ERYTHROCYTES


A boy who developed pernicious anemia at 13 years demonstrated a normal gastric biopsy and free HCl in the stomach. No parietal cell antibodies or evidence of endocrinopathy was found in him or other members of his family. Thus, this youngster resembled cases of juvenile P.A. which present in infancy or early childhood. The authors suggested that adolescents may present with the features of congenital P.A. and that they may represent a group in whom intrinsic factor was secreted during early childhood, disappearing only after they reached school age.—J. B. S.


A group of 36 normal infants, age 2 to 24 months, on an optimal diet showed a mean hemoglobin of 10.26 ± 0.42 Gm. per cent, mean lobe average 3.00 ± 0.184, mean serum B12 713.66 ± 322.5 μg/ml and mean serum folic acid 17.95 ± 9.39 μg/ml.—J. B. C.


Megaloblastic anemia and hypothyroidism occurring simultaneously were documented in 8 subjects. Serum folate concentrations were subnormal in 7, red cell folate concentrations were subnormal in 3, and serum vita-
min B\textsubscript{12} concentrations were normal in all 8. Five patients treated with 100 μg/day of oral folic acid in addition to undergoing thyroid replacement achieved complete hematologic remissions within 2 months. The factors responsible for folate deficiency under this circumstance were not identified.—F. A. K.


Conjugated and unconjugated serum folate levels of ten subjects were studied before and two hours after intramuscular injection of 5 mg. folic acid. A significant increase in conjugated folate level took place after the injection. This observation indicated that when folic acid was introduced into man by the intramuscular route, a significant portion was converted into the polyglutamyl form.—J. B. C.

**Inborn Errors in Folate Metabolism—A Cause of Mental Retardation?** V. Herbert. From the Mount Sinai School of Medicine, New York, Ann. Intern. Med. 68:956–957, 1968.

This editorial note calls attention to a series of reports emanating from Japanese investigators which have described 3 separate congenital enzyme deficiencies, all of which result in mental retardation and abnormally high serum concentrations of folate.—F. A. K.


This report, which describes the occurrence of a megaloblastic anemia during four successive pregnancies, re-emphasizes the fact that exfoliative cytology of the cervical epithelium demonstrates macrocytosis in subjects with a megaloblastic anemia.—F. A. K.


In 47 cases of anemia in the second and third trimester of pregnancy, megaloblastic hemopoiesis was observed in 23 patients. Urinary excretion of FIGLU was abnormal in 17. Good agreement between FIGLU excretion and bone marrow morphology was found in 11. Iron deficiency and low serum vitamin B\textsubscript{12} levels in 24 cases were also recorded. The high incidence of multiple deficiencies suggested a nutritional basis for the anemia.—J. B. C.


Saliva was found to have marked iron binding ability which was a function of both high molecular weight (over 200,000) and lower molecular weight fractions. Both fractions retained their iron binding properties after acid-peptic digestion. The authors suggested that the high molecular weight iron binding substance in saliva may have a function similar to that of the iron binding protein of gastric juice.—A. L. B.


In high altitude dwellers flown down to sea level there was a rise of plasma iron, a decrease of the plasma iron turnover rate, an increase of the iron-59 clearance time and a decrease of the reticulocyte count during the first two weeks. The red cell volume remained constant, but the hematocrit fell, due to increased plasma volume. The results suggested a relationship between hypoxia and erythrokinetics in permanent high altitude dwellers and that red cell production was inhibited when they were brought down to sea level.—A. L. B.

Erythropoietin, together with calf serum erythropoietin enhancing factor, accelerated the disappearance of cytoplasmic basophilia from rabbit erythroblasts of varying diameter in vitro and increased the score of benzidine staining for hemoglobin. The incorporation of labeled glycine into heme and porphyrin was completely nullified. The observations suggested that erythropoietin acts not only on stem cells, but also on already differentiated basophilic erythroblasts increasing their rate of maturation.—A. L. B.


In one week old rats, the bone marrow and spleen contained a high proportion of line 1 cells (erythroblasts) and a low proportion of line 2 cells. During growth, the proportion of line 2 cells in the marrow decreased and normoblasts almost completely disappeared from the spleen. In adult animals after severe hemorrhage, line 2 cells appeared in large numbers at both sites, and in the marrow types intermediate between basophilic erythroblasts (line 1 cells) and line 2 cells were seen. The findings suggested that the differentiation step to major hemoglobin production may take place at either the stem cell or the committed erythroid cell level.—A. L. B.


Peripheral blood obtained from patients with β-thalassemia synthesize excess free structurally intact α-chains. These α-chains are capable of forming normal Hb A when added to Hb β₄ (Hb H). Free α-chains appear to form a series of aggregates, the size of which depends upon the concentration of the free chains. Intracellular precipitation of such aggregates may contribute to the preferential destruction of excess α-peptide containing red cells.—T. F. N.


Iron deficient erythrocytes demonstrated increases in enzymatic activity in both the Embden-Meyerhof and hexose-monophosphate shunt pathways. Hexokinase, LDH, G-6-PD and 6-phosphogluconate dehydrogenase activity were significantly increased, as was the GSH concentration. Glucose utilization was also increased. With iron administration, all parameters studied became normal by three months. Acetylcholinesterase levels did not deviate from normal in iron deficiency, but were increased in a group of patients with hereditary spherocytosis. There was no evidence that the increased enzyme levels in iron deficiency resulted from the presence of a younger red cell population, and the author suggested that these changes may result from a compensatory mechanism directed against a defective synthesis of hemoglobin and stroma.—J. B. S.


In 14 patients with iron deficiency, activity of aconitase and succinic dehydrogenase was depressed in 4 and 10 subjects, respectively.—J. B. C.

ERYTHROCYTE GLUTATHIONE-PEROXIDASE DEFICIENCY AND HEMOLYTIC DISEASE OF THE NEWBORN INFANT. T. F. Necheles, T. A. Boles and D. M. Allen. From the
ABSTRACTS


Four infants with neonatal hyperbilirubinemia and evidence of hemolytic anemia demonstrated low levels of erythrocyte GSH-P which remained low when retesting was done at 1 month of age. In those instances where parents were studied, GSH-P levels in paternal erythrocytes were significantly below the normal adult range. The authors suggested that genetically determined erythrocyte GSH-P deficiency may represent another cause of neonatal jaundice.—J. B. S.


Activity of pyruvate kinase in 17 patients with Hb.E-thalassemia varied from 2.58 to 11.4 units/10^11 RBC/min. Low values were obtained in two. High activity of PK was usually associated with instability of ATP.—J. B. C.


Activity of diaphorase was studied in Hb. E-thalassemia disease (11), thalassemia trait (3), G-6-PD deficient subject (1) and normals (4), employing the technic of Scott. Enzyme activities in the 4 groups were: 20 to 66; 33, 34 and 13.5; 75; and 25 to 51, respectively.—J. B. C.


Seven cases of familial methemoglobinemia due to failure of the erythrocyte redox system were described. The erythrocytes of three patients failed to utilize both glucose and lactate for metHb reduction. Deficiency of only one reducing system was found in other patients. The possible role of structural changes in the Hb molecule in this disorder was discussed.—M. K.


Reduced or absent erythrocyte NADase activity was common among adult Negroes. Preliminary studies suggested an autosomal transmission of the deficiency.—A. L. B.


Comparative studies on blood preserved with ACD and CPD were carried out over a period of 28 days. Values for ATP-P, GSH and GSH stability, G-6-PD and CR were higher and the fall of K+ was less marked in blood preserved with CPD than that preserved with ACD.—J. B. C.

LEUKOCYTES


Karyotype studies were performed on the family of an infant with clinical and cyogenetic features of partial D trisomy who developed acute leukemia. The infant had a partial D trisomy of the translocation type, modal number 46. No other member of the family carried a translocation and all had normal karyotypes. The mother, her twin brother and the maternal grandmother,
however, demonstrated chromatid exchanges in leukocyte cultures, usually accompanied by increased breakage of chromosomes, endoreduplication and occasional acrocentric fragments. The mother and maternal uncle had positive antiglobulin reactions of their erythrocytes, and the maternal grandmother had hematologic findings suggesting early chronic lymphocytic leukemia. The authors suggested that the chromosomal instability in the maternal line, associated with congenital anomalies in three generations, culminated (in a sense) in a special case of gross cytogenetic mishap, and that the chromosomal instability facilitated the occurrence of exogenous mutagenic events, such as the entry of hypothetical leukemia viruses into the unstable genome of the rapidly replicating cells of the bone marrow.—J. B. S.


In two sets of infant siblings with Ph1-negative juvenile CML, leukocyte alkaline phosphatase was low and fetal hemoglobin slightly to moderately increased in the three infants so examined. Three infants underwent splenectomy with marked improvement in two and mild improvement in the third. Chemotherapy did not appear to be very effective, but very little data concerning medication was presented.—J. B. S.


Results of treating ALL in children by induction with vincristine and prednisone, followed by a week of intensive therapy with methotrexate, 6-MP and cyclophosphamide, and then by irradiation of the craniospinal axis and maintenance therapy with daily 6-MP and weekly injections of MTX, VCR and cyclophosphamide were described. Median duration of remission among patients entering the maintenance phase was 78 weeks to time of submission for publication. Six of the 27 patients in this group were still in remission 133 to 177 weeks after initial treatment. Despite the nervous system irradiation (1200 r), meningeal leukemia occurred in half. The intensive therapy phase was generally well tolerated, but two patients in complete remission succumbed from what seemed to be the effects of marrow depression and there was a general tendency to leukopenia in patients on the maintenance regimen for more than two years.—J. B. S.


A beneficial effect of melphalan was found in 56 per cent of cases of myeloma treated during five years. The best therapeutic results were observed during its administration together with Duraboli.—M. K.


A cytochemical study of RNP, DNP, basic proteins, alkaline phosphatase, glycogen and lipid was done with cells of the granular series of rat bone marrow. Cytoplasmic RNP stained intensely in the myeloblast. There was a progressive decrease in the staining intensity with maturation. Peripheral chromosomal and nuclear parachromatin in RNP showed an increase in their staining intensities with cell differentiation, while chromosomal RNP did not reveal any change. The DNP and basic proteins of the nucleus showed similar changes. Their staining intensity increased with cell maturation. Alkaline phosphatase appeared at the myelocyte stage and showed a slight but definite increase in its staining intensity in subsequent stages. Only 10 to 20 per cent of cells of each stage showed a positive reaction. Glycogen was observed in all stages of development with a rising concentration as maturation proceeded.—J. B. C.
ABSTRACTS


After transit doses of 500 rads 4 hours daily to blood circulated extracorporeally from nine patients with acute leukemia, peripheral leukemic cell counts decreased without change in bone marrow, but sometimes reticulocytes and platelets improved. In 3 chronic myelocytic leukemia patients, similar results were obtained. In two patients with chronic lymphocytic leukemia, peripheral lymphocyte numbers, but not glands, decreased. (Abstracter’s note: After thoracic duct drainage, glands but not lymphocyte counts decrease).—P. G. R.


The authors studied the action of a virilizing androgen, metenolone, in 63 cases of primary or secondary bone-marrow insufficiency. The drug was administered alone or with cortisone. Favorable results were noted in 50 per cent of the cases. Improvement bore first and foremost on the red cells; anemia was eliminated completely about two months after a reticulocyte outburst. Elimination of leukopenia and thrombopenia was even more tardy and variable. Several cases of complete elimination were noted, but some recurrences were ascertained after stopping either corticoids or metenolone. Clinical tolerance turned out to be relatively satisfactory. The most favorable results were obtained in idiopathic bone marrow insufficiency in children and during moderate chronic pancytopenia in women in pre- or post-menopausal periods. Very favorable results also were reached during chronic lymphoid leukemia complicated by bone marrow insufficiency.—J. C.

HEMOSTASIS


Patients with systemic poisoning due to the bite of the Malayan pit viper, Agkistrodon rhodostoma, always had incoagulable blood, but spontaneous bleeding was trivial. Venom administered intravenously caused defibrination with easily dispersed clots; it acted at the fibrinogen-fibrin level and did not affect other coagulation or hemostatic factors. Its action could be reversed by specific antivenom and it produced transient increase of fibrinolysis. The defibrinating fraction of the crude venom has been separated and called ‘Arvin’. It was suggested that the fibrinogen-fibrin reaction played little part in preventing spontaneous bleeding and that the pure defibrination induced by Arvin was a relatively benign state which may be useful for the short-term treatment of occlusive cardiovascular disease.—A. L. B.


Nine patients were treated for periods up to 15 days with intravenous Arvin, the coagulant fraction of the venom of the Malayan pit viper, in order to produce controlled defibrination. An urticarial reaction occurred once, but there were no other clinical complications. Abnormal bleeding did not occur even during menstruation. Rapid relief from signs and symptoms occurred in patients with venous thrombosis. Plasma fibrinogen fell rapidly within the first 10 hours and was maintained at less than 40 mg. per 100 ml. during treatment. Levels then rose slowly to reach normal values up to three weeks later. Transient anticoagulant activity appeared at first, and fibrinogen and fibrin split products were detected. Plasminogen levels fell, but other tests for increased fibrinolysis were negative. Platelet number and adhesiveness and other coagulation factors were not altered and routine blood counts were unchanged. Fragmented red cells were not seen.—A. L. B.

DEFIBRINATION SYNDROME IN AN INFANT BORN AFTER ABRUPTIO PLACENTA. J. R.

An infant born following labor complicated by abruptio placenta and maternal hypofibrinogenemia began bleeding from mouth, umbilicus and puncture sites at 10 hours of age. Coagulation studies revealed almost total deficiency of fibrinogen, prothrombin and Factor V, and a Factor X level of 20 per cent. Factor VII was reported as normal, Factors VIII and IX were significantly elevated. Despite fresh plasma infusion, she died within the day. The authors suggested that abruptio placenta or neonatal hypoxemia may lead to “hemorhagic disease of the newborn” which results from intravascular coagulation with resultant defibrination.—J. B. S.


A concentrated preparation of antihemophilic globulin of pig origin was used during an extremely serious peritoneal hemorrhage in the course of an appendectomy in a major hemophiliac. Efficiency of hemostasis was remarkable: the Factor VIII was maintained between 60 and 90 per cent. Nevertheless, a reversible episode of glomerulonephritis was noted towards the third week, but was cured without sequelae. Its heteroimmune origin seemed most probable. In fact, nephritis coincided with very high contents of anti-A and anti-B specific iso-antibodies, either complete or incomplete (the latter fixed on pig erythrocytes) and also of pig anterythrocyte antibodies. Thus, proteins of animal origin have determined heteroimmunization, the most conclusive serological translation of which was the appearance of high content anti-A and anti-B antibodies. These facts never constituted for the authors an obstacle to the use of animal antihemophilic fractions which, when appropriately used and reserved for very serious cases, represent a most precious acquisition in the treatment of hemophilia.—J. C.


Starch block electrophoresis of a Factor VIII inhibitor present in the serum of a hemophilic revealed the maximum activity in the region of fast and intermediate migrating gamma globulins. The inhibitor could be absorbed with anti-IgG and anti-kappa antisera. A moderate amount was also removed by anti-IgM antiserum. The in vivo activity of the inhibitor was temporarily depressed by the administration of large amounts of cryoprecipitate. Following this administration of Factor VIII, there was a sharp rise in inhibitor titer.—J. B. S.


The propositus was a 5½-year-old girl whose parents were first cousins. Clotting time was markedly prolonged (31 minutes by Lee-White). Dr. O. D. Ratnoff and Dr. J. P. Soulier confirmed that her plasma was deficient in Hageman factor (less than 1 per cent), whereas PTA activity was normal. Neither the proposita nor anyone else in the family has had any abnormal hemorrhagic symptoms. Family study revealed that this disorder was probably inherited as an autosomal recessive characteristic and that the consanguinity was responsible for the manifestation of the abnormality in the proposita.—K. F.


In newborns, the mean concentration of Factor XIII was 65 per cent with a range between 50 and 78. By one month, normal adult levels were achieved and these levels
were maintained through the age of 1 1/4 years. Factor XIII levels in a patient following administration of fresh frozen plasma (10 ml./Kg.), rose from 1 to 42 per cent. Assays indicated an in vivo half life of 6.3 days. Assays on plasma of the patient's parents and siblings revealed levels between 48 and 77 per cent.—J. B. S.


The hexose content of an abnormal fibrinogen was half that of the normal one, due to disappearance of D-galactose, although D-mannose was in the normal range, as was hexosamine. On the contrary, neuraminic acid was twice normal.—J. C.


In 7 of 25 rabbits sensitized with autologous platelets incubated and washed in quinidine solution, thrombocytopenia was produced by I.V. quinidine, while no significant changes in red and white cell counts were observed. Cinchonine, a dextrorotatory derivative of quinidine, could take the place of quinidine, while quinine and cinchonidine, levorotatory isomers of quinidine and cinchonine, respectively, could not. Platelet agglutinin (autologous and isologous) and complement fixing antibodies were present in sera obtained from some of the successfully sensitized rabbits. Isoantibody developed in the course of sensitization with autologous platelets modified with quinidine. Incomplete allergic antibodies were demonstrated by antiglobulin test on platelets and antiglobulin consumption test on platelets. These antibodies combined with platelets only in the presence of quinidine. —K. F.

STUDIES ON EXPERIMENTAL IMMUNE THROMBOCYTOPENIA V. SEROLOGICAL STUDIES ON THROMBOCYTOPENIA IN RABBITS INDUCED BY QUINIDINE WITH SPECIAL REFERENCE TO THE ROLE OF QUINIDINE IN THE IMMUNOLOGICAL REACTIONS. M. Okuma. From Faculty of Medicine, Kyoto University, Kyoto, Japan. Acta Haemat. Jap. 30:785–799, 1967.

If quinidine reacted with platelets and serum in the absence of complement and the platelets were washed in saline, both quinidine and serum factor were removed. The serum factor of sensitized rabbits remained attached to the platelets if the serum and platelets were incubated in the presence of quinidine and were washed, not in saline, but in quinidine solution. This platelet-quinidine-serum factor complex alone could fix complement. When the complex was analyzed against normal saline, quinidine could be removed from the complex and the serum factor was eluted from the platelets. Quinidine may have linked platelets to the serum factor. The serum factor thus separated was shown to be gamma-globulin by immunoelectrophoresis and fixed complement in the presence of quinidine and platelets. It must, therefore, be a complement fixing antibody. It was concluded that quinidine combined with platelets to form an antigen, and that when the quinidine molecule which acted as a hapten and supplied the determinant group was removed, the platelets were no longer antigenic and separated from the antibody. Thrombocytopenia observed after quinidine injection must result from lysis of the platelet-quinidine antigen by antibody and complement.—K. F.

STUDIES ON EXPERIMENTAL IMMUNE THROMBOCYTOPENIA VI. THROMBOCYTOPENIA IN RABBITS INDUCED BY ANTI-HUMAN PLATELET IMMUNE GUINEA PIG SERUM WITH SPECIAL REFERENCE TO ANTIGENS COMMON TO PLATELET OF DIFFERENT SPECIES OF ANIMALS. M. Okuma. From Faculty of Medicine, Kyoto University, Kyoto, Japan. Acta Haemat. Jap. 30:800–812, 1967.

Injection of anti-human platelet immune guinea pig sera produced thrombocytopenia which resembled that produced in rabbits by anti-rabbit platelet immune guinea pig sera. This observation suggested the presence of antigens common to human and rabbit platelets. Antigens of human platelets...
common to those of rabbit, porcine, bovine and guinea pig platelets, as well as species specific platelet antigens, were demonstrated by complement fixation. Anti-human platelet immune sera had titers of antibody against various platelets in the following order: man, rabbit, pig, cow and guinea pig.—K. F.


Hemostatic investigations on 4 females and 2 males with Von Willebrand’s disease, all six with bleeding manifestations, were reported. Bleeding time was prolonged in all, capillary resistance was poor in two, platelet counts were 300,000 to 500,000/mm³ and whole blood clotting time and one stage prothrombin time were normal. Prothrombin consumption was slightly abnormal in one case. Level of Factor VIII varied from 3 to 120 per cent. In two cases, platelets were normal in the TGT and ADP aggregation tests.—J. B. C.


Blood coagulation was studied before and after intrauterine application of radium for therapy of uterine carcinoma. The total dose was 8.4000 mgh. After gamma irradiation, decrease in platelet count with concomitant prolongation of bleeding time, increase of antithrombin activity, activation of fibrinolysis and prolongation of clotting time were observed.—M. K.

IMMUNO-HEMATOLOGY


These authors studied the behavior of lymphocytes of 14 patients with congenital sex linked and 3 patients with acquired agammaglobulinemia in tissue culture. In contrast to the findings of several previous investigators, the lymphocytes of the patients in this study were found to produce normal amounts of immunoglobulin G and were stimulated to proliferate by phytohemagglutinin and antigens. The discrepancy between their data and those of previous investigators may in part be due to the longer period of lymphocyte observation used in the present study. The authors concluded that the abnormality in congenital agammaglobulinemia does not appear in the peripheral blood lymphocyte.—I. G.


Seventy day survivals of heart allografts were obtained with the use of an antilymphocyte serum or the gamma globulins of this serum with good behavior of the grafted heart and of the dog. The antilymphocyte serum was specific for the lymphocytes and its local and general tolerance were good.—J. C.


When sensitized lymphocytes from animals manifesting delayed hypersensitivity are incubated in vitro with the sensitizing antigen, a material is released which is capable of inhibiting the migration of normal macrophages. The present paper further characterizes this material and indicates that it is a protein with a molecular weight of 67,000. Furthermore, injection of this material into the skin of normal guinea pigs produces a lesion with many of the gross and microscopic characteristics of a delayed reaction. The authors feel that many aspects of delayed hypersensitivity can be accounted for by the presence of such a material.—I. G.

Hyperimmune mouse isoantisera were prepared by injecting C57BL mice or A/SI1 mice with DBA/2 mastocytoma cells. Localization of these antisera on cell surfaces was studied by both direct and indirect immunofluorescent technics. H2-isoantigens were found in discrete areas on cell surfaces. The thymus lymphocytes of young mice were found to be deficient in isoantigenic content.—I. G.


Site Pg is supported by serum α- as well as β-lipoproteins. It reacts with some myeloma A immunoglobulins, giving positive passive hemagglutination tests and also precipitates in gels or in saline. These reactions are inhibited by very small amounts of the phospholipid-containing fraction of lipoprotein extracts and also by some purified phospholipids, specially by lysolcithin. Many other chemicals tested have little or no inhibitory effect.—J. C.

MISCELLANEOUS


Besides osteosarcomas, leukemias and oral tumors occur after Sr90. After 0.2 µc/Gm. body weight, none were seen, but half of the mice getting 1.6 µc/Gm. had carcinomas, most often in the hard part of the mandible and of the squamous cell type. None were found in the soft palate or tongue.—P. G. R.

THE COPPER SULFATE METHOD OF SCREENING FOR ANEMIA IN CHILDHOOD. E. Okorome and E. Charney. From the University of Rochester School of Medicine, Rochester, N. Y. J. Pediat. 72:384–387, 1968.

Comparison of microhematocrit and hemoglobin determinations with CuSO4 densitometry revealed equally good correlation between the CuSO4 method and the hemoglobin, and between the hematocrit and the hemoglobin. For screening hemoglobin levels below 10 Gm. per cent, a CuSO4 specific gravity of 1.046 was recommended.—I. B. S.


A case of myocardial infarction complicated by an atrioventricular block evolving in two phases led to death. This case was of interest as the coronary thrombosis was not due to atheroma but to polycythemia secondary to a renal carcinoma discovered at post mortem. The relationship between the three conditions was briefly discussed.—J. C.


A simple device was described to measure pH in 0.5 to 1 ml. fluid with an accuracy of ±0.1 pH unit, using ordinary glass and calomel electrodes supplied with commercial pH meters. The distal end of the KCl bridge connection of the calomel electrode was expanded into a cup coated with hard paraffin to reduce the space of the cup. This cup will accommodate the glass bulb, leaving a small empty space to be filled with test fluid.—J. B. C.