ERYTHROCYTES

Ferritin Metabolism in Reticulated-Siderocytes. A. Deiss and G. E. Cartwright. From the Department of Medicine, University of Utah, College of Medicine, Salt Lake City, Utah 84112. J. Clin. Invest. 49:517-523, 1970.

During rapid regeneration of blood, reticulocytes contain Prussian blue positive material that consists of cytoplasmic aggregates of ferritin. By contrast, nonreticulated siderocytes contain nonferritin iron in mitochondria. When reticulated siderocytes obtained from pigs after vigorous phlebotomy were incubated in vitro, the ferritin iron rapidly disappeared from reticulocytes over 24 hours as siderotic granules appeared in monocytes and ferritin accumulated in the media. This reticulocyte to plasma to monocyte ferritin pathway seems a morphologic demonstration of the labile iron pool described by Pollycove in his model for movement of radioiron in the body.—R.O.W.


Conflicting reports have appeared about the role that the nonheme iron in the intestinal mucosa plays in controlling iron absorption. It has been suggested that the iron content of the intestinal mucosa is responsible for controlling iron absorption. Other data failed to confirm an inverse correlation between intestinal mucosal iron content and iron absorption in rats and men. In these experiments, the authors bled guinea pigs and produced a sixfold increase in iron absorption. The nonheme iron content of mucosal homogenates obtained from these bled animals was virtually identical with the iron content of mucosal homogenates from iron-loaded animals. Differences between these observations in the guinea pigs are probably due to the type of feed given to the animals.
pig and observations cited for the rat might perhaps be attributed to differences in methodology or be due to species differences. It is suggested however, that the iron content of intestinal mucosa cannot be assigned a regulatory role in iron absorption.

—M.C.V.


When protohematin reacts with alkali denatured α-chymotrypsin, trypsin or ovalbumin in a solution containing an excess of protein, the progressive reduction of the ferrihemochrome to the ferrocompounds can be spectrophotometrically detected. The minimal protein : hematin molar ratio necessary to induce the reduction of α-chymotrypsin ferrihemochrome is 10:1. The ferrocompounds of trypsin appear to be less readily reduced (this protein seems to be rather sensitive to desintegration by alkali) and even slower is the formation of the ferrohemochrome of egg albumin (more resistant to alkali denaturation). The three proteins, subjected to alkali degradation in anaerobic conditions, liberate free SH groups. The fact that their ferrihemochromes are transformed into ferro compounds when treated with Na₂S in amounts equivalent to the thiol groups present in the denatured proteins, suggests the role of sulfhydryl groups in the reduction of the ferrichromes, when an excess of the corresponding protein prevails.—E.S.


Glutathione reduction was investigated using the azoester test of Kosower. Addition of methylphenylazoformiate caused quick oxidation of GSH in washed erythrocytes. Addition of glucose leads to reduction of glutathione. The azoester produced no inhibition of glycolytic and glutathione reducing enzymes. The ATP-content of the cells did not decrease. In erythrocytes with a G-6-PD deficiency the velocity in glutathione reduction was diminished. The glutathione reduction in the Kosower test was not decreased in glutathione reductase deficient cells. The authors suggest that the rate-limiting enzyme reaction in glutathione reduction seems to be G-6-PD.—M.C.V.


With hyperactivity of the pentose phosphate shunt in erythrocytes after methylene blue treatment, the authors found an electrophoretic doubling of red cell G-6-PD band.—J.C.


By electrophoretic studies, the authors found in rabbit erythrocytes two types of aldolase, an A type as the one in muscle, and a C type as the one in the brain.—J.C.


A study was made of glycolysis and some membrane abnormalities in the red cells of six patients with hemoglobin H disease. GSH values for whole blood were low or subnormal. No instability of GSH could be demonstrated by short-term incubation with acetylphenylhydrazine. HMP activity was increased in the red cells of all patients. Anaerobic glycolysis was also increased, but the levels of red cell ATP were low. The values of red cell phospholipid were abnor-
mally high. Further evidence of membrane abnormalities was obtained from changes in membrane AChE-activity. These results are discussed.—M.C.V.


Successful treatment of megaloblastic anemia with uridine in a boy with hereditary orotic aciduria, is described. On a dosage of 150 mg. per Kg., uridine-induced remission was maintained for almost seven years. Growth and general health have been normal, however intellectual development is moderately retarded. Substitution of uracil for uridine led to a prompt relapse, which responded quickly to reinstitution of the uridine therapy.—J.B.S.


Splenectomy performed in normal female albino rats was accompanied by mild anemia which recovered very slowly, persisting for 120 days. Splenectomized mice exposed to acute hypoxia showed a modest increase in erythropoiesis. Red cell counts due to chronic intermittent hypoxia were also lower than in nonsplenectomized animals.—E.S.

**Studies on the Effect of Phototherapy on Neonatal Hyperbilirubinemia Among Low-Birth-Weight Infants. I. Skin Color, II. Protein Binding Capacity.** S. O. Porto, R. S. Pildes and H. Goodman. From the Loyola University Hospital, Chicago, Ill. J. Pediat. 75:1045-1050, 1969.

Significantly lower serum bilirubin levels were seen after the second day among premature infants exposed to blue light during the first five days after birth, than in controls. The findings were the same in white and black infants, indicating that dark skin does not interfere with photo-oxidation of bilirubin. Among the treated babies, albumin binding capacity was greater than among the control infants who had higher levels of serum bilirubin. Thus, it appears to have been demonstrated again that the photo-oxidative derivatives of bilirubin are not significantly bound to albumin.—J.B.S.


Sickle cell disease is the most common chronic disease of Negro children yet, as pointed out by the authors, there is little public awareness of this condition, especially in comparison with other much less common diseases. The authors conducted a large scale survey among adult Negroes in Richmond, Va. Only 30.3 per cent of those interviewed indicated that they had ever heard of sickle cell anemia. Although the awareness of this disease increased markedly with the educational level, of those who had attended college, only 65.5 per cent indicated an awareness of this disease. *Abstractor’s comment:* The results of this survey indicate a widespread lack of knowledge about this economically important disease among the population at risk. Education of the population on the genetic implications of sickle cell trait must be preceded by a significant increase in public awareness of the existence of this disease. It appears to me that the medical community bears at least partial responsibility for such an educational program.—T.F.N.


The adrenal cortical function and reserve were determined and assessment of recent results of prednisone treatment was done in 10 cases of pernicious anemia. The activity of the adrenal cortex was, as a rule, normal. After several weeks of corticosteroid treatment the improvement in vitamin B12 58Co absorption continued for 2-3 months in nine
cases and for over 6 months in one case. This finding was observed in patients with or without antibodies against intrinsic factor in the serum.—S.R.H.


Two-hundred Gr. of synovial membrane removed from the knee of a patient with rheumatoid arthritis contained 50 mg. elemental iron. In 96 of 100 joints, the membrane contained more or less extensive deposits of iron in the form of ferritin. There was a highly significant correlation between the presence of anaemia and the degree of iron deposits. It is suggested that the synovial membrane in rheumatoid arthritis is an important site for iron sequestration consequent upon oozing of blood from granulation tissue into the synovial cavity. Some of the deposits may be derived from parenterally administered iron.—F.W.G.

LEUKOCYTES


The authors studied the effects of hydrocortisone on lysosomal enzyme production and morphology of mouse peritoneal macrophages in vitro. Pinocytosis was not influenced by the hormone. However, hormone-treated macrophages were smaller and rounder than the untreated cells, and showed a marked diminution in dendrite-like cytoplasmic prolongations. Hydrocortisone retarded the rise in intracellular cathepsin and acid phosphatase activity which occurred in differentiating control macrophages. The lower levels might be due to reduced synthesis of enzyme, hydrocortisone-induced inhibition of enzyme activity, or augmentation of release of hydrolases into the medium. The experiments detailed here provided evidence for reduction in enzyme synthesis or accelerated breakdown of enzyme as the explanation for reduced activity levels. The mechanism by which hydrocortisone effects lysosomal enzyme synthesis appears to be independent of the pinocytotic mechanism.—P.F.


Neutrophils were found to be the source of a substance which inhibits migration of (guinea pig) macrophages in vitro. The inhibitory factor (from guinea pig and human white blood cells) was stable at 56°C for 30 minutes, dialyzable, and could be eluted from Sephadex G50 in a position which indicated a molecular weight of about 4000. Supernatants from purified human lymphocyte suspensions did not show macrophage migration inhibition. The authors suggest that the migration inhibitory factor may play a role in the development of chronic inflammatory reactions.—P.F.


This very important paper describes the results of experiments in which a myeloperoxidase-halide-peroxide system was tested against polio and vaccinia virus. The authors found that the infectivity of polio virus was reduced by 10,000-fold in titer (measured by plaque assay or cytopathic effect). Similar effects were observed against vaccinia virus. Peroxidase-mediated systems may provide a potent virucidal mechanism in leukocytes and in extracellular fluids in which system components are present.—P.F.


Interferon production was quantitatively determined in human leukocytes from subjects from 16 weeks of fetal life to adulthood. The range of production of interferon varied over a relatively wide range in subjects of all ages. No consistent trend in quantitative production of interferon could be defined with advancing age. Factors other than lack of interferon production may be important in explaining severity of some viral infections in the very young age group. The absence of circulating leukocytes in
significant numbers prior to the 12th gestational week may be an important factor in fetal viral infections such as rubella.

-P.F.

**CHROMOSOME PATTERN OF BONE MARROW FIBROBLASTS IN PATIENTS WITH CHRONIC GRANULOCYTIC LEUKAEMIA. A. K. Maniatis, S. Ansel, W. J. Mitus, and N. Coleman.** From Blood Research Laboratory, New England Medical Center Hospitals and Department of Medicine, Tufts University School of Medicine, Boston, Mass. Nature (London), 222:1278-1279, 1969.

Bone marrow was cultured from seven patients with Ph1 positive chronic granulocytic leukemia. After 10 days, cells adherent to glass and resembling fibroblasts were found to be Ph1 negative. This suggests that they were not derived from granulocytic, erythrocytic or megakaryocytic precursors. The insult leading to the formation of the Ph1 chromosome may occur at the level of the “hemocytoblast” rather than at that of the undifferentiated mesenchymal cell. The authors also speculate that the myelofibrosis accompanying chronic myeloid leukemia may be reactive rather than neoplastic.—A.L.B.


Genetic and immunologic factors in the pathogenesis of leukemia in man are reviewed. Hereditary and congenital evidence give support to the theory that some genes regulate liability to the disease. Although direct immunologic studies have not been conclusive, indirect evidence of an immune defense mechanism against leukemia is stressed by the authors.—J.C.

**THE NEED FOR CHEMOTHERAPY AFTER PROLONGED COMPLETE REMISSION IN ACUTE LEUKAEMIA OF CHILDHOOD. W. Krikit, G. Gilchrist and E. C. Beatty, Jr.** From the University of Minnesota Hospitals, Minneapolis, Minn. J. Pediat. 76:138-141, 1970.

Fifteen children with acute lymphatic or stem cell leukemia whose initial remission had been maintained for at least 2½ years were divided into two groups. One group continued on therapy; in the other group, therapy was discontinued. Two years later one patient from each group had relapsed, suggesting that after prolonged remission, maintenance therapy may not be necessary.—J.B.S.


Among the interesting observations in this group of patients were: the very frequent spread to contiguous lymph node groups; that solitary supraclavicular node enlargement suggests infradiaphragmatic disease; and the conversion to a negative Mantoux in 11 of 15 children previously vaccinated with BCG.—J.B.S.

**ACUTE TOXOPLASMOSIS COMPLICATING LEUKAEMIA. DIAGNOSIS BY BONE MARROW ASPIRATION. C. Abell and P. Holland.** From the University of Kentucky Medical Center, Louisville, Ken. Amer. J. Dis. Child. 118:782-787, 1969.

A febrile illness complicated by evidence of disseminated intravascular coagulation appeared in a child with acute leukemia who was in her sixth month of methotrexate remission. Bone marrow examination revealed the presence of toxoplasma gondii along with evidence of methotrexate toxicity. Therapy with sulfonamides and pyrimethamine was initiated and heparin plus fresh plasma were administered for the severe bleeding resulting from the coagulopathy. The child’s condition deteriorated, she developed Klebsiella meningitis and died 18 days after admission.—J.B.S.


Two patients manifested the typical clinical and pathological features of malignant
histiocytosis. Objective remissions of 3 months and 2 months, respectively, were induced by combination chemotherapy with vincristine and prednisone. The patients eventually died from complications of this rapidly progressive and uniformly fatal illness without significant prolongation of survival time. Combined chemotherapy may be useful for induction of remission in this disorder and suitable maintenance programs should be developed.—J.E.U.


In 31 cases the drug was given continuously: an initial dose of 85 µg./Kg./day until the white cells fell below 3000/cu. mm. and the platelets below 100,000 per cu. mm. and a maintenance dose of 50µg./Kg./day, then 50 to 85 µg./Kg./week. The following results were obtained: subjective improvement (46 per cent), fall in urinary proteins (37 per cent), fall in abnormal plasma protein level (35 per cent), improvement of anemia (18 per cent). Benefit was obtained in 21 of the 35 cases, but the improvement lasted for more than 6 months in only 11 patients. The authors compared this group with a nontreated control group (57 cases) and found a significant difference in survival rate. Abstractor's comment: The authors had done a very valuable study of the literature in order to consider the factors which could influence the therapeutic response to melphalan.—J.C.

HEMOSTASIS


A previously healthy boy suddenly developed abdominal pain, melena and spontaneous hemarthroses, associated with a fall in hemoglobin level to 5.6 Gm. per 100 ml. No history of exposure to drug or toxin could be elicited and no evidence for concomitant infections or malignant disease was found. Coagulation studies indicated a severe factor X deficiency with no in vitro evidence of inhibitor. Therapy with Vitamin K was ineffective, however clinical improvement was noted by the eighth day, and 2 weeks later coagulation studies were almost normal.—J.B.S.


After 6, 30 and 60 days of estro-progesteron treatment, three women suffered from thrombosis and embolism of moderate degree. Two of them had hypercholesterolemia and hyperlipemia. Abstractor's comment: Attention has recently been drawn on the high risk of thromboembolic episodes in subjects having an abnormal constitutional pattern of serum lipids.—J.C.


Three functional platelet diseases were compared by 10 different tests. The most significant alterations were connected with aggregation and factor 3 activity of the platelets. Platelet factor 3 availability decreased in congenital platelet disorders and in thrombocytopenia and showed alterations also in Von Willebrand's disease. The disturbances of in vivo adhesiveness and of aggregation of platelets were detected in most of the cases. Significance and sensitivity of the applied methods are discussed.—S.R.H.

ABSTRACTS

A virus suspension infused into rabbits produced a sharp and sustained drop of the platelet count. Survival of radioactively labeled platelets treated with virus prior to infusion was markedly shortened when live virus was used and was only slightly reduced with dead virus. It is concluded from these results that the interaction of influenza virus with human platelets is fundamentally the same as with human red cells and that the virus receptors on the platelets and RBC are probably identical in nature and location. Following inoculation of influenza vaccines or live measles vaccines, thrombocytopenia frequently occurred. The injection in rabbits of vaccines of influenza, encephalitis japonica and poliomyelitis anterior acuta induced a sharp decrease in platelets during the first 24 hours. Recovery occurred within 5 days. It seems therefore, apparent that influenza vaccines have a thrombocytopenic effect and that vaccines of live measles, encephalitis japonica and poliomyelitis anterior acuta may have a similar effect. Following infusion of influenza virus into rabbits, the serum levels of lactic dehydrogenase (LDH) and a-hydroxybutyric dehydrogenase (HBC) were markedly elevated within 1-4 hours. These enzymes were probably liberated from the platelets destroyed by the virus. Statistical studies on various viral infections of childhood revealed that thrombocytopenia below $10 \times 10^4$ per cu. mm frequently occurred in the case of exanthema subitum, rubella, mumps, chickenpox, measles, etc. It is suggested from these and other experiments that blood platelets may serve as carriers of viruses in the circulation and that in this process they may be in part destroyed. These results may explain the mechanism of the thrombocytopenia frequently observed during the acute, viremic phase of virus infections.—K.F.

IMMUNOHEMATOLOGY


The authors investigated the effects of crude pokeweed mitogen in intradermal injections in normal human volunteers. An initial granulocytic response was followed by lymphocytic infiltration, in which "blast-like" pyroninophilic cells were observed. Some of the cells were in mitosis. Tissue mast cells were also prominent. After 7-9 days, there was reduction in the cellularity of the infiltrates, with histiocytes and fibroblast-like cells present as well as lymphocytes. Intradermal injections of tuberculin provoked similar early responses, but during the later phases there was significant increase in histiocytic and fibroblast-like cells. Abstractor's comment: No plasmacytic reaction was described.—P.F.


The purpose of this presentation is to investigate the localization of antigens and antibodies in lymph nodes at various stages of an immune reaction, with special reference to the function of germinal centers. For the detection of antigen localization, two tracer antigens of different sorts were employed: (1) Fibrous bacteriophages 8A which were isolated and were proved by I. Watanabe et al. to be composed of DNA molecules into which $^{3}H$-thymidine was evenly incorporated; (2) horse radish peroxidase (HRP). These antigens were injected into the hind footpads of Wistar rats and ICR mice and their localization in the popliteal lymph nodes was visualized by means of autoradiography and enzyme histochemistry of peroxidase. For the demonstration of antibodies in lymph nodes, Wistar rats and albino rabbits were immunized with HRP. Thin frozen sections of their popliteal lymph nodes were incubated in the antigen (HRP) solution to produce the insoluble antigen-antibody precipitates at the sites of antibody localization, then the peroxidase activity of these precipitates was histochemically demonstrated. The primary sites of antigen localization were macrophages in the marginal and medullary sinuses and medullary cords. Unconjugated HRP with the complete Freund's adjuvant was most rapidly catabolized in those macrophages and cleared out of lymph nodes.
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Within 48 hours after inoculation, while $^3$H-4A phage and conjugated HRP still remained in the macrophages even at the fourth day, though the number of those macrophages was apparently diminished. At this stage (the fourth day), the grains of $^3$H-4A phages were located in closest relation to the nuclei of the mature and immature plasma cells and the reticulum cells. Anti-HRP antibodies were most intensely localized in both mature and immature plasma cells and the rest appeared to be adsorbed to the reticular network of the processes of the reticulum cells. The antibodies were occasionally seen in the intercellular spaces of the reticulum cells in the germinal centers of hyperimmunized animals. The problems lying between the antigen and the antibody localization and the chemical nature of the antigens were discussed.—K.F.


There is a good correlation between HL-A system antigens and kidney graft tolerance. HL-A system and mostly 2-ilL-A sub-loci predominate over all the other systems of histocompatibility.—J.C.


The phenomenon of lymphocyte-platelet adherence has a different incidence when lymphocytes and platelets come from the same individual (0.35 per cent) rather than from different individuals (1.05 per cent). The difference is highly significant ($p < 0.001$). Abstractor’s comment: This phenomenon seems to be very important and is compared with antigenic differences in the histocompatibility HL-A system.—J.C.


The synthesis of immunoglobulins by cells infiltrating the labial salivary glands has been studied by radioimmunoelectrophoresis in 20 patients with Sjögren’s syndrome (SS) and in 14 control patients with related disorders. The patients with SS were producing significantly greater quantities of IgG, IgM and IgA. Synthesis of IgG and IgM correlated with the degree of lymphoid infiltration, but not with serum immunoglobulin concentration. Patients with SS and rheumatoid arthritis (RA) showed greater synthesis of IgG and IgM than those with uncomplicated RA. The only extensive lymphoid infiltration was seen in patients with SS. One patient with SS and primary macroglobulinemia was synthesizing the paraprotein in the lip biopsy as well as in the bone marrow. These results establish the immunologic competence of the infiltrating lymphoid cells and suggest their origin from an extrasalivary source.—J.E.U.


A patient is reported who developed monoclonal gammopathy, autoimmune phenomena, and acute leukemia in that sequence over a 7-year period. A comparison is made with Aleutian mink disease as well as with the autoimmune and lymphomatous disorders observed in New Zealand black mice. The relationship between gammopathy, autoimmune disease and development of neoplasm in the patient is unclear but open to several possible interpretation. (1) The neoplastic process was primary and led to the gammopathy and autoimmune findings. (2) Chronic stimulation of immunologically competent cells, as in autoimmune disease, eventually resulted in neoplasm. (3) The same stimulus resulted in both the autoimmune and malignant disease. (4) The relationship is coincidental. Abstractor’s comment: A thought-provoking case report.—J.E.U.

Rheumatoid Arthritis, Dysproteinemic Arthropathy, and Paraproteinemia.
ABSTRACTS


The results of clinical and immunochimical studies of 16 patients with rheumatoid disease and two with secondary joint disease who had coexistent paraproteinemias are presented. The former include eight cases of lanthanic dysimmunoglobulinemia, six cases of multiple myeloma, and one case each of Waldenström’s macroglobulinemia and heavy chain disease. The latter group consisted of two patients with multiple myeloma in whom dysproteinemic arthropathy developed. Other primary neoplasms occurred in six of the patients with rheumatoid arthritis. The onset of rheumatoid arthritis antedated the detection of paraproteinemia by 1–44 years (average 15).—J.E.U.


The presence of dysimmunoglobulinemia in twenty cases of chronic hepatobiliary disease is documented. Evidence for the transformation of polyclonal to monoclonal gammopathy was found in two cases of alcoholic cirrhosis, in one of which the patient died of overt multiple myeloma. There was coexistence of paraproteinemia with cirrhosis of the liver in two cases and with chronic obstructive biliary tract disease in four cases. In twelve cases of chronic hepatic or biliary tract disease the presence of paraproteinemia of low concentration was detected by immunoelectrophoretic analysis, even though serum electrophoresis disclosed only polyclonal hypergammaglobulinemia. This and the preceding paper offer important clues to the pathogenesis of immunoproliferative disorders.—J.E.U.


The authors report the results obtained in 41 women with high risk of rhesus isoimmunization and treated with small doses of specific γ-globulin. Immunization did not occur in them whereas it occurred in 20 per cent of the control group. Abstractor’s comment: It is difficult to express a definitive opinion on a small group of subjects studied during a short period of time.—J.C.

LONG-TERM PLASMA INFUSIONS IN A PATIENT WITH ATAXIA-TELANGIECTASIA AND DEFICIENT IGA AND IGE. A. J. Amman, R. A. Good, D. Bier and H. H. Fudenberg. From the Variety Club Heart Hospital, Minneapolis, Minn. J. Pediat. 44: 672-676, 1969.

A girl with A-T received regular infusions of her father’s plasma over a 3-year period. Despite development of IgA antibodies, the infusions were not attended by any untoward reactions. During the 3-years, respiratory infections have been mild and infrequent. Following each infusion, her IgA level rose to levels approximating her father’s. The circulating immunoglobulin T% was about 3 days. No IgA could ever be found in her saliva. Following each infusion, the Ishizaka skin test for IgE became positive and remained so for at least five days.—J.B.S.

MISCELLANEOUS


A radiochromatographic method was used to measure in heparinized human platelet-poor plasma an adenosine deaminase activity which could degrade 16 mM adenosine. The effects of heating and of various inhibitors as urea were studied as well as the role of the concentration of enzyme and substrate.—J.C.
Five of seven children infused with large volumes of plasma (mean: 203 ml./Kg. for correction of coagulation factor deficiencies developed transient proteinuria during 10 of 21 infusions. The mean serum protein level at onset of proteinuria was 9.6 Gm. 100 ml. As the serum protein concentration rose, so did the serum cholesterol level. At total protein concentrations above 10 Gm./100 ml., serum cholesterol was always above 300 mg./100 ml. The proteinuria was highly selective suggesting an increase in glomerular permeability to proteins of low molecular weight. Proteinuria usually cleared 2–7 days following termination of plasma infusions.—J.B.S.