ERYTHROCYTES


The peripheral red blood cells of six splenectomized and five nonsplenectomized patients with $\beta$-thalassaemia major were studied by electron microscopy. Intracellular changes were present particularly in late normoblasts and young reticulocytes, in all 11 patients examined and were more striking in splenectomized patients. Many cells were distorted with marked indentations of the cell membrane and irregular cytoplasmic projections which contained intracellular inclusions or organelles. Many cells showed large vacuoles containing residual organelles, mitochondria, iron and electron dense material. Other reticulocytes contained residual mitochondria showing degenerative changes and containing dense aggregations of hemosiderin. Intracellular iron occurred either as fine granular deposits or as dense coarse aggregates of ferritin. Glycogen accumulations were prominent in the cytoplasm of normoblasts and reticulocytes. The most striking finding (occurring in well over half the reticulocytes and almost all the normoblasts) was Heinz bodies at various stages of development and differing from those found in phenylhydrazine induced hemolysis, not being attached to cell membrane. The wide spectrum of ultrastructural changes found may be an expression of multiple intracellular defects involving the biosynthesis of globin, heme, glycoprotein and membranes in $\beta$-thalassemia.—J. A. W.

Transfusion-induced Decrease in Spleen Size in Thalassemia Major: Documentation by Radioisotopic Scan. R. T. O'Brien, H. A. Pearson, and

ABSTRACTS

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Among the advantages of maintaining the hemoglobin level above 10 g/100 ml in children with thalassemia major is a significant decrease in clinically evident splenomegaly, in this case, substantiated by radioisotopic scans. The author suggests that this reduction in spleen size is due primarily to lessened extramedullary erythropoiesis. — J.B.S.


A 72-yr-old woman with primary sideroblastic anemia showed no response to treatment with pyridoxine but had a reticulocyte response and a sustained improvement of her anemia following intramuscular pyridoxal-5-phosphate. The authors postulate a deficiency of the enzyme pyridoxal kinase required for the conversion of pyridoxine to its active form pyridoxal-5-phosphate and suggest that intramuscular pyridoxal-5-phosphate should be used in all cases of primary sideroblastic anemia not responsive to oral pyridoxine. — J.A.W.


Two men with extensive skeletal metastases of prostatic carcinoma had 8-8.6 g hgb/lOO ml, about 40 nucleated red cells/lOO WBC, hemolysis, and decreased 59 Fe incorporation into red cells. After sodium-phosphoestrol (Honvan) 500-1000 mg/day, the anemia improved considerably. — P.G.R.


Special blue fluorescent lamps with a narrow spectral emission, and peak output at 445 nm, were more effective than either "daylight" or standard blue lamps, in reversing hyperbilirubinemia. In this paper, as well as in a brief report in the same issue, by S. Yasrunaga and E. H. Kean (pp. 89-90), it is clear that the plexiglas hoods of incubators do not interfere with photooxidation of bilirubin. — J.B.S.


At 12 hr of age, 3 hr after an initial exchange transfusion for Rh-erythroblastosis this infant became febrile and manifested lethargy, anorexia, and abdominal distension. At 46 hr, flat plate of the abdomen revealed a pneumoperitoneum, and laparotomy revealed a small cecal perforation. Post surgery, his serum bilirubin rose to 26.5 mg/100 ml, but repeated exchange was not done. Unhappily he developed severe kernicterus. The authors review the previously reported cases of intestinal perforation following exchange transfusion, and speculate on the etiology, which remains a mystery. — J.B.S.


Studies of bone marrow and blood using in vitro H3 thymidine culture, and routine hematologic methods, were conducted in 20 patients with polycythemia vera. A definite reduction in erythroid precursors synthesizing DNA and participating in cell division was noted. It is suggested that there is a prolongation of the synthetic period in erythroid cells in this disease. — J.V.


Unsaturated vitamin B12-binding capacities of transcobalamin "large" (TC L) and that of transcobalamin "small" (TC S) were determined in fractions separated by gel filtration. TC L bound 57 ± 37 pg B12/ml EDTA-plasma, TC S bound 980 ± 257 pg/ml. When left standing in the serum or in heparinized plasma leukocytes released TC L. — P.G.R.

Determination of Iron Absorption from the Whole Diet. A New Two-Pool Model Using Two Radio-
ABSTRACTS


Only 1.5%-2.5% of inorganic 59Fe added to maize, wheat, wheat bran, eggs, and soy beans were absorbed, and similar percentages were absorbed with biosynthetically labeled foods. Of white flour iron, 27%-29% was absorbed. From a minced average Swedish diet (homogeneous paste) 2.6%–14.8% of nonheme, and 6.7%-12.2% of heme iron was absorbed. Abstractor's comment: In the present study, more iron (80%) was in the form of heme than in the normal diet (20%), and heme iron absorption was, therefore, a little lower than in a recent study of Layrisse.—J.B.S.


Human transferrin has 83,000 molecular weight, and binds 2 molecules of iron per molecule. Amino acid composition was also studied as were some animal transferrins.—P.G.R.


Iron deficiency in infancy is known to be associated with loss of red cells and plasma proteins into the gastrointestinal tract. In this study, evidence collected suggests that the cause of the exudative enteropathy is the ingestion of fresh cow's milk. The abnormal albumin turnover seen in iron-deficient infants approached normal when evaporated milk was substituted for fresh cow's milk, and returned to normal, if soybean formula was given. The improvement was within 2 days. No such improvement was seen if cow's milk was continued, despite a substantial injection of iron dextran. Although not all iron-deficient infants demonstrated a rapid albumin turnover, most demonstrated melena, and all those with rapid albumin turnover had antibodies to milk in their serum and stool water. It would appear that unheated cow's milk protein is antigenic and that the offending protein also causes an exudative enteropathy which may play a significant role in the development of iron deficiency in infants.—J.B.S.

Subnormal catalase and glutathione peroxidase activity was found in the red cells of iron-deficient children, as was decreased serum vitamin E concentration. Increased susceptibility to oxidant hemolysis, induced by H₂O₂, was also noted but the tendency to hemolysis could not be correlated with severity of anemia, the serum vitamin E level, or the activity of erythrocyte catalase or GSH-P. The authors conclude that the impaired enzymatic mechanism for detoxifying H₂O₂ is probably not the cause of the susceptibility to oxidant-induced hemolysis seen in iron deficiency anemia.—J.B.S.


Four girls with iron deficiency anemia consumed between four and ten glasses of ice per day. In each instance, the pagophagia disappeared during oral iron therapy, before the
anemia was cured. Abstracter's comment: Regression of pica associated with iron deficiency anemia, shortly after institution of the iron therapy, is quite frequent in my experience.—J.B.S.


Author studied various clinical signs of hemolysis. Simultaneous total body heme estimates by the alveolar CO-technique were strongly correlated with those obtained with $^{51}$Cr-labeled red cells, but when the total hemoglobin increased, so did the $^{51}$Cr-CO difference. Author suggests effect of 2,3 di-phosphoglycerate on heme CO affinity as cx-difference. In iron deficiency anemia, subjective symptoms were correlated with red cell turnover, but was also influenced by respiratory function and heme oxygen. Plasma lactic dehydrogenase, but in pernicious anemia both (CO method) and plasma masses in the spleen of 73 splenomegaly patients, who had median red cell $^{51}$Cr-T 22 to 23 days as compared to the normal 27 days. The total plasma volumes were increased in 14 of 18 patients studied. The spleen contained 10%-30% of all red cells, as compared to the normal 3%. Only 1/3 of autoimmune hemolytic anemias benefited from splenectomy. Twenty-six of 31 anemia patients (particularly with IgA or IgG non-complement-fixing-antibodies) had a mean $^{51}$Cr-red cell-T 1/3 of less than 22 days. Thirty of 31 sequestered red cells in their spleens (mainly after prednisone) and 15 of 31 in their livers.—P.G.R.


Radiosensitivity of extramedullary hemopoiesis of tench (Tinca vulgaris, Fleming) was studied at 10°C and at 18°C. The LD 50/30 was found to be 1200 rads at 18°C and 55,000 rads at 10°C. About 1100 rads reduced red-cell values and $^{59}$Fe incorporation into erythrocytes 50% at 18°C. At 10°C these values were not influenced by doses up to 55,000 rads. At 18°C leukocytes were depressed to 50% with about 100 rads. At 10°C about 16,000 rads were needed for the same effect.—P.G.R.


Using autotransfusion of blood labeled in vitro with $^3$H-disopropylfluorophosphat followed by autoradiographs of leukocyte concentrates these authors studied the fate of the monocyte population in eight normal subjects and 27 patients. Total blood monocyte pool (TBMP) was calculated from the dilution of labeled cells, the count of labeled monocytes in the infusion fluid, and the monocyte labeling index in circulating blood 5 min after com-
pletion of autotransfusion. Circulating monocyte pool (CMP) was calculated from the blood volume and the mean monocyte count. TBMP was larger than CMP and the existence of a marginal monocyte pool (MMP) was postulated (TBMP—CMP). In normal subjects CMP:MMP ratio averaged 1:3.5. Moderate deviations occurred in disease states. Monocytes left the vascular system at an exponential rate (mean T½ = 8.4 hr). T½ was prolonged up to 15 hr in patients with monocytosis and shortened in one patient with acute infection (4.0 hr) and in another with gross splenomegaly (3.5 hr). Monocyte turnover rate (MTR) was $7 \times 10^6$ monocytes/hr/kg in normal subjects. Highly significant positive correlations were evaluated between blood monocyte count and TBMP or MTR, respectively.—J.A.W.


Included in this paper is a review of 18 patients who were splenectomized following a first drug induced remission (hydroxyurea) of chronic myeloid leukemia. They are compared with 25 patients who refused operation after explanation, but who were otherwise similarly treated. The cumulative duration of survival was 51 mo (mean) in the splenectomized group and 43 mo (mean) in the nonsplenectomized group. A controlled trial of splenectomy would appear ethical and needed.—J.A.W.


Neither the results of serologic tests nor of attempts at EB-virus (EBV) culture indicated any likely etiologic relationships between the EBV and childhood acute lymphocytic leukemia. Perhaps the most interesting finding was the appearance in two children in remission of clinical evidence of infectious mononucleosis, accompanied by serologic and cell culture evidence of primary EBV infection.—J.B.S.


A 1-yr-old girl with trisomy 21 developed acute myeloblastic leukemia with unusual myeloproliferative aspects, including peripheral blood normoblastosis and megakaryocytosis. Postmortem examination revealed numerous mitoses, along with immature myeloid and erythroid cells.—J.B.S.


During the years 1964–1968, 99 children with acute leukemia of 18 mo average duration, had an average of three hospitalizations totaling 4 wk. Thus, this group of patients with all types of acute leukemia, treated with a variety of therapies, spent only 4.5% of their time in the hospital.—J.B.S.


Phagocytosis by the neutrophils of juvenile diabetics was found to be normal; however, chemotaxis by their PMNs was subnormal and the plasma of these patients failed to elicit normal chemotaxis in the presence of albumin-anti-albumin, or Staphylococcus albus. Insulin administration did not reverse this defect. The
The authors suggest that previous studies indicating that phagocytosis is subnormal in diabetes may have misinterpreted the effect of chemotaxis upon such assays.—J.B.S.


This study of peripheral blood and bone marrow from patients with acute leukemia was designed to test the capacity of immature cells to divide. By the use of such techniques as in vitro culture (with 3H-thymidine), radioautography and cytochemistry, cell division could be demonstrated among these cells especially in acute reticulo, myeloblastic and myelomonocytic leukemias; even “dormant” blast cells could be shown to participate in the cellular cycle in vitro.—J.V.


Blood coagulation, studied in 43 acute leukemia patients (17 myeloblastic, 23 lymphoblastic, and 3 histiomonoblastic) showed abnormalities, hypocoagulation being significantly most common in the myeloblastic form. Hypocoagulation was revealed by reduction of platelets, decreased prothrombin utilization, altered clot retraction, decreased plasma heparin tolerance, thromboelastographic changes, and altered formation of the fibrin clot. These deficiencies appear to be largely due to inadequate platelet coagulation factor both quantitatively and qualitatively, and are related to depression of platelet formation which, like the hemorrhagic complications, is more common in the myeloblastic form of the disease.—J.V.


Severe diabetic ketoacidosis developed quite rapidly in an 11-yr-old leukemic girl who was receiving both prednisone and L-asparaginase. Insulin therapy was required for about 3 wk. The authors suggest that L-asparaginase may either inhibit insulin synthesis by depleting L-asparagine, a constituent of insulin, or may denature preformed insulin.—J.B.S.


Rats injected intravenously with daunorubicin, 25 mg/kg, were killed 1-5 days after injection. No changes in the myocardium were seen by light microscopy, but in electron micrographs there were early changes in or near the mitochondria (membranous whorls) and later more severe degeneration in the mitochondria was associated with swelling of the capillary endothelium. Changes were most marked in the ventricular myocardium; they may partly explain the cardiotoxicity of rubidomycin in leukemia patients.—F.W.G.


The medical records of 494 patients who underwent splenectomy, including 269 patients with lymphoma, were analyzed for the occurrence of postsplenectomy bacteremia. Twenty-three episodes of bacteremia were identified among patients in the nonlymphoma group, and 12 episodes in the lymphoma group. Five cases of pneumococcal bacteremia were identified, and all occurred in patients with lymphoma. The fatality rate did not differ among patients with or without lymphoma in whom bacteremia developed after splenectomy. The findings do not indicate that splenectomy alters the fatality rate in patients with serious associated disease in whom bacteremia subsequently develops.—J.E.U.


An assessment has been made of the potential value of 67Ga citrate scanning in the management of Hodgkin’s disease, based on 54 scans carried out on 50 patients, investigating 216 potential areas of involvement. Uptake was de-

Cases with extranodal Hodgkin’s disease located in sites outside those defined as lymphatic structure are quite rare. Even rarer are cases with disease completely limited to those extranodal sites. The exact incidence of this localized form of Hodgkin’s disease is unknown, but it is estimated to be one-fourth of 1%, of the overall incidence of Hodgkin’s disease. World literature was reviewed for well-documented cases of localized, primary extranodal Hodgkin’s disease, to define its prognosis. Localized primary extranodal Hodgkin’s disease seems to have an excellent prognosis in some cases, including skin, tongue, lung, stomach, small bowel, and thyroid. Data are insufficient for specific conclusions about most other areas of localized Hodgkin’s disease. Hodgkin’s disease can arise and may be localized in surprisingly diverse sites and may well be related to small foci of lymphatic tissue within these extralymphatic organs that undergo malignant transformation. — J. E. U.


Five-year survival in 45 Hodgkin’s patients given radio- and chemotherapy was 47% (57% for stage I-II, 20% for III-IV). — P. G. R.


3H-thymidine labeling (13%, 23%) of myeloblasts in five CML patients was normal, but CML myeloblasts had a low labeling index (12%, 19%). Mitotic indices were 0.4%, 1.5%, and 0.6%, 1.9%, respectively, as compared to normal 2.5%. Based on vincristine stathmokinetic indices, mitotic times of 0.8 1.9 hr were calculated for myeloblasts, 1.0 8.4 hr for basophilic erythroblasts. The corresponding DNA-synthesis times were 9-20, 15-182, and 19 hr. An increased production of myeloblasts is suggested in CML. — P. G. R.


A double Ph1-chromosome was found during a blast crisis in a CML patient. — P. G. R.

HEMOSTASIS


The fibrinolytic system was studied in 16 patients with primary biliary cirrhosis and ten patients with large bile duct obstruction (nine carcinomas). Plasma plasminogen activator activity determined by measuring euglobulin lysis time and fibrin plate lysis was decreased and fibrinogen was increased in both groups particularly in those with large duct obstruction and the changes in both groups were related to the degree of cholestasis. Fibrinogen degradation products (asayed on microtiter plates by a modification of the tanned red cell hemagglutination inhibition technique) were normal in primary biliary cirrhosis and moderately increased in large duct obstruction. Antiplasmins were increased in patients with large duct obstruction and urokinase inhibitors were decreased in both groups. None of these indices was related to the degree of cholestasis. Fibrinolytic activity and fibrinogen returned...
almost to normal levels after palliative surgery in three patients with large duct obstruction.—J.A.W.


In a series of experiments on dogs and rabbits given massive transfusions of incompatible blood, disseminated microthrombosis, connective tissue changes, and degenerative changes in parenchymal cells were noted in the organs and a sustained impairment of renal function occurred. When an intravenous injection of fibrinolysin with heparin was given within 24 hr of the incompatible transfusion, restoration of the structure and parenchymal changes of the organs took place with rapid, complete and stable resumption of renal function. It is suggested that there is, within the interstitial connective tissue, a coagulation system similar to that of the blood, disturbance of which is responsible for these organ changes. The introduction of fibrinolysin into the disturbed cytohisto-hemocoagulation system prevents the development of serious tissue changes.—J.V.


Thromboelastographic measurements were made in 35 patients with acute leukemia and revealed plasma hypocoagulation and whole blood hypercoagulation, thus suggesting an association between formed elements and thromboplastic activity. Further studies showed that while leukocytes could accelerate plasma coagulation, red cells did not. The authors consider that blast elements possess considerable thromboplastic effect but such cells, however, could not correct a variety of coagulation deficiencies and no correlation was detected between the number of leukocytes, the degree of hypercoagulation or the severity of the associated hemorrhagic syndrome.—J.V.


$^{51}$Cr labeled platelets had a mean T½ of 3.1 ± 0.5 (SD) days in polycythemia vera (PCV) as compared to normal 3.9 ± 0.5 days. Platelet production rates were 1.6 and 0.2 × 10¹² per day, respectively, and values of body platelet mass were 7.7 and 1.4 × 10¹². PCV patients had 85 and controls 19 megakaryocytes per μl of bone marrow, and the PCV megakaryocytes had a surface of 431 μm² as compared to the normal 296 μm². Abstracter’s comment: The originally Swedish observation that PCV marrow sections show many large megakaryocytes is now being better documented and quantified. It has a great practical diagnostic value.—P.G.R.

IMMUNOHEMATOLOGY


Circulating peripheral blood lymphocytes from Balb/c mice were studied in animals receiving pertussis vaccine, and in a control group. Peripheral blood cells, spleen and thymus cells were studied in the two groups. Cells were tested for PHA response in vitro and for ability to induce GvH reaction. Pertussis-treated cells showed enhanced PHA responsiveness, without increased GvH reactivity. Pertussis-treated nucleated spleen cells showed no increased response to PHA, and slight increase in GvH reactivity. The authors conclude that the pertussis-treated spleen is not immunologically depleted, and that effects of pertussis vaccine may include redistribution and possibly cell multiplication.—P.F.


Acute hemolytic anemia with positive Donath-Landsteiner test, and positive direct antiglobulin test using nongamma antiserum was seen in two young children. The tests for syphilis were negative. The DL antibody was an IgG with a broad thermal amplitude, active only against Tfα-positive red cells. In both
patients the disease was self-limited, lasting about a month. — J. B. S.


A 1-wk-old boy developed streptococcal pyoderma. At 2 wk of age leukocyte count was 12,000/cu mm; however, no neutrophils were seen in peripheral blood smears, and the bone marrow examination revealed myeloid maturation arrest at the myelocyte level. A leukoagglutinin was demonstrated in the mother's and infant's serum which reacted with paternal leukocytes. Using fluorescein-labeled anti-IgG, fluorescence of bone marrow neutrophilic precursors was demonstrated. During the third week neutrophils began to appear in the peripheral blood and by 6 wk the differential count was normal. — J. B. S.


Thirty-three patients with Hodgkin's disease were studied. The cases were grouped according to the histopathological picture: ten, lymphocytic predominance; seven, nodular sclerosis, eight, mixed cellularity; eight, lymphocytic depletion. The clinical staging was the following: Stage I, four cases; stage II, six cases; stage III, ten cases; stage IV, 13 cases. Fifteen of these 33 patients were staged surgically. The cases were also grouped considering the immunological capacity: lymphocyte counts and lymphocytic function, delayed hypersensitivity, and PHA-induced lymphocytic transformation, as well as serum globulin levels. Each one of these findings was correlated to the EB-virus antibody titers, as obtained by immunofluorescence technique with Jijoye cells. The titers were also correlated with the pro-

MISCELLANEOUS


A self-teaching audiotype slide system was used to provide programmed instruction for the second-year Harvard Medical students following their basic hematology course. A self-learning system for anemia was developed, which included basic workup, correlated pathophysiology, and case solving problems. — P. F.


The biological decay of 51Cr-labeled sheep red cells, injected intraperitoneally into mice, was determined by repeated total body counts, measurement of urinary and fecal excretion of 51Cr and radioassay of liver, spleen, and carcass. Elimination of the radiolabel was most rapid (25% of initial total body count) during the first 24 hr after injection. By the 12th day after injection, the decay stabilized at a rate of 0.5% to 1% total body count per day. Selective localization of radiolabel was found in liver, spleen, and peritoneal lining. Hepatic and splenic uptakes of the radiolabel, expressed as percentages of the final total body count, remained stable from 1 to 60 days after injection. Radioactivity did not localize selectively in liver and spleen after intraperitoneal injection of hemolyzed 51Cr-labeled sheep red cells or inorganic Na2Cr51O4. These observations confirm the usefulness of administration of Cr-51-labeled sheep red cells for testing reticuloendothelial phagocytic activity. — B. R.

Two effects of administration of lipopolysaccharide (LPS) to C57BL mice were studied: (1) changes in levels of plasma hemopexin (hpx) and (2) phagocytic uptake in liver and spleen of $^{51}$Cr-labeled sheep red cells (SRC). Levels of hpx were markedly elevated 24 hr after injection of LPS and returned to normal values 2 wk later. Hepatic phagocytosis of SRC was significantly impaired between 2 to 7 days after LPS treatment, while after 2 wk normal function was recovered. Splenic phagocytosis was less markedly affected. There was a significant increase of splenic weight from two to seven days after LPS injection, whereas hepatic weights were unchanged. The possible relationship between elevation of hpx and interference with phagocytic function resulting from administration of LPS is considered and the findings are discussed within the framework of previous investigations of the interactions of LPS with the reticuloendothelial system.—B.R.

CORRESPONDENCE

To the Editor:

In a recent article, Tisman and Herbert 1 reported that bone marrow cells from patients with untreated pernicious anemia show defective uptake of 5-methyltetrahydrofolate (methylfolate) and that this can be corrected by the in vitro addition of vitamin B12. In this paper, a previous study by Das and Hoffbrand 2 was mentioned in which uptake of methylfolate by vitamin B12-deficient PHA-stimulated lymphocytes was found to be defective. Tisman and Herbert considered these previous studies to be invalid, however, because of an apparent discrepancy of 250 times between the uptake of folic acid and of methylfolate by normal PHA-transformed lymphocytes. After correspondence between us, however, it has become clear that this discrepancy did not exist but appeared to be so because of the far greater quantity of methylfolate than of folic acid put into the lymphocyte cultures by Das and Hoffbrand (because of the low specific activity of the methylfolate available to them). Thus, the results of Das and Hoffbrand suggesting defective uptake of methylfolate by vitamin B12-deficient cells remain valid. The present experiments of Tisman and Herbert 1 confirm these results using physiological rather than supra-physiological amounts of methylfolate, using bone marrow cells instead of lymphocytes, and also extend the observations by showing that defective uptake of methylfolate by vitamin B12-deficient cells can be reversed in vitro by addition of vitamin B12.

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