ERYTHROCYTES


A female patient, born in 1951, had suffered from anemia since the age of 12 yr. Examination of the blood showed occasional bi- and trinucleate erythroblasts and marrow examination showed erythroid hyperplasia and numerous abnormal multinucleate erythroblasts. The acidified serum test on the patient's red cells was positive with six of nine normal sera, but the sugar water and buffered sucrose tests were negative. Normal results were obtained from blood and marrow examination on the patient's parents and from blood examinations on four siblings. The case was considered to be one of congenital dyserythropoietic anemia type II.—A.A.M.

Hemolytic Anemia in Wilson's Disease (Hepatoleueticular Degeneration). B. Wilms K. G. Blume, and G. W. Lühr. Department of Medicine, University of Göttingen and Department of Medicine, University of Freiburg, Germany. Klin. Wochenschr. 50:995, 1972.

The authors report on four cases of Wilson's disease. Hemolytic anemia preceded the diagnosis of Wilson's disease, at times, for years. It is claimed that the premature destruction of red cells was caused by acute periodic increases of unbound copper in both plasma and red cells. The enzyme pyruvate kinase was inhibited by low copper concentrations, while fructose 1,6-di-phosphate was able to overcome this inhibition. The authors propose that the mechanism of hemolysis may be due to the inhibition of pyruvate kinase and other erythrocyte enzymes. Abstractor's comment: It is not proved that pyruvate kinase is inhibited by copper in vivo. More evidence can be obtained by estimation of glycolytic intermediates such as ATP, DPG and PEP. In case of an inhibition of pyruvate kinase by copper in vivo, DPG and PEP would be increased and the level of ATP decreased.—K.P.

It is well known that blood δ-aminolevulinic acid dehydrase activity may be reduced in subjects working with inorganic lead. The authors have studied the enzyme activity in a group of men exposed to tetraethyl lead and have demonstrated significantly lower levels than in a control group. Diethyl lead, a metabolic product of tetraethyl lead, had a similar effect when tested in vitro.

—J.A.W.


Injected δ-aminolevulinate and the δ-aminolevulinate synthetase inducers allylisoproplacetamide and phenobarbital had no effect on the concentration of hepatic mitochondrial cytochromes in male Sprague-Dawley rats although microsomal heme appeared increased indicating the formation of a free heme pool. Heme synthesis does not appear rate limiting for hepatic cytochrome synthesis in the rat.—J.A.W.


A Greek male presented with severe anemia at the age of 38 and thalassemia was diagnosed on the basis of high levels of Hb A<sub>2</sub> and Hb F. It was not possible to obtain genetic support for this diagnosis. Ninety-eight units of blood were transfused over 7 yr. In January 1969 oxymetholone was begun and over the ensuing 2 mo there was a marked reticulocytosis, up to 25%, and then a rise in hemoglobin level from 6 to 12 g/100 ml. The hemoglobin remained at this level for the next 18 mo without transfusion. The levels of Hb A<sub>2</sub> and Hb F returned to normal. The authors discuss possible mechanisms for this effect of oxymetholone.—A.A.M.


Erythropoietic activity and erythropoietic inhibition in the urine and plasma of 39 patients with iron deficiency anemia was measured by observing the mitotic activity of erythroid cells in bone marrow cultures in the presence of colchicine. By this technique, erythropoietin was detected in the plasma of 22 patients and inhibitors in the plasma of 12. In the urine, erythropoietin was detected in 13 cases and inhibitors in 14. Compared with normal subjects, patients with iron deficiency anemia showed erythropoietin less frequently and inhibitors more frequently. Fractionation of plasma indicated that the inhibitors were concentrated in the beta and gamma globulin fractions.—J.V.


The results of follow-up examination in 100 patients treated for peptic ulcer by partial gastrectomy by the Reicher-Poyla method in the period 1952–1963 are presented. In 51 cases the hemoglobin level was found to be reduced. The diagnosis of iron deficiency anemia was established in 38 patients and of vitamin B<sub>12</sub> deficiency in six. No correlation was observed between the Hb level, erythrocyte count, Fe and vitamin B<sub>12</sub> levels and the time interval between gastrectomy and examination.

—M.K.

Erythrocytosis Associated With Hemoglobin Malmö, Accompanied by Pulmonary Changes, Occurring in the Same Family. S. Berglund. Department of Internal Medicine, Malmö General Hospital, University of Lund, Malmö, Sweden. Scand. J. Haematol. 9:365, 1972.
Hb Malmö (987 (FG4) His → Gln) has increased affinity for oxygen. Separate genes seem to cause Hb and pulmonary changes. —P.G.R.


Study of erythrocyte biochemistry in 15 cases of hereditary elliptocytosis showed a constant and significant increase of GSH, both before and after incubation with APH, and an increase of G6PDH, NADPH-GR, HK, PFK, ENOL, and LDH activities. A slight decrease in ALD and ATPase was also observed. The raised values of many enzymatic activities may be a consequence of hyperhemolysis and thus the presence of a young erythrocyte population containing an increased concentration of enzymes. The normal but low values of ATPase and the ALD deficiency may be the result of structural alterations of the erythrocyte membrane.—K.P.

Altered Kinetic Property of Erythrocyte Phosphoribosylpyrophosphate Synthetase in Excessive Purine Production. O. Sperl- ing, P. Boer, S. Persky-Brosh, E. Kan- arek, and A. de Vries. Metabolic Unit, Department of Medicine D and Rogoff Wellcome Medical Research Institute, Tel-Aviv University Medical School, Beilinson Hospital, Petah Tikva, Israel. Rev. Europ. Etude Clin. Biol. XVII, 703, 1972.

A mutant phosphoribosylpyrophosphate synthetase was found in the erythrocytes of a subject with excessive purine production, not associated with hypoxanthine-guanine phosphoribosyltransferase deficiency. The mutant enzyme was characterized by an increased activity at low inorganic phosphate concentrations, while at saturated phosphate concentrations the activity was normal. In the patient’s erythrocytes the phosphoribosylpyrophosphate generation was increased. The enzyme mutation is implicated in the purine overproduction through increased cellular phosphoribosylpyrophosphate availability.—K.P.


A study of 169 frequently transfused Italian patients with thalassemia major has suggested a difference in survival between one group (10%) developing Australia antigen and a second group (20%) developing antibody to Australia antigen. Australia antigen was more common in males and patients less than 7-yr old and was associated with an earlier death than antibody to Australia antigen which was seen more frequently in females and patients over 7 yr old.—J.A.W.

LEUKOCYTES


Rats were challenged with injections, given by different routes, of Trichinella spiralis larvae, either as intact larvae, homogenate or saline extract. Increased eosinophil production followed only if local cellular response had been provoked. If the initial challenge did not result in eosinophilia, an augmented response occurred upon subsequent effective challenge.—J.M.B.


The present study was undertaken to define the cytochemical peculiarity and the genesis of giant granules observed in blood cells of mink with an “aa” homozygous recessive genetic type. The positive
reaction against peroxidase was not represented in low electron dense granules but only in high electron dense granules and the reaction against acid phosphatase was positive in all the granules and the limiting membrane. Rarely the crystalline inclusions were seen to originate from the giant granules. It was assumed that the giant granules were similar to secondary lysosomes built from the fusion of azurophilic granules and primary lysosomes into phagosomes and/or into autophagic vacuoles or from the fusion of azurophilic granules with each other. It was also postulated that the formation of giant granules might be concerned with the protein accumulated in the Golgi apparatus.—K.F.

Comparison of Isoenzymic Composition of Urinary Ribonucleases in Normal Subjects and in Patients With Chronic Granulocytic Leukemia. J. Naskalski. Department of Clinical Chemistry, Institute of Internal Medicine, School of Medicine, Kraków, Poland. Przegl. Lek. 29:295-301, 1972.

Urinary ribonucleases from normal subjects and from patients with chronic granulocytic leukemia (CGL) were separated by column chromatography on CM-Sephadex C-50. Three differing fractions were obtained: fraction I with optimal activity at pH 6.0, fraction II with optimal activity at pH 7.8-8.0 (alkaline RNase) and fraction III with optimal activity at pH 6.4-6.9. It was concluded that at least two different RNases are present in urine: alkaline RNase (pH 7.8-8.0) and RNase (or RNases) with optimum activity in acidic pH region. In urine of normal subjects fraction II was the most abundant fraction. The activity of this fraction represented about 70% of the total RNase activity of urine. The amount of fraction III in normal urine was negligible. Fraction I in urine of normal subjects was barely detectable after chromatographic separation. In urine of patients with CGL, fraction III was the most abundant, representing about 75% of the total urinary RNase activity. Fraction I emerged too as a distinct and separate component of urinary RNase. Thus, the increase in amount of fractions I and III with the pH optimum in acidic pH region constitutes the chief source of the observed increase of urinary RNase activity in patients with CGL. In remission, the content of fractions I and III in urine was about half of that observed in the period of full manifestation of the disease, but still remained at a level about five times higher than the content of these fractions in urine of normal subjects. In the period of myeloblastic crisis in CGL and in the urine of patients with acute myeloblastic leukemia the content of all RNase fractions was comparable to that observed in urine of normal subjects.—M.K.


Although cytogenetic studies of most patients with chronic lymphocytic leukemia have given negative results, abnormalities have been described in some cases. These include the familial presence of a deleted G-group chromosome (the Christchurch chromosome), and other forms of pseudodiploidy and an increase in random aneuploidy. This paper records the findings of 40 patients and discusses the value of cytogenetic studies in the diagnosis, prognosis, treatment and pathogenesis of this disorder. Conventional methods were used in the diagnosis and cytogenetic examinations were made by the usual technique. No abnormalities were detected in 10 patients, but the other 30 showed an increased aneuploidy. No aneuploid cell lines were detected and, although pseudodiploidy was noted in some metaphases, in none was there a persistent marker chromosome. Special attention was paid to the G-group chromosomes and no deletion was detected. No correlation was found between the degree of aneuploidy and survival.—J.E.U.


The normal evolution of adult osteomyelosclerosis is cachexia, more rarely acute myeloblastic transformation, but terminal cirrhosis is frequent. Three of 21 subjects

Thirteen patients with myelofibrosis were studied cytogenetically, using both unstimulated and PHA stimulated peripheral blood cultures. Abnormal lines were found in unstimulated cultures from two cases. In one patient, who had never received either radiotherapy or chemotherapy, a C group monosomy was found in the unstimulated culture and a normal karyotype in the PHA stimulated culture. In the second patient, who had previously received radiotherapy to the spleen, metaphases containing three extra C group chromosomes and one F-like marker chromosome were observed in unstimulated cultures whereas normal karyotypes were observed in stimulated cultures. The Ph1 chromosome was not detected in any patient. The results suggest a relationship between C group anomalies and myelofibrosis.—A.A.M.


Two sibs in an Icelandic family died of acute myeloid leukemia, one with myelofibrosis associated with acute leukemia and two remain alive with preleukemia. Both subjects with preleukemia have 47 chromosomes including an extra C group chromosome. All five sibs had the acquired Pelger-Huët anomaly of their granular leukocytes suggesting a cellular defect with autosomal dominant transmission. The propositus failed to produce normal numbers of monocyteid cells in a Rebuck skin window and his lymphocytes failed to transform after candida and PPD activation. Three family members had skin warts and the authors postulate that susceptibility to an oncogenic virus may have played a part in pathogenesis.—J.A.W.


The chlorhydrate of benzoyl hydrazine of daunorubicin (22050 R.P.) has been tried in 57 cases of acute lymphoblastic (ALL) or acute myeloblastic (AML) leukemia. In 24 cases of ALL, most of whom had been resistant to other drugs and were in relapse, 11 complete remissions were obtained after a median total dose of 20 mg/kg. In 32 cases of AML, 17 complete remissions were recorded after a median dose of 23 mg/kg. The 22050 R.P. appears to have a more progressive and prolonged action than daunorubicin, as shown by a slower regeneration of normal hematopoietic series and delayed occurrence of remission in some patients. Bone marrow hypoplasia and probably also cardiac toxicity were less frequent than with the parent compound.—J.M.P.


Five patients with chronic myelocytic leukemia had normal in vitro thymidine labeling and mitotic indices for myelocytes (13%–26%), but myeloblast indices (12%–19%) were low. In the blood, the myeloblast labeling indices were even lower. This pattern is reminiscent of what is seen in acute myelocytic leukemia.—P.G.R.

Rate of inactivation of cytosine arabinoside by deamination in human leukemic leukocytes as well as leukemic serum (plasma) was determined in patients with various types of leukemia and its possible relationship with the hematological effect of the agent was studied. Ara-C-3H (final conc.: 11 μg/ml) was incubated with 3 × 10^6/ml of leukocytes separated from peripheral blood or serum (plasma) of patients with leukemia. After removing the acid insoluble fraction, the neutralized supernatant was chromatographed with ara-C and uracil arabinoside (ara-U) as carriers in a solvent system of isopropanol, ethylacetate, and water (2:2:1). Radioactivity of ara-C and ara-U was determined in a liquid scintillation counter. Ara-C deaminase activity of CML leukocytes and serum (plasma) was generally higher than that of acute leukemia. A significant negative correlation was obtained between ara-C deaminase activity of leukemic cells and percent of immature cells. Serum ara-C deaminase activity in CML changed in parallel with the leukocyte counts of the peripheral blood. Serum ara-C deaminase of patients who had good hematological response to ara-C was significantly lower than in those who had not, suggesting that inactivation of ara-C to ara-U by leukemic serum and cells is one of the important factors related to the hematological effect of the agent. Deamination of the ara-C administered was considered to take place more moderately in plasma than in leukocytes because of the high content of ara-C phosphates and low content of ara-U in leukocytes and moderate concentration of ara-U in plasma (serum). Cytosine nucleosides and nucleotides inhibited the ara-C deaminase activity. Cytidine was shown to increase the hematological effects of ara-C by reducing the inactivation of the agent.—K.F.


Patients with chorioncarcinoma receiving methotrexate were randomized to a single intramuscular dose of nandrolone decanoate or oral oxymethalone for 28 days. During chemotherapy no protective effect on bone marrow suppression could be shown in either group, compared with a control group receiving no androgen therapy, but the time interval between lowest leukocyte count and return to pretreatment value was significantly shorter in patients receiving anabolic steroids.—J.A.W.


Cultures of blood and bone marrow (181) were taken from 98 patients with various forms of acute leukemia. Sixty-three patients proved to have bacteremia and of the organisms isolated, one-third were typical bacteria, while two-thirds showed atypicalities and were mostly L-forms. Isolation of L-forms was more frequent in patients with increased proportions of blast cells in the peripheral blood.—J.V.


In Hodgkin's disease, nodular sclerosis is perhaps as well defined a variant clinically as histologically. This form was noted in 32 of 132 lymphogranuloma patients and seemed to be more frequent in women (72%) and in the young (47%). It arose most commonly in the mediastinal nodes (56%) or cervico-supraclavicular nodes, and the disease was localized above the diaphragm in 70% of patients. Duration of this variant is longer than in the mixed cellular form and remissions were more prolonged after radiation therapy than after chemotherapy.—J.V.

ABSTRACTS


Chromosome studies of cells of the bone marrow and lymph nodes of patients with Hodgkin’s disease showed no remarkable chromosome anomalies, but disturbances such as heteroploidy and polyploidy were noted in the metaphases on direct preparations from lymph nodes.—J.V.

HEMOSTASIS


The authors studied platelet function in 11 patients with chronic ITP, most of whom had had a splenectomy and were in hematologic remission. Impaired platelet aggregation was found in these patients and was more severe in the four patients with incomplete hematologic remission than in the seven patients in complete remission.—H.J.W.


Massive staphylococcal contamination occurred in 3 of 162 platelet concentrates preserved for 1–5 days at room temperature, according to the method of Murphy et al. (Blood 35:549, 1970). This report confirms similar results obtained by Bucholz et al., New Engl. J. Med. 285:538, 1971.—J.M.B.


The author found that peritoneal leukocytes harvested from rabbits that received two spaced doses of endotoxin had significantly greater coagulant activity than leukocytes from control rabbits. The coagulant activity had the property of a tissue factor and could be reduced if polymyxin B was administered with the first dose of endotoxin.—H.J.W.


The authors isolated and purified a procoagulant enzyme in the venom of the eastern diamond-back rattlesnake (Crotalus adamanteus). The purified enzyme, similar to previous findings with the crude venom, acts directly on purified fibrinogen, does not activate the extrinsic system and is not inhibited by heparin. Dogs who received the enzyme by transfusion developed intense fibrinolysis. In vitro, however, the enzyme showed little fibrinolytic activity in clinically relevant concentrations.—H.J.W.


Study of a 62-yr-old male, with a 10-yr history of rheumatoid arthritis and recent onset of spontaneous bruising, revealed potent Factor VIII inhibitor. Immunosuppressive therapy with azathioprine resulted in improvement in the clinical state and disappearance of the inhibitor with a rise in Factor VIII levels from less than 1% to 35% and 50%.—J.M.B.

IMMUNOHEMATOLOGY


A 65-yr-old woman with splenomegaly, leukopenia, hemolytic anemia, and macro-
globulinemia, was shown to have a gross deficiency of lymphocytes cytotoxic to antibody coated target cells; the delayed hypersensitivity response to tuberculin, secondary antibody response to tetanus toxoid and the response to phytohemagglutinin were normal.—J.M.B.


Peripheral blood lymphocytes from normal subjects were stimulated by irradiated cultured lymphoid cells (normal and leukemic), whereas they were not so stimulated by irradiated nonlymphoid neoplastic cells. It is therefore postulated that factors other than HL-A incompatibility are involved in the mixed cell interaction.—J.M.B.


Positive delayed cutaneous sensitivity reactions to protein extracts of autologous Burkitt lymphoma cells were observed in 15 of 30 patients tested in clinical systemic remission and in only 1 of 16 patients tested with active extradural disease. Positive responding patients who eventually relapsed had significantly longer remission durations than did their negative responding counterparts. Seven patients with positive reactions were negative when retested in relapse. Positive reactions were not observed at extract protein concentrations of 0.1 mg/ml and were maximally evident at 1 mg/ml. Negative skin tests could not be attributed to generalized anergy because of the simultaneous observation of positive reactions to common antigens in over half the negative responders. Cutaneous reactivity to autologous tumor extract may serve as a sensitive test for extradural disease activity, and, because of its association with remission duration, suggests a role for the specifically sensitized lymphocyte in tumor regression and prognosis.—J.E.U.


Hemagglutination in A-anti-A and B-anti-B interactions varies with the nature of the solute in electrolyte and nonelectrolyte-containing media. If the nonelectrolyte solute species is closely related structurally to the terminal units of the immune determinant, highly specific inhibition of hemagglutination is observed.—J.M.B.


The half-life of IgG was determined in a patient with chronic hypergammaglobulinemic purpura and was found to be decreased; it is postulated that the elevation of serum IgG reflects increased production of the protein.—J.M.B.


Gel radial immunodiffusion was used to quantitate pathologic globulins in patients with Waldenström's disease and myeloma. Determination of levels outside the range of the standards used was unreliable and, even within this range, pathologic globulins tended to form greater precipitates than did normal globulins, leading to over estimation of the paraprotein levels. This technique, thus, should not be used for precise quantitation of abnormal globulins but may be used for the evaluation of changes in individual patients and for qualitative studies.—J.V.

This report presents the morphological details of the drug induced lipidosis caused by 4,4'diethylaminoethoxy hexestrol dihydrochloride. Under light microscopy most of the leukocytes had small vacuoles in their cytoplasm. The vacuoles in the neutrophils were smaller and more abundant than in the lymphocytes, plasma cells and monocytes. Eosinophils seldom showed a few vacuoles, but their specific granules were obviously irregular in shape and size. Foamy cells with or without deep blue granules were constantly found on examination of the bone marrow smears. Under phase contrast microscopy these vacuoles corresponded to dense, slightly refractile granules in the same distribution and size as in the smear preparation. Lipid was revealed in vacuoles of lymphocytes and foamy cells by histochemical procedures. On electron microscopy the vacuoles were dense and compact showing myelinated or periodical structures. Such granules in the neutrophiles were distorted, larger, and denser than the specific granules, and scarcely appeared in the younger stages of the cells. Lymphocytes had large granules or rather, inclusion bodies in which a myelinated structure was frequently observed. Monocytes also showed similar structures, but they were generally smaller than those of the lymphocytes. Basophils had a few small granules with myelinated structure, and their specific granules contained uniform particles. It was peculiar that the appearance of every inclusion body in plasma cells was definitely membraneous. Foamy cells contained many large vacuoles. Almost all these granules or inclusion bodies showed reaction deposits of acid phosphatase by the electron microscopic, cytochemical technique. It seems that the disorder can be called an “acquired lysosomal disease” in contrast with the inborn lysosomal disease of Hers.—K.F.

BOOK REVIEWS


The relatively new field of thrombo-hemorrhagic disorders, encompassing the extremes of hypocoagulable and thrombotic states, has a much broader scope of interest than that confronted by the traditional coagulationist. This first volume of Progress in Hemostasis and Thrombosis fulfills the need for up-to-date, scholarly reviews in this field. The choice of subjects is appropriately divided between basic molecular biochemistry and cellular physiology and applications to clinical problems, thus spanning the natural interests of both the researcher and the clinician. The articles contain the detailed data and extensive bibliographies essential to source articles, yet are highly readable and relevant. Stand-out chapters probably reflect only the individual’s subject preference, since all are written to a high standard of excellence. A particularly informative and fresh section is that by Nemerson on the extrinsic clotting pathways. This series will probably become a must for investigators and clinical hematologists, but the scope of the discussions will attract the interest of other specialties such as cardiology. It will also