The infant died of sepsis at 5 weeks of age.—J. B. S.

POSTOPERATIVE DEFIBRINATION SYNDROME.

Seven patients with the defibrination syndrome and severe bleeding after surgical operations were described. The pathogenic mechanisms and therapeutic possibilities were discussed.—M. K.

ERYTHROCYTES


The author reexamined the sickle hemoglobin gene-malaria hypothesis and its interaction with the development of agricultural systems in tropical Africa, and presented evidence to show that the introduction of a specific type of agriculture, the cultivation of root and tree crops, was particularly conducive to the spread of malaria through the tropical rain forests of central Africa. Tribes which practiced this type of agriculture had a particularly high frequency of the sickle cell trait. It was suggested that the spread of the sickle hemoglobin gene through the population allowed the survival of this type of agricultural system, even in the face of unfavorable environmental changes, i.e., increased incidence of malaria. Mathematical models were developed which showed that an increase in the incidence of the sickle gene reduced the intensity of the malarial parasitism by reducing the proportion of the population susceptible to heavy infestation. Thus, the spread of the sickle cell gene allowed the survival of an agricultural system which itself had initially promoted the spread of a disease (malaria) detrimental to the agricultural population. This paper was of some interest in that it threw further light on the possible interaction between genetics, environment and culture.—T. F. N.


The distribution of genotypes for Hb S and Hb A was determined in Negro children admitted to hospital with infections due to various organisms. The proportion of cases with sickle cell anemia was greater than expected in all bacterial groups studied, but especially in children with pneumococcal infections. On the other hand, except in the case of children with staphylococcal infections, the proportion with Hb AS was unexpectedly small. Possibly, sickle cell trait was linked with lowered sensitivity to bacterial infections.—A. L. B.

PATHOGENESIS OF HEMOLYTIC ANEMIA IN HOMOZYGOUS HEMOGLOBIN C DISEASE.

Hemoglobin C is shown to be less soluble than Hb A in red cells, hemolysates and in dilute buffers. Crystallization could be induced under a propane atmosphere, conditions under which Hb S does not sickle. Thus, the type of molecular interaction which leads to increased crystal formation in Hb C syndromes probably is different from
Cardiovascular studies were carried out on three individuals heterozygous for Hb Yaki- that which leads to sickling. Hb C-containing erythrocytes are also shown to be less "deformable" than cells containing Hb A; they pass through membrane filters at a slower rate and exhibit a markedly higher viscosity than normal red cells. The retardation of passage of Hb CC cells through membrane filters could be a function of their shape ("target cells"), but the changes in viscosity probably are related more directly to the abnormality within the hemoglobin molecule. These changes in viscosity and increased crystal formation may, at least in part, explain the mild hemolytic anemia seen in association with Hb C disease.—T. F. N.


Hb Yakima is yet another hemoglobin variant which is found in association with erythrocytosis. On starch gel electrophoresis at pH 8.6, the mobility is slightly less than Hb A. The structural formula can be written as α₂β₂θθθθ. The father and two daughters, heterozygous for this hemoglobinopathy, exhibit (1) hemoglobins in the range of 15.9–22.9 Gm./100 ml., (2) no splenomegaly, elevated leukocyte counts or other hematologic abnormality, (3) 37–38 percent abnormal hemoglobin, (4) elevated urinary erythropoietin levels. The authors consider various structure-function relations which could account for the increased oxygen affinity of Hb Yakima. The most likely appears to be an effect of the substituted side chain on the region of contact between the α and β chains, limiting the normal motion which occurs between these chains during the processes of oxygenation-deoxygenation.—T. F. N.


A case of congenital methemoglobinemia was reported. Starch-gel electrophoresis of a partially purified red cell extract with an appropriate staining system indicated the presence of an electrophoretically distinct enzyme, suggesting that the defect resulted in the synthesis of a structurally altered enzyme protein. Normal individuals possessed at least two isoenzymes, while the mother of the propositus showed both normal and abnormal forms.—A. L. B.


In iron deficiency anemia, the catalase concentration per ml. of red cells was normal. Although not expressly stated, this finding suggested that the absolute content per cell was reduced, an interpretation supported by the author's data showing that the catalase content of red cells was positively correlated with the M.C.V. In most cases of megaloblastic anemia, the concentration of catalase was at the upper part of the normal range and the mean was significantly greater than normal. During treatment, the concentration fell excessively at first and then rose to reach a steady state. The author suggested that the
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Blood cells produced at the start of therapy were relatively deficient in catalase. In patients with advanced carcinoma or the malabsorption syndrome, catalase concentration was low, irrespective of the presence of anemia. The author suggested that impaired synthesis of the protein part of catalase due to malnutrition may account for the low concentration in these diseases. Catalase concentration was reduced in two cases of hemolytic anemia and this deficiency may potentiate oxidative mechanisms leading to hemolysis.—A. L. B.


Hemolytic crises, occurring at nearly the same time in three siblings with hereditary spherocytic anemia, were described. Similar crises have been observed twice in their mother, at age 31 and 39. The author was not able to detect any crisis-provoking factor.—M. K.


This substantial paper describes the experience of the Newcastle group in the use of intrauterine transfusion for the prevention of stillbirths in Rh-hemolytic disease. The clinical and hematological aspects are discussed and it is concluded that this form of treatment has an important part to play in the management of selected cases. The original should be read by workers interested in this field.—A. L. B.


Blood loss was measured by means of Fe59 and a simple whole body counter. Seven to ten days after administration of Fe59, all or most of the dose was considered to be incorporated into red cells and the subsequent fall of whole-body radioactivity indicated the degree of blood loss. The technic was assessed in patients with polycythemia from whom known quantities of blood were removed by venesection. The method would not reliably detect blood loss of the order of 100 ml., but could detect losses of 700–3000 ml. over periods of up to three months. The method was useful in the investigation of patients with hypochromic anemia.—A. L. B.

STUDIES ON IRON ABSORPTION AFTER NORMAL DELIVERIES. S. Waluszkiwicz. From the School of Medicine, Białystok, Poland. Przegl. Lek. 23:382–384, 1967.

Iron absorption was found to be increased in approximately 50 percent of women after normal delivery when puerperal loss of blood did not exceed 300 ml.—M. K.


Serum folate, hemoglobin and serum vitamin B12 levels declined during pregnancy. There was no correlation between fetal weight and maternal serum folate levels, except in the case of patients with uterine bleeding, most of whom showed the combination of low serum folate and low fetal weight. The serum folate levels of those patients who bled at any time during pregnancy and of those with bacteriuria were lower than those of patients without these disorders, but cause or effect was not established.—A. L. B.


The modern concepts on the chemical nature, site of production and mechanism of action of erythropoietin were described. The mechanism of renal activation and inactivation of erythropoietin was discussed in detail, based on the results of the author’s own experiments. The hopeful prospects of the application of erythropoietin in research on cellular differentiation were suggested.—M. K.

A rapid drop of erythropoietin level in the blood of children during the first days of life was found to explain the early anemia of newborns. The disproportion between erythropoietin activity in plasma of pregnant women and that of cord plasma indicated independent erythropoietin production by the fetus. No erythropoietin was found in ten infants in the period of so-called "physiological anemia" at the age of 3–5 months. High levels of erythropoietin were found in most cases of primary blood diseases with anemia. Plasmas of patients with anemia in the course of severe kidney disease and infections were devoid of erythropoietin activity.—M. K.


Intraperitoneal injection of hemolysates of homologous erythrocytes into rats was found to induce the appearance of an active substance inhibiting erythropoiesis. This factor, injected into mice, diminished differentiation and proliferation of erythroblasts and caused significant changes in iron storage and turnover. Forty-eight hour dialysis of plasma inactivated the erythropoiesis-inhibiting factor.—M. K.


Hemoglobin A and F synthesis was measured in an in vitro system in reticulocytes from infants with Rh hemolytic disease. Addition of an isoleucine analogue, L-O methylthreonine, led to the inhibition of the synthesis of Hb F, but not of Hb A. This inhibition appeared to be competitive and could be reversed by the addition of L-isoleucine to the medium. The author concluded that the biosynthetic pathways for Hb A and F synthesis must be independent and that the presence of O-methylthreonine exerted a selective inhibition on the synthesis of gamma chains. (Abstracter’s comment: The author also stated that Hb A and F synthesis must be occurring simultaneously in about 50 percent of the reticulocytes, but he presented no data, save for the morphologic appearance on the Betke smear to substantiate this thesis).—T. F. N.


In a case of pure red cell anemia in a 61 year old male with thymic tumor, thymectomy revealed a thymoma of the spindle cell type. The operation was not followed by recovery from anemia. There were no erythroblasts in the bone marrow and no reticulocytes in the peripheral blood. Vitamins B6 and B12, anabolic steroids and testosterone, inosine, implantation of autologous lymphocytes stimulated by phytohemagglutinin and transfusion of plasma from a patient with secondary polycythemia were therapeutically ineffective. Up to 3.4 percent reticulocytes, however, were seen after intramuscular injection of γ-globulin. The patient died soon after with hepatitis.—K. B.

LEUKOCYTES


Adults and children suffering from acute lymphoblastic leukemia were treated with a simultaneous combination of prednisone, vincristine and rubidomycin. Complete remissions were obtained in a high proportion of both previously untreated patients and treated patients in relapse. In most cases in remission, leukemic cells were not detected by detailed investigation. Results in acute leukemia complicating lymphosarcoma were much less satisfactory. The overall tolerance of the combination of drugs was at least as good as when used separately, but temporary
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bone marrow aplasia was common. This complication was managed by treating patients in a pathogen-free room which prevented infections. Three elderly patients developed heart failure due to rubidomycin. The combination of drugs was used only to induce remission and therapy was maintained with other cytotoxic drugs, irradiation and immunotherapy.—A. L. B.


A child who had what appeared to be acute myelogenous leukemia demonstrated, during remission, varying numbers of bone marrow cells which were Ph1-positive. Also, during remission he had a tendency to polymorphonuclear leukocytosis, eosinophilia and thrombocytosis, suggesting an incipient CML. When he went into final relapse, all the blasts were Ph1-positive in addition to showing aneuploidy. From their observations, the authors suggested that the blastic crisis was not a phase of CML, but represented the appearance of AML in a cell population which by its g-chromosome abnormality was predisposed to acute leukemic transformation within the mutant clone.—J. B. S.


Lymphocytes of peripheral blood, labeled in vitro with Na51CrO4, were re injected. After 13 days, more labeled cells could be found in the blood of eight patients with chronic lymphocytic leukemia than in controls. The half life of the radioactivity studied from the thirteenth day after injection was 5.6 ± 1.8 days in the patients and 13.0 ± 2.6 days in normals. In chronic lymphatic leukemia, there was a decreased redistribution of peripheral lymphocytes into the tissues and an increased destruction of the cells.—K. B.

THE EFFECT OF THERAPY ON THE HAPTOGLOBIN LEVEL IN LEUKEMIC PATIENTS. B. Turowska and M. Gurda. From the School of Medicine, Kraków, Poland. Przegl. Lek. 23:381-382, 1967.

The haptoglobin level was determined before and after treatment in 26 patients with various types of leukemia. The level was higher in patients with leukemia, particularly with lymphatic leukemia, than in healthy people. After treatment, the level rose in myeloblastic leukemia, remained unchanged in chronic granulocytic leukemia and decreased in lymphatic leukemia.—M. K.


An SS myeloma component, isolated from serum of a patient with myelomatosis is described, which appears to have no antigenic determinants in common with human α-, β-, γ- or μ-polypeptide chains, as revealed by immunoelectrophoresis and Ouchterlony gel diffusion analysis. The myeloma protein migrates in the fast γ-region on electrophoresis at pH 8.6 and has an elution volume on Sephadex G-200 similar to that of 6.5S IgA. The isolated myeloma component has an approximate molecular weight of 300,000 and a total carbohydrate content of 10.7 percent. Reduction with β-mercaptoethanol and acid dissociation yields light polypeptide chains of Type L and a carbohydrate-rich component, in the ratio of 1:4. Antisera specific to determinants on the heavy chains of the myeloma protein show no reaction with the immunoglobulins A, D, G or M. Instead, unique determinants are found on the heavy polypeptide chains.—H. H. F.


IgG and/or IgA "paraproteins" were detected in the sera of 104 individuals without clinical, cytological or radiological evidence
of overt myeloma. Group I included 47 cases with complete post-mortem study or with 1–7 years follow-up, while group II included 57 cases with 6 months to one year follow-up or long-term follow-up with insufficient clinical or post-mortem data. The “paraprotein” was an IgG globulin in 82 cases and an IgA globulin in 19. The simultaneous occurrence of IgG and IgA “paraproteins” was found in 3. The characteristics of these pathologic immunoglobulins were similar to those of myeloma globulins. Light chain antigenic types were tested in 31 instances; type K was found in 20 and type L in 11. Individual antigenic specificity was demonstrated for 8 of 9 paraproteins. Absorption of these rabbit antisera with large amounts of normal fraction II led to the same results as with myeloma globulins. None of the sera had an extremely high content of antistreptolysin. The concentration of the paraprotein was less than 2 gm./100 ml. in 89 percent. In some instances, the abnormal spikes were faint and were easily detected only on agar-gel electrophoresis. The levels of the normal immunoglobulins were often within normal limits and were strikingly increased in four cases. Proteinuria was looked for in 66 cases. The Bence-Jones thermosolubility test was positive in only two instances, but immunoglobulin abnormalities (electrophoretic spike and presence of only one light chain antigenic type) were found in all cases with proteinuria of more than 50 mg./100 ml. and in 30 percent with lower concentrations. Although a further increase in paraprotein concentration was noted in six patients, none had developed the signs or symptoms of overt myeloma. A considerable decrease in the level of the paraprotein was observed in four cases and, in four others, no subsequent spike was detectable on agar-gel electrophoresis. In one patient with untreated myelofibrosis and transient paraproteinemia, later serum samples tested with individual specific antisera to the paraprotein were negative. The mean age was similar to that of multiple myeloma patients. Paraproteins, however, were detected in the sera of three children (5 months, 3 and 8 years old) affected with Aldrich's syndrome, myelomonocytic leukemia and familial lymphohistiocytosis. Long-term studies may prove that some of these cases were presymptomatic myelomas. Some individuals were apparently heal-
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intestinal lymphangiectasia are generally quite healthy, despite their profound anergy. —T. E. B.


A technic for the production of profound and sustained lymphocytopenia in the dog by irradiation of the subcutaneously implanted spleen (whose neural and vascular structures are maintained intact) is described. This technic is compared with that of repeated extracorporeal irradiation of the blood. Superiority of splenic irradiation is demonstrated, since marked and long-lasting reduction of absolute lymphocyte counts are obtained without the development of anemia and thrombocytopenia. The simplicity of the technic, as compared to extracorporeal circulation, is emphasized. Despite profound levels of lymphocytopenia in selectively irradiated host animals, albogenic renal grafts develop destructive changes and lymphoid infiltrates typical of the rejection reaction. —T. E. B.


Extracts from human leukocytes were unable to catalyze the synthesis of long-chain fatty acids because they lack acetyl CoA carboxylase, the first enzyme unique to the fatty acid synthesis pathway and, thus, were unable to form malonyl CoA. This inability to synthesize long-chain fatty acids could be corrected by addition of either acetyl CoA carboxylase or of malonyl CoA to the leukocyte extracts. Leukocytes, therefore, contained the enzymes of fatty acid synthesis, except for acetyl CoA carboxylase. The latter was, however, found in extracts from human leukemic blast cells and so might be present in a normal precursor hematopoietic cell. The incorporation of labeled acetate into fatty acids by intact leukocytes was shown to represent chain elongation of preformed fatty acids, rather than de novo synthesis, by the fact that most of the label incorporated resided in the carboxyl carbon of the fatty acids formed. The inability of mature leukocytes to synthesize fatty acids raised a question as to how these cells were able to maintain the complement of complex lipids which are required for cell membranes, as well as for other cell structures and functions. Perhaps leukocytes can use preformed fatty acids for complex lipid biosynthesis. —T. E. B.


By using the histochemical method of Kaplow as modified by Catanzano, the authors studied the behavior of LAP in 76 patients with various hepatobiliary diseases. The results were compared to those determined in 60 healthy control subjects. In viral hepatitis the results were normal, even with corticosteroid therapy or cholestasis. With jaundice due to extrahepatic obstruction, 41 percent were above normal, especially in patients with bile duct stones with inflammation, or with neoplasms developing for more than two months. In cancer (liver, bile ducts, pancreas) 53 percent were above normal. The values were more often higher with hepatic metastasis, whereas two primary neoplasms of the liver gave normal figures. In cirrhosis, 49 percent were above normal. The values were statistically higher in jaundiced patients or with rapid death and they were always high during hepatic coma. Normal values were found in some cases of steatosis, amyloidosis, hydatid cyst and cardiac cirrhosis. The authors proposed the following conclusions: (1) In cirrhosis, increase of LAP was variable and indicated increasing severity of the disease. (2) During aplasia of the hepatobiliary system and, in particular, in secondary cancer of the liver, the LAP increased provided the evolution was quite long. (3) In jaundice, a normal value did not permit any conclusion, but a high value excluded viral hepatitis. This test was especially interesting in prolonged jaundice, since an increase in LAP would permit exclusion of the diagnosis of cholestatic hepatitis. (4) Corticosteroid therapy did
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not influence LAP during hepatobiliary infectious diseases.—G. M.

MISCELLANEOUS


Results of investigations of antitumor properties of 14 new acridine derivatives in mice bearing sarcomas or malignant lymphomas were presented. Study of two in vitro tests was included. On the basis of the biological results, the relationship between chemical structure and antitumor properties was discussed. Four derivatives of 9-aminoacridine (C-136, C-138, C-139 and C-140) showed antitumor activity.—M. K.


The temperature of the marrow cavity has been proposed as an important factor for hematopoietic localization and activity. Experiments made on the rat tail have been the basis for this commonly accepted hypothesis. It was considered of importance to re-examine the caudal vertebra model upon which this hypothesis was based. Sacral and coccygeal vertebrae were examined in rats, mice and humans with respect to marrow cellularity and temperature. In rats, mice and man, it was observed that the transition between hematopoietically active and inactive (fatty) vertebral marrow cavities was abrupt, occurring at the level of the first and second caudal and coccygeal vertebrae. All vertebrae distal to this point had fatty marrow. Of significance was the finding that the vertebral and coccygeal temperatures, as measured with a thermister needle, remained unaltered over this area of changing cellular activity. These anatomical and thermal observations indicated that the use of the tail as an experimental model did not support the hypothesis that temperature was a prime factor in the physiological maintenance of hematopoiesis in bone marrow.—R. O. W.


Syngeneic marrow cells were injected into lethally irradiated mice which had either been rendered anemic by bleeding or were given erythropoietin in order to stimulate erythropoiesis. In both groups, the leukocyte response to bacterial endotoxin was less than in control groups treated similarly, but without stimulation of erythropoiesis. The authors considered that there was competing proliferative demand on a pool of common stem cells in the grafts demonstrable when erythropoiesis was stimulated and that this implied a multipotent stem cell able to produce either red or white cell progeny.—A. L. B.


Study of homogenates of irradiated or non-irradiated bone marrow or marrow cell fractions obtained after centrifugation in a density gradient by immunoelectrophoresis allowed the authors to resolve 5 front lines of precipitation. After irradiation, some marrow cell antigens disappeared. A correlation was noted between the disappearance of these antigens and the radiation dose administered. After sublethal irradiation, the modifications were only temporary.—G. M.
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