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ERNST R. JAFFÉ, M.D., Editor

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LEUKOCYTES


Three members of a family showed consistent, marked neutropenia, associated with normal to decreased total leukocyte counts, usually with relative lymphocytosis, monocytosis, and eosinophilia. Bone marrow aspirates showed marked reduction in granulocytes older than myelocytes. All 3 patients were in good health, though 2 had been suspected of having leukemia because of unusual peripheral blood counts. It was thought that this disorder was inherited as a nonsex-linked dominant.—T. E. B.


The seasonal variations in leukocyte counts in healthy individuals resident in the Moscow region or in Eastern Siberia proved to be identical: maximum in autumn and minimum at the beginning of summer. Seasonal variations in leukocyte count were not connected with changes in solar activity.—J. K.


Although delayed hypersensitivity reactions were obtained in 7 patients with congenital nonlymphopenic agammaglobulinemia, none could be obtained in a boy with thymic aplasia until he had received a thymic transplant from a healthy donor. A skin graft from the same donor was present, without evidence of homograft rejection, when the patient died 40 days after transplantation. The thymic graft also appeared to have survived, but had undergone considerable degeneration so that it resembled the patient’s own thymus.—J. B. S.


A 2-week-old girl who died from overwhelming sepsis had peripheral white counts between 200 and 600 cells per cu. mm. Most of these cells were reported to be mononuclear. Necropsy revealed a small thymus with no Hassall’s bodies.
and very few small lymphocytes. The cells of the lobules were reticular cells, so-called large thymocytes. The spleen and lymph nodes were of normal size, but contained few lymphocytes. The predominant cell was similar to the reticular cells of the thymus. Also present were plasmacytoid cells whose derivation was unclear. Structures of the thymus. The spleen and lymph nodes were of normal size, but contained few lymphocytes. The cells of the thymus, lymph nodes, spleen and bone marrow were almost entirely of reticular cells with few small lymphocytes. The bone marrow or postmortem peripheral blood specimens showed a phenomenal increase in peripheral white count to levels of 135–200,000 per cu. mm. Much of the increase was due to a rise in small lymphocytes. Leukocytosis, maximal 4 days after injection, persisted for more than 2 weeks. Rabbits, guinea pigs and rats responded in similar fashion. Intravenous injection of other bacteria, including even a rough strain of B. pertussis, did not result in striking leukocytosis. Mice previously actively immunized to pertussis vaccine given subcutaneously showed almost no rise in peripheral white count after intravenous injection of vaccine. The effects of passive immunization, thorotrast administration, splenectomy, thymectomy and several other variables were also studied. Histologic examination of animals at the time of vaccine-induced leukocytosis showed that the thymus, lymph nodes, spleen and bone marrow were virtually denuded of small lymphocytes. It was suggested that the increase in circulating lymphocytes following injection resulted from release of formed small lymphocytes from tissue reservoirs into the circulation.


Mice injected intravenously with 0.3 ml of a concentrated suspension of killed pertussis organisms showed a phenomenal increase in peripheral white count to levels of 135–200,000 per cu. mm. Much of the increase was due to a rise in small lymphocytes. Leukocytosis, maximal 4 days after injection, persisted for more than 2 weeks. Rabbits, guinea pigs and rats responded in similar fashion. Intravenous injection of other bacteria, including even a rough strain of B. pertussis, did not result in striking leukocytosis. Mice previously actively immunized to pertussis vaccine given subcutaneously showed almost no rise in peripheral white count after intravenous injection of vaccine. The effects of passive immunization, thorotrast administration, splenectomy, thymectomy and several other variables were also studied. Histologic examination of animals at the time of vaccine-induced leukocytosis showed that the thymus, lymph nodes, spleen and bone marrow were virtually denuded of small lymphocytes. It was suggested that the increase in circulating lymphocytes following injection resulted from release of formed small lymphocytes from tissue reservoirs into the circulation.

**Inhibition of the Lymphocyte Response to Inflammation with Antimetabolites.** A. R. Page. From the Variety Club Heart Hospital, Minneapolis, Minn. Am. J. Path. 45:1029–1044, 1964.

Actinomycin D (known to inhibit production of messenger RNA) was shown specifically to block lymphocyte participation in a nonspecific inflammatory response in rabbits. It had been shown previously that 6-mercaptopurine treatment eliminated the lymphocyte response to inflammation without altering the neutrophil response. Treatment of rabbits with aminopterin, 5-fluorouracil, cyclophosphamide, 8-azaguanine and chloramphenicol at dosage levels which were toxic did not block the lymphocyte response. In rabbits with a preexisting inflammatory lesion, actinomycin failed to block the emigration of lymphocytes into a newly produced inflammatory lesion at a different site. It was suggested that
lymphocytes must be stimulated to produce a new protein before they become capable of emigration into an inflammatory lesion.—T. E. B.


Infection with Rauscher leukemia virus produces sustained viremia in BALB/c mice. C57BL mice are highly resistant and respond to infection by forming antibody with specific cytotoxic activity against these cells. Production of disease in susceptible strains and production of cytotoxic antibody in resistant strains can be used to titrate infective virus. The plasma of mice infected with Rauscher virus contains both infective virus and a soluble antigen which has the same specificity as the cellular antigen. Soluble antigen is adsorbed onto certain cells and renders them susceptible to lysis by specific cytotoxic antisera.

An antigen with the same specificity appears in the plasma of mice with transplanted Rauscher leukemias of lymphatic type. The plasma of mice with primary leukemias induced by Moloney or Friend (but not Gross) viruses similarly sensitizes indicator cells to the cytotoxic activity of Rauscher antiserum, indicating that leukemias induced by Friend, Moloney and Rauscher viruses are immunologically related.—H. H. F.

Erythrocytes


Thirteen of 14 patients from Puerto Rico who developed symptomatic tropical sprue while resident in New York City were found to have megaloblastic anemia. Serum folate concentrations were subnormal in 11 and folic acid absorption was subnormal in 6 of 8 patients tested. Serum vitamin B12 concentrations were subnormal in all 13 and the absorption of Co<sup>57</sup>B<sub>12</sub> was subnormal in all 10 tested. Only one was iron deficient. Tropical sprue should be considered as a possible etiology of megaloblastic anemia when seen in Puerto Rican patients, even in those subjects who have remained asymptomatic in a temperate climate for as long as 15 years.—F. A. K.


Serum from normal subjects and from patients with either folate or vitamin B<sub>12</sub> deficiency was chromatographed and activities charted by bioautography with 3 folate-requiring bacteria (L. casei, S. faecalis, and P. cerevisiae) before and after an oral loading test with 5 mg. folic acid (PGA). Patients with B<sub>12</sub> deficiency had normal L. casei and elevated S. faecalis activity after the test dose; treatment with parenteral vitamin B<sub>12</sub> resulted in a return of S. faecalis activity to normal. These findings were interpreted by the authors to indicate that B<sub>12</sub> deficiency is characterized by accumulation of S. faecalis active folymeroglutamates and to suggest that B<sub>12</sub> deficiency interferes with formiminogluterase and that principally PGA, and not N<sub>5</sub>-methyl THF, accumulates during B<sub>12</sub> deficiency.—F. A. K.


Two patients were described in whom the diagnosis of pernicious anemia was documented by subnormal serum B<sub>12</sub> concentration, absence of intrinsic factor activity in gastric juice and subnormal urinary excretion of a test dose of Co<sup>57</sup>B<sub>12</sub> when given alone, with an intrinsic factor preparation of proven potency and following 1 week of oral oxytetracycline therapy. Other studies of intestinal absorptive capacity, and a jejunal biopsy in one case, were normal. Repeat studies of Co<sup>57</sup>B<sub>12</sub> absorption following treatment with parenteral vitamin B<sub>12</sub> for 11 weeks in one patient and 20 months in the other showed normal absorption when administered with intrinsic factor.—F. A. K.


Two sisters presented during early childhood with megaloblastic anemia due to vitamin B<sub>12</sub> deficiency. Subsequent studies revealed an absorptive defect of vitamin B<sub>12</sub> which was not corrected by addition of intrinsic factor. From a consideration of the 29 adequately studied patients with juvenile pernicious anemia previously described in the literature, the authors proposed...
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that the syndrome can be divided clearly into 2
types. In the first, the defect appears to be failure
of an otherwise normal stomach to elaborate in-
trinsic factor. The second is characterized by a
selective intestinal malabsorption of vitamin B₁₂
and, in the majority of cases, an unexplained per-
sistent proteinuria. The available evidence sug-
gests that both types are inherited in a simple
recessive genetic pattern.—F. A. K.

CYANOCOBALAMIN-DEPENDENT DEPRESSION OF THE
SERUM ALKALINE PHOSPHATASE LEVEL IN PA-
TIENTS WITH PERNICIOUS ANEMIA. C. K. V.
Van Dommelou and C. H. L. Klaassen. From
the Zuidziekenhuis, Rotterdam, Holland. New

The mean serum alkaline phosphatase activity
in 56 patients with untreated pernicious anemia
was significantly lower than in similar size groups
of normal subjects and patients with iron de-
iciency anemia. Treatment with vitamin B₁₂ re-
sulted in return of the alkaline phosphatase ac-
tivity to normal. The authors suggested that
cyanocobalamin deficiency impairs osteoblast func-
tions and synthesis of alkaline phosphatase.
—F. A. K.

INVESTIGATIONS ABOUT THE SITE OF PRODUCTION
OF CASTLE’S GASTRIC INTRINSIC FACTOR. P. J.
Hoedemaeker, J. Abels, J. J. Wachten, A. Arends
and H. O. Nieweg. From the University of Groningen,
Groningen, The Netherlands. Lab. Invest. 13:1394–1399,
1964.

Autoradiography was performed on rat and hu-
man stomachs after incubation with Co⁵⁸B₁₂.
Vitamin B₁₂ was shown to have a strong affinity
for the chief (pepsinogen) cells in the rat and for
the parietel (hydrochloric acid secreting) cells
in man. Uptake of labeled vitamin by these cells
was inhibited by exposure to anti-intrinsic factor
γ-globulin obtained from patients with pernicious
anemia.—F. A. K.

VITAMIN B₁₂ ABSORPTION FOLLOWING VAGECTOMY
AND GASTRIC SURGERY. M. Mouhoudt and S. I.
Schwartz. From the University of Rochester
School of Medicine, Rochester, N. Y. Ann.

Vagotomy and pyloroplasty in dogs resulted in
a decrease in the urinary excretion of Co⁵⁸B₁₂
to the subnormal range but not to the very low
levels observed after total and subtotal gastrec-
tomy. Absorption following any of the 3 surgical
procedures was improved by the addition of in-
trinsic factor.—F. A. K.

STUDIES IN SICKLE CELL ANEMIA. XXI CLINICO-
PATHOLOGICAL ASPECTS OF NEUROLOGICAL
MANIFESTATIONS. R. L. Baird D. L. Weis, A.
From Howard University College of Medicine,

Sickle cell disease may present with signs
suggesting central nervous system disease. Eight
children who presented thus were described.
Headache, convulsions, hemiplegia, personality
changes, convulsions and coma were noted. The
pathologic findings in the brains of 5 persons
were described and included changes in both
blood vessels and parenchyma. Where death oc-
curred during a crisis, there was severe general-
ized congestion of small vessels, many of which
were occluded by masses of sickled erythrocytes.
Ar-
teriolar diameters varied widely, frequently be-
ing considerably widened. Localized arteriolar
dilatations containing impacted erythrocytes tap-
ered abruptly into a trailing capillary structure.
These lesions were widespread and resembled
tadpoles. Iron pigments and lipid-filled macro-
phages were seen in perivascular spaces and
microinfarcts were scattered throughout the white
matter.—J. B. S.

RETICULOCYTOPENIA IN SICKLE CELL ANEMIA. E.
Charney and G. Miller. From University of
Rochester School of Medicine, Rochester, N.

Nine of 20 children with sickle cell anemia
had an episode of transient reticulocytopenia dur-
ing observation periods averaging 5 years. In 4
instances, there was no evidence of accompanying
infection. Clear-cut evidence of folic acid de-
iciency was not demonstrable in bone marrow
aspirates; no other evaluation of folate metab-
olism was obtained. The possible etiologic signif-
icance of folic and ascorbic acid deficiency was
discussed.—J. B. S.

PRESENCE OF ANTI-GAMMA-GLOBULIN FACTORS
OF THE Gm GROUP IN POLYTRANSFUSED CHIL-
DREN WITH COOLEY’S DISEASE. A. Vierucci, D.
Varone, L. Borgatti and M. Dettori. From the

In 15 of 46 children who had received 3 to
more than 100 blood transfusions, the Gm pheno-
type and the agglutinating anti-γ-globulin factors
of Gm (a), (b) and (x) groups were found. A moderate increase in γ-globulins and a clear decrease in haptoglobins and hemopexins were noted on immunoelectrophoresis.—P. D. N.

**SOME IMMUNO-SEROLOGICAL ASPECTS OF COOLEY’S DISEASE: PRESENCE OF “RHEUMATOID FACTORS.”**

Seven of 46 children who had been given 10 to over 150 blood transfusions had a positive latex test. In 6 cases, anti-Gm (a) and anti-InV (1) antibodies were noted in 1 case. Absorption and neutralization experiments were carried out to determine specificity.—P. D. N.


In 22 patients with Cooley’s disease, G-6-PD activity in erythrocytes was found to be significantly higher than in normal subjects. In 12 splenectomized patients, the values were slightly lower than in other patients. In thalassemia trait, the values were lower than in homozygous patients, but significantly higher than in normals. —P. D. N.


Fifty-eight children with this syndrome were described. Mean age was 1 year and there was no sex predisposition. The characteristic onset occurred in a previously healthy infant who developed fever, anorexia and evidence of coryza and/or gastrointestinal upset with vomiting and diarrhea. After a short prodromal period, pallor and oliguria appeared, often accompanied by evidence of CNS irritation. The mean BUN on admission was 278 mg. per 100 ml and hyperkalemia and hyperphosphatemia were frequently present. The serum CO₂ ranged between 4.5 and 18.3 mEq./L. The mean hemoglobin level on admission was 6.5 Gm. per 100 ml and the mean reticulocyte count was 7.8 per cent. Distorted, fragmented and crenated erythrocytes were constant findings and persisted in decreasing numbers for an average of 70 days. Thrombocytopenia was almost always present and persisted for up to 1 month. Most infants developed hemorrhagic signs, especially melena, small intradermal hematomas and bleeding from injection sites. Petechiae were infrequent. Hypertension and some degree of congestive failure were not infrequent during the oliguric phase which lasted from 3 to 48 days (mean 12 days). Half the patients had a period of total anuria. Neurologic manifestations were very frequent and included convulsions, stupor or coma, irritability, tremors and ataxia. Corticosteroids were administered to a small group without apparent effect. The overall mortality was 29 per cent and most deaths occurred in children with more than 4 days of total anuria. Many of the early deaths appeared to result from mismanagement and, more recently, the rate has been below 10 per cent. Postmortem examination frequently revealed bilateral cortical necrosis, apparently secondary to fibrinoid necrosis of medium-sized arteries. In other patients, scattered glomerular and tubular necrosis were seen. Among the survivors were several who were left with residual neurologic or renal damage. The precise cause of the hemolytic-uremic syndrome is unclear, but preliminary evidence for a viral etiology was claimed.—J. B. S.


The capacity of serum to bind phenolsulfophthalein (PSP) is related to the concentration of “unbound” serum albumin. Determination of PSP binding capacity can thus be used to estimate the circulating albumin available for binding free bilirubin. Low PSP binding capacity predisposes to kernicterus and appears to be a better criterion for evaluating the need for exchange transfusion than is serum bilirubin level. Addition of 6–12 Gm. of albumin to donor blood results in higher post-transfusion PSP binding capacity than is obtained when nonsupplemented blood is used.—J. B. S.

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Iron (5 mg.) as ferrous sulfate labeled with 8 µg. Fe⁵⁹ was given orally to 9 patients with hemochromatosis and 4 with hepatic cirrhosis before and following 2 doses of a potent pancreatic extract. Seven patients in the first and all in the second group showed pronounced diminution in iron absorption. The authors postulated that pancreatic fibrosis leads to increased iron absorption.—F. W. G.


Five patients were noted to have low serum iron levels, normal iron binding capacity with reduced per cent saturation, rapid plasma clearance of injected Fe⁵⁹ with early and marked utilization for synthesis of hemoglobin and normal plasma iron restoration rate. Survival of erythrocytes in 2 patients was slightly below normal.—P. D. N.


Prevention of iron deficiency anemia in premature infants was achieved with a formula containing 12 mg. of iron per quart. Despite adequate intake of solid foods, more than a third of infants in the control group developed evidence of iron deficiency anemia.—J. B. S.


Hemoglobin levels in several thousand babies and young children were estimated in capillary blood by the oxyhemoglobin method. These were town children living in a subtropical climate. Babies weighing less than 5.8 lbs. at birth had, throughout their first year, an average of hemoglobin 1 Gm. per cent lower than those weighing 5.8 lbs. or more. They reached their lowest hemoglobin level at 9-10 weeks, 1 week earlier than the larger infants. Those whose mothers had had adequate antenatal iron therapy showed higher hemoglobin levels throughout the first year.

No difference was found in the effectiveness of 7 iron preparations used in treatment.—F. W. G.


Remissions occurred in 5 of 9 children with acquired aplastic anemia 2 to 9 months after institution of corticosteroid and testosterone treatment. Hemoglobin and leukocyte levels rose at about the same time; sustained platelet responses were not observed before 9 months of therapy. Remission was maintained following cessation of therapy. All 4 children with congenital aplastic anemia responded somewhat more rapidly to similar therapy. Platelet counts remained below 80,000, however, and relapse occurred quickly if therapy was stopped.—J. B. S.


Manganese sulfate therapy in cases of chronic hypoplastic anemia which had been treated previously for long periods without success was associated with general improvement; skin and external mucosa appeared less pale, hemorrhages stopped, hemoglobin and erythrocytes increased to near normal or normal values and there was remission of disease.—J. K.


Four cases were reported. Three developed malignant conditions (leukemia, carcinoma of caecum, abdominal tumor of unknown primary site) and the other myelofibrosis. The prognostic value of recognizing the tendency to neoplasia in this disorder was stressed.—H. H. F.


Changes in erythropoiesis in healthy women at various periods of the menstrual cycle, in patients with dysfunctional uterine hemorrhages and in pregnant women were studied. A reduc-
tion of erythrocyte count in blood and erythroblasts in bone marrow with an increase in transport iron, siderocytes and free erythrocyte protoporphyrin was noted during the rise of blood estrogens. It was concluded that estrogens depress hemoglobin synthesis and they were recommended for the treatment of polycythemia.—J. K.

**HEMOSTASIS**


The authors confirmed the rise in plasma levels of Factor VIII during pregnancy in normal females. This increase was usually evident in the second trimester and in the third trimester averaged about twice the normal nonpregnant range. The increase was not reflected in cord blood. In 5 carriers of hemophilia with low Factor VIII levels, there was significant rise in Factor VIII which again averaged about twice the nonpregnant level. One pregnancy resulted in a severely hemophilic newborn and both cord and baby’s blood were practically devoid of Factor VIII. In 1 woman with von Willebrand’s disease, there was a rise in Factor VIII from 20 to 45–55 per cent at delivery. Increases in Factors I, VII, IX and X were also observed in pregnancy.—R. G.


Autotransfusion of Cr<sup>51</sup>-labeled platelets showed decreased survival in 8 of 12 patients with polycythemia vera, 1 with hemorrhagic thrombocythemia and 1 with chronic granulocytic leukemia. The reduction in polycythemia appeared to be due to an intrinsic platelet defect and, in the leukemia patient, to splenic sequestration.—F. W. G.


One-stage prothrombin times and factor V assays were essentially equal to normal adult values in infants 1–18 months old. The median value for factor VII-X complex was 56 per cent of normal without any evidence of age-related upward trend. Prothrombin content, as measured by TMe assay, increased from subnormal toward normal adult levels with increasing age. The highest levels and the most rapid increases in activity occurred in infants with greatest birth weights. The differences among infants of varying weight were most evident below 2 months of age and were no longer present at a year. —J. B. S.


Addition of glucose to heparinized blood causes clotting, as does addition of fructose, mannose, galactose, 2-deoxyglucose, saccharose, mannitol and glycine, but not of sodium chloride or thiourea. For clot formation, platelets, calcium ions and the components of the prothrombin complex are necessary. No clotting occurs on incubation of decalcified, citrated or prothrombin-deficient blood with glucose. Since heparinized blood is largely used for extra corporeal transfusion technics, it is important to realize that, to prevent dangerous clot formation, it must not be mixed with fluids containing glucose.—F. W. G.