ERYTHROCYTES


The effect on serum iron of white bread with 40 mg iron as FeSO₄ or as metallic ferrum reductum was studied. The serum iron increased more when ferrous sulfate was used, and the increase was partially inhibited by the use of whole-meal rather than sifted flour. When bread with ferrous iron was fed for 12 weeks to 77 female mental patients, hemoglobin rose significantly. No significant increase was caused by bread with ferrum reductum. Abstracter's comment: Swedish studies demonstrate variable and poor intestinal absorption of ferrum reductum, which caused Swedish authorities to question authorization to use ferrum reductum as food additive.—P. G. R.


Results of fecal ⁵⁹Fe excretion studies by 4 authors are reviewed. Three of them are labeled as “doubtful”. Of 5 whole body counter studies, 3 are called “doubtful”: Author is one of the other two. Abstracter's comment: Otherwise excellent review.—P. G. R.

A GASTRIC FACTOR PROMOTING IRON ABSORPTION. M. J. Murray and N. Stein. From the Department of Internal Medicine, University of Minnesota, Minneapolis, Minnesota. Lancet 1, 614-616, 1968.

Gastric juice from patients with iron deficiency anemia hemochromatosis caused slightly increased absorption of Fe⁵⁹ (as ferrous citrate) in normal sham-operated rats. Gastric juice from normal, iron-deficient hemochromatotic patients caused markedly
increased iron absorption in gastrectomized anemic rats. The authors conclude that in iron deficiency and hemochromatosis a gastric factor is secreted which promotes iron absorption.—A. L. B.


Plasma iron was assayed by releasing the bound iron at about pH 5.8 and allowing it to dilute added radioactivity. Re-binding at about pH 7.5, and removing free iron—labeled and unlabeled—with hemoglobin-coated charcoal permitted the calculation of the plasma iron level. Recovery of added, unlabeled iron was “excellent”. The correlation coefficient to colorimetric assays was 0.78. Sixty-eight per cent of radioassay values equaled colorimetric values ± about 40 μg/100 ml. Earlier radioassays of iron-binding were reviewed. Buffer contamination with iron was studied. Radioassay was felt to permit study also of icteric, hemolyzed, and lipemic plasmas.—P. G. R.


A good correlation was evident between abnormalities in bone marrow and crypt cell morphology in subjects with tropical sprue who were folate deficient, whereas crypt cell changes were minimal but marrow changes were striking in persons with nutritional folate deficiency or pernicious anemia. Treatment with either folic acid or vitamin B₁₂ improved, but did not return to normal, crypt cell morphology in tropical sprue. The authors considered that this suggests that the initial intestinal lesion in tropical sprue is unrelated to folate deficiency.—F. A. K.


Among 8 homocystinuric children, serum folate concentrations were low in 6, the plasma clearance of an intravenous test dose of folic acid was abnormally rapid in 6, and peak serum folate concentrations were subnormal in 4 of 7 subjects tested following an oral test dose of 5 mg. folic acid without previous saturation. The abnormal values in these subjects were considered by the authors as indicative of folate depletion due to increased utilization of the folate co-enzyme N⁵-methyltetrahydrofolic acid in the remethylation of L-homocysteine to L-methionine. In support of this was the observation that oral folic acid therapy in 2 patients brought about a decrease in the urinary excretion of homocystine and an increase in methionine excretion. The finding of consistently negative urinary FIGLU excretion in these children was attributed to inhibition of FIGLU formation by the high blood levels of homocystine and methionine.—F. A. K.


The site and mechanism of absorption of pteroylglutamic acid (PGA) was determined in man by means of intestinal intubation with a double-lumen tube and a perfusion technique. In controls absorption occurred principally in the proximal part of the small intestine and was poor in the distal ileum. None occurred from the distal ileum. In patients with adult coeliac disease there was malabsorption of folic acid in the proximal jejunum but absorption in the distal jejunum was comparable to that in controls. When the concentration of PGA infused into the upper jejunum in controls was increased the percentage absorbed fell and the relationship between the concentration infused and the absorption-rate was not linear. In one patient with obstructive jaundice absorption of PGA was not altered after an intravenous dose of PGA which
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raised the serum concentration thirty times as high as that of the perfusate. The authors consider that absorption of PGA is an active process which can take place against a concentration gradient. Abstracter’s comment: The mathematical analysis in this paper and the conclusions drawn from the loading experiment have been the subject of critical correspondence. See Lancet 2:775–776, 1968.—A. L. B.


Folic acid absorption was studied by determining serum folate levels after an oral pharmacologic dose. In eight patients with folic acid malabsorption the malabsorption was reversed when folic acid was fed together with lyophilized human jejunal juice. The absorption promoting activity of calf jejenum was heat-stable and present in every fourth patient. Maximum collection of feces indicated erroneous collection of feces in every fourth patient. Maximum collection loss was 8 per cent. Abstracter’s comment: No information about age, condition, or hospitalization of patients.—F. G. R.


Among the forms of hemolytic anemia due to enzymatic deficiencies of erythrocytes, the deficiency of magnesium-activated-adenosine triphosphatase (ATPase) in the red blood cells is very rare. Only three cases with partially defective enzyme have been described. The authors describe clinical and biological symptoms of a case of MgATPase deficiency which is the fourth case actually published. The total ATPase activity in erythrocytes was estimated by the method of Löh. This enzyme has an important role in the energy metabolism of red cell; it catalyses the conversion of ATP into ADP and orthophosphate: ATP + H2O $\rightarrow$ ADP + Orthophosphate. The patient was a three year old female child who was the seventh of a family of eight. She was admitted to the hospital for treatment of a lacrimal glands infection. She showed a hypochromic anemia with splenomegaly. Estimation of the glycolytically linked enzymatic reactions showed a general enhancement of all enzymatic activities except for ATPase which showed a marked diminution to 50 per cent in the erythrocytes. A normal rate of ATPase was found in thrombocytes and in white blood cells. This deficiency was not found in the patient’s family: her father, mother and seven siblings, and one cannot say exactly how this defect was transmitted. In conclusion, it is a new case of partial deficiency of ATPase associated with a hemolytic anemia which could not otherwise be explained by other causes of hemolysis.—G. M.


The activity of acetylcholinesterase in erythrocytes was investigated in a series of 120 patients with primary or secondary anemia. Reduced activity of the enzyme may be present not only in paroxysmal nocturnal hemoglobinuria, but also in auto-
immune hemolytic disorders. Subnormal acetylcholinesterase activity values were also found in hypoplastic pancytopenia, chronic myelosis, myeloma, a majority of reticuloses and some lymphadenoses.—L. D.


The possibility to influence the speed and intensity of regeneration of normal and abnormal erythropoiesis damaged by ionizing radiation in rats was investigated. A single loss of blood enhanced erythropoiesis inhibited by a single whole body irradiation dose of 600 r. Hypoxia stimulated erythropoiesis up to the seventh day after irradiation. Cobalt administration did not affect erythropoiesis after a single whole body irradiation dose of 600 r. Exogenous rabbit erythropoietin increased 59Fe incorporation into erythrocytes in rats during the first days after irradiation. Daily administration of hemolysate obtained from erythrocytes of other rats increased erythropoiesis on the seventh day after irradiation. A favorable effect on irradiated rats was seen also after daily administration of vitamin B12 and tetrahydrofolic acid. Administration of hydrocortisone and 19-nortestosterone-phenylpropionate was without effect on the irradiated animals. Administration of hydrocortisone affected unfavorably the weight of the irradiated rats.—L. D.


Eleven patients with sickle-cell crises were treated with intravenous or subcutaneous arvin—a purified fraction of the venom of the Malayan pit viper in order to produce controlled defibrination. The rationale of the treatment is based on the suggestion that intravascular fibrin deposits play a part in the pathogenesis of sickle-cell crises and can be dispersed by arvin. The treatment was apparently effective in eight of the patients and warrants further trial. Abstractor’s comment: W. R. Pitney, Lancet 2:682, 1968, points out that subcutaneous administration of arvin may induce resistance to treatment and he recommends the intravenous route.—A. L. B.


The authors report a case of Shigella osteomyelitis in a 23-month-old Negro girl with sickle cell disease. The clinical picture was initially suggestive of the hand-foot syndrome (dactylitis), but then developed into a multifocal osteomyelitis similar to that seen with salmonella infection. The authors review the possible causes of osteomyelitis in sickle-cell disease. This case points up a very important and difficult diagnostic problem in the infant with sickle cell disease.—T. N.


The authors describe an abnormal hemoglobin characterized by low oxygen affinity and decreased heme-heme interaction. Although the substitution appears to be distant from the heme group (β102), the authors point out that in the three-dimensional model, (the heme tetramer formation was also described), the molecule dissociates into dimers upon oxygenation at protein concentrations at which normal hemoglobin does not dissociate significantly. Despite the substitution of one neutral amino acid for another (threonine for arginine), electrophoretic and chromatographic separation from normal hemoglobin was possible.—T. N.

HEMOGLOBIN CC DISEASE: RHEOLOGICAL PROPERTIES OF ERYTHROCYTES AND ABNORMALITIES IN CELL WATER. J. R. Mur-
Suspensions of erythrocytes from patients with Hb CC disease showed an increased viscosity and decreased filterability suggesting a less deformable cell. Hemolysates prepared from Hb CC erythrocytes had an increased viscosity compared with hemolysates of normal cells, suggesting that the increased viscosity of Hb CC cells in serum was the result of an increased internal viscosity of the cell. These abnormal rheological properties of Hb CC erythrocytes were associated with a decreased content of cations and an abnormality of cell water. The fraction of the cell volume which is water in Hb CC cells was 95.5% of normal. The amount of cell water in Hb CC cells available for osmotic equilibrium, termed solvent water, was only 67% of that in normal cells. The smaller amount of solvent water in Hb CC cells indicates a greater amount of water bound to protein.—T. N.


Human fetal Hb in the normal infant at birth is composed of at least 2 components that are not separable by column chromatography or electrophoresis. At a minimum, they differ in the exchange of glycine and alanine in position 136 of the γ chain. On the basis of evidence from abnormal human fetal hemoglobins, it is concluded that these types of γ chains are the products of more than one structural gene and are not the results of ambiguity of translation of the genetic material. The quantitative relationships that have been observed are not easily explained on the basis of current concepts on the control of protein synthesis. Abstracter's comment: A very important paper in that it may explain many of the findings in patients with persistent elevations of fetal hemoglobin.—T. N.

LEUKOCYTES


The author suggests that some leukemic cells may differentiate, and that acute leukemia is a stem cell disorder involving all poises. Normal hemopoiesis might be suppressed because part of a hypothetical reserve pool of "sleepers" (dormant) normal cells turns leukemic, and prevents the remaining normal sleepers to become active and form normal cells.—P. G. R.


Nineteen myeloma patients were given 200 mg. NaF daily for 3 to 20 months. Fifteen patients showed radiographic bone changes after about 6 months. Abstracter's comment: No report of effect on pain or other symptoms is given.—P. G. R.

Incidence and pathogenesis of megablastic erythropoiesis in multiple myeloma. A. V. Hoffbrand, J. R. Hobbs, S. Kremenchuzky, and D. L. Mollin. From

Every fifth patient had intermediate megaloblastic changes, but 26 of 32 patients had low serum folate. Five of them had low B$_{12}$ but normal B$_{12}$ absorption. Abstract's comment: Whether the low B$_{12}$ was related to possible transcobalamin deficiency was not studied. Myeloma seems to affect folic acid metabolism as leukemia, lymphoma, and cancer do.—P. G. R.


The injection of 12 mg/kg of actinomycin D into Balb/c mice infected with Friend's virus prevented the appearance or caused the regression of splenomegaly that is usually early and marked in this disease. The viremia was also very much reduced in the treated animals. On the other hand, histologically, the appearance and multiplication of Friend's cells could be seen in the spleen of mice in which the treatment was commenced before the virus infection. Interpretation of these results takes account of the inhibitory action of actinomycin D, in the doses used, upon erythropoiesis and enables discussion of the problem of the origin of the Friend's cell.—C. M.


In cases of refractory anemia and in preleukemic states the authors found frequent changes of erythrocyte antigens and also modifications of erythrocyte enzymes, namely pyruvate kinase and 2–3 disphosphoglycerate mutase. In the white cells, alkaline phosphatase was at a low level. More recently, J. Caen et al. (Nouv. Rev. Franc. Hémat. in press) have found that platelet metabolism is also frequently disturbed. They have shown that the content of platelet ADP is very low. The authors discuss these findings with regard to a possible common enzymatic defect affecting the various cell series.—J. C.

**PLATELETS**


The authors report 39 cases of thrombocytopenia with a platelet count exceeding one million and study the clinical, hematological and biochemical aspects and the course of the disease. Some form part of a recognised syndrome of bone-marrow hyperplasia (13 polycythemia vera, 12 myelocytic leukemia, and 5 cases of myelofibrosis). Nine cases were apparently primary and may be divided into two groups: 1) Essential thrombocytopenia, which may evolve into leukemia and resembles myelocytic leukemia without being identical. The essential characteristic is the presence of a Philadelphia chromosome (2 cases reported). 2) Essential thrombocytopenia with a prolonged course and without a chromosome abnormality, in which the prognosis seems to be better even in the absence of treatment.—J. C.


Phenylbutazone and Ketazone inhibited ADP as well as adrenaline induced platelet aggregation in vitro. Phenylbutazone acted more potently than Ketazone upon ADP induced platelet aggregation. Its action upon adrenaline induced aggregation, however, appeared biologically negligible, yet statistically significant. Ketazone also influenced
adrenaline induced platelet aggregation markedly less than that induced by ADP. Both drugs acted in high concentrations only. —L. D.


The author has found an enzyme in human platelet extracts which in the presence of O₂ catalyzes the aminodiphenol oxidation. This enzyme was found by starch gel electrophoresis followed by incubation with specific substrates. In the platelet extracts of subjects affected by myopathy (Duchenne de Boulogne’s type) the author has found that the speed of electrophoretic migration of this enzyme is slower than normal. —I. C.


ADP inhibits ATPase activity but not superprecipitation of thrombosthenin. When incubated with platelet extracts, ADP "protects" platelet fibrinogen and FSF from thrombin action. The authors stress the point that ADP can be bound on platelet fibrinogen and FSF, and present the theory by which ADP-induced reversible aggregation can protect the platelets from thrombin-induced irreversible aggregation. —J. C.

HEMOSTASIS


Abnormal fibrinogen from a patient with a severe bleeding disorder (Fibrinogen Detroit) was purified. The fibrinogen was subjected to fractionation processes on Sephadex columns followed by two-dimensional electrophoresis-chromatography of tryptic digests of an abnormal fraction. Amino-acid analysis was performed on an abnormal peptide from the resulting fingerprint. The results suggested that in the N-terminal part of the α(A)-chain of the abnormal fibrinogen an arginine residue No. 19 is replaced by serine. The substitution is close to the bond which is split by thrombin and may adversely influence the polymerization stage. —A. L. B.


The authors report nine cases of gastrointestinal hemorrhage in latent hemophilia. No local lesion was found in 7 cases, but there was a peptic ulcer in 2 cases. Thus a gastrointestinal hemorrhage necessitates the search for a localized lesion even in frank hemophilia. Coagulation studies are also necessary for latent hemophilia. This had remained undetected for a long time in 8 of these patients. This led to very severe hemorrhage during surgery in 6 cases. The only patient in which the hemophilia was known underwent surgery without complications, because of appropriate treatment. Prevention of these complications depends on knowledge of the clinical condition which is very different from the classical form. The
study of coagulation factors for the clotting time is here normal. An unresolved patho-
genetic problem is raised by these gastro-
intestinal hemorrhages without a detectable lesion, for latent hemophilia does not usually give rise to spontaneous hemorrhage. When the diagnosis is unknown and even not sus-
ppected, mild hemophilia can be considered even more dangerous than classic hemophilia, at least during surgery.—J. C.


Three individuals with "near-drowning" hemoglobinemia (plasma hemoglobin levels reported in one case only) showed unmit-
takable evidence of intravascular fibrinolysis, which was preceded by a very limited activation of the intravascular clotting sys-
tem. Two cases without obvious hemolysis showed only minimal evidence of fibrinolysis. The authors postulate that a clotting activa-
tor is released from the erythrocytes which initiates coagulation. This factor is sup-
pessedly similar to platelet factor III. Support-
ing evidence for the presence of tissue damage caused by thrombosis was obtained by observed increase of tissue enzymes which commonly do not rise through hypoxia alone (serum amylase, creatinin-
phosphokinase). Fibrinolysis was assumed to be a reactive mechanism, caused primarily by the intravascular clotting.—
H.-J. H.


Clotting factors and fibrinolysis were studied in a patient with march hemoglo-
binuria and in a normal control, covering the same distance in the same time. There was an appreciable fall in factors I, II, V and VIII in the patient while the clotting factors of the normal subject remained un-
affected. Both individuals presented evidence of fibrinolysis, which was more pronounced in the patient than in the control subject. Results of repetition of the study in both individuals after heparinization sug-
gests that intravascular coagulation was caused by hemolysis since no fall of factors testable in heparinized blood was observed. Marching *per se* induced only a moderate degree of hemolysis.—H.-J. H.

IMUNOHEMATOLOGY


Four Rh-negative women received 170-300 ml of Rh-positive blood, two by trans-
placental hemorrhage and two by transfu-
sion. Treatment was given with incomplete anti-D consisting of 1000 μg of anti-D gammadoglobulin in two cases and of blood or plasma containing anti-D in the other two. Rh immunization occurred only in the pa-
tient who had received the largest transfu-
sion. It is suggested that Rh immunization by quite large transplacental haemorrhage can be safely prevented by giving anti-D gammadoglobulin. *Abstracter's comment:* More data may be needed before drawing a firm conclusion on this point. As the authors point out, even without treatment only fifty per-
cent of Rh-negative recipients of Rh-positive blood are immunized—A. L. B.

Failure of Relatively Small Dose of Passively Administered Anti-Rh to Suppress Primary Immunization by a Relatively Large Dose of Rh-positive Red Cells. N. C. Hughes-Jones and P. L. Mollison. From St. Mary's Hospital Medi-

Injection of 500 μg and 1000 μg of anti-D gammadoglobulin into two Rh-negative women who had received approximately 60 ml and 400 ml of Rh-positive red cells respectively failed to prevent primary immu-
nization. It is suggested that larger doses of anti-D, possibly in divided doses, may be needed to prevent immunization after such
large doses of Rh-positive red cells.—
A. L. B.


Four Rh-negative women received transplacental transfusions of about 140 ml.-350 ml. of Rh-positive blood. Injections of 250 pg-750 pg of anti-D gammaglobulin in single or divided doses failed to prevent Rh immunization in all patients. The failure may have been due to a long interval between the transplacental transfusion and the administration of anti-D or to the relatively small doses of anti-D administered.—A. L. B.


The serum of six patients who had suffered serious reactions after administration of blood, plasma or gammaglobulins contained anti-IgA antibodies. The serum of three of the patients was deficient in IgA and their antibody reacted broadly with a panel of red cells coated with eight IgA myeloma proteins. They developed an anaphylactic response to injection of material containing IgA protein. The three other patients had received many transfusions. They had normal serum IgA levels and their antibody reacted more specifically with red cells coated with only one IgA myeloma protein. They developed urticaria and anaphylactoid symptoms after transfusion of blood from certain donors. In one of these patients further evidence was obtained implicating anti-IgA as a cause of the reaction.—A. L. B.


This paper deals with the extraction of transplantation antigens from human spleen cells, solubilized and separated from the bulk of impurity by gel filtration and ion exchange chromatography. In all aspects so far examined they have behaved as H-2 antigens, the major transplantation antigens of the mouse. Both HL-A and H-2 antigens are glycoproteins with molecular weights of about 50.000 and are stable on storage up to at least two years for the human material. It is concluded that the HL-A and H-2 systems are likely to be genetically homologous and that the extensive mouse data may be used to hasten the clarification of the transplant rejection system in man.—J. C.


In an elderly woman the authors observed two red cell populations the relative proportions of which remained unchanged for six years: one was A1 and AK 2–1, the other was weak A and AK 1–1, while both had the same type for the other twelve genetic variation systems investigated. This fact may support the idea of linkage between the ABO and AK loci, the implication being that the weak A and AK 1–1 population is the product of a clone of erythroblasts carrying chromosomal damage. Such an observation should indicate search for associated abnormalities of this type in acute leukemias involving modifications of the ABO blood groups.—G. M.

Thin red cell films were covered with 500 Å gold and palladium to render their surfaces conducting and then examined in the Cambridge Stereoscan electron microscope. Incubation with cold agglutinin of anti-A specificity caused roughening of, and finger-like processes from normally smooth red cell surfaces. They grew with longer incubation and disappeared after heating to 37°. Heparin did not prevent agglutination if added in vitro, but it did in vivo. It is believed that the processes, also caused by iso-antibodies, disrupt the normal electronegative charge produced by the carboxyl group of sialic acid.—P. G. R.


The authors show that these cells can easily be demonstrated in histological sections using stains such as Mann-Dominici or slow Giemsa. Their morphology and distribution enable one to distinguish 4 types: pulp or follicular basophilic cells which give birth to lymphocytes in the resting or hyperplastic lymph node, to plasmocytes and irritative basophilic cells in response to antigenic stimulation. Recent experimental work, e.g. lymphocyte culture and drainage of stimulated nodes, seems to prove the lymphocytic origin of the irritative cells. The latter give rise to plasmocytes and diffuse throughout the lymphatic system to increase the immune response. Cytoplasmic basophilia and pyro-ninophilia, which are found in all these cells, are due to the presence of RNA and correspond under the electron microscope to the appearance of numerous ribosomes and/or an ergastoplasm which are signs of increased protein synthesis. The Authors insist on the fact that in human pathology, the basophilic cells are stimulated by various types of aggression which lead to hyperplastic reactions. Their localisation is of help in diagnosis.—J. C.


Six chronic lymphocytic leukemias with 20,000 to 130,000 lymphocytes received 0.9-29.5 ml doses of horse antilymphocyte serum during 13-18 days. No anaphylaxis. The lymphocytes decreased after 30 minutes to a minimum of half the original value, but rose again. Abstractor’s comment: Unfortunately bone marrow lymphocytes were not followed regularly.—P. G. R.

MISCELLANEOUS


Of the 1,313 patients reported in the literature and 154 Mayo Clinic patients, 85 had serious infections at some time after splenectomy. Forty-four of these patients had infections that were operative complications, consequences of underlying disease, or minor in nature. The remaining 41 patients were presumed to have infections possibly related causally to the asplenic state. The mortality rate due to infection in these 41 patients was 47%: 35% for 17 patients less than 1 year old and 78% for 24 patients 1 year old or older at the time of splenectomy. The frequency of infection was 2.8% for the composite series and 1.1% for those 1 year or older. The frequency of meningitis and sepsis in an unrelated group of normal children was 0.7%. The frequency of infection in 68 patients with H.S. requiring splenectomy before 1 year of age was 18%.—T. N.


Erythrocyte sedimentation rates of 20-50 in Bantu school children are associated with excellent attendance and aptitude but with ill health in white subjects. Serum iron are lower in white persons than in Bantu. Babies weighing less than 5.5 lb include 5.6 per...
cent of English and 30.1 per cent of Kavreng (New Guinea) babies. New Guinea native babies weighing 3 pounds have the same mortality rate as babies weighing 4 pounds in England. Similar examples are cited for growth, puberty and aging, overweight, subcutaneous fat and serum cholesterol. What is "normal" and what is optimal? Should there be one single or multiple standards?—P. C. R.


Twenty subjects including 6 cretins from the Kysuca endemic area in northwestern Slovakia were submitted to bone marrow examination and cytologic abnormalities in the smears were searched for. In all persons examined, the incidence of polyploid erythroid cells and of atypical mitoses was definitely enhanced. A similarity of these findings to the pattern of cytologic abnormalities in the late phase of radiation injury was pointed out and the possibility that some (goitrogenic?) substances may have radiomimetic properties was put forward.—L. D.


Authors stress that probability calculations cannot be made for unexpected findings, where no prior commitment to that particular question was made. The reason is that comparisons must not be determined by the outcome of an experiment. Similarly, such calculations can not be made for "matched" patient groups, where bias may be present in spite of matching, but only for truly randomly selected groups. Abstracter’s comment: The fact that clinical studies must often have samples smaller or less randomly selected than statistically required should not exclude semi-quantitation of probability. More rigid tests can be used for small samples and the meaning of the calculated p-value can perhaps be defined and qualified.—P. C. R.