ANEMIA


This useful review mentions work on the liver factor, extrinsic and intrinsic factor, yeast and yeast products and folic acid. Animal factors related to vitamin B₁₂ are discussed; also methods of assay and procedures used in isolation of B₁₂.

Animal experiments designed to produce a megaloblastic anemia are reviewed with their response to pteroylglutamic acid and B₁₂. The clinical application of vitamin B₁₂ is described.

An outline of what is known of the chemical and physical properties of B₁₂ is given and finally a brief discussion of the possible relationships of B₁₂ and folic acid. There is an extensive bibliography.—S.C.


At this meeting, E. Lester Smith (Research Division, Glaxo Laboratories, Ltd., Greenford, Middlesex) reviewed the steps in isolation and the chemistry of vitamin B₁₂.

C. C. Ungley (Royal Victoria Infirmary, Newcastle-upon-Tyne) discussed the relation of vitamin B₁₂ and other dietary factors in megaloblastic anemias and in subacute combined degeneration of the spinal cord, bringing together a number of observations and facts which cannot be summarized briefly.

D. L. Mollin and J. V. Dacie (Department of Pathology [Haematology], Postgraduate Medical School of London) reported observations on the relationship between red cell and reticulocyte responses and changes in the bone marrow of patients with pernicious anaemia treated with injections of liver extract or vitamin B₁₂. They showed that with single doses, 30 to 40 gamma of vitamin B₁₂ equivalent are needed to maintain a normoblastic marrow for fifteen days. With doses sufficient to give an “average satisfactory” rise according to the criteria of DellaVida and Dyke, the marrow is likely to revert to a partially megaloblastic state by the end of fifteen days. It is suggested that the potency of an extract may be assessed by studying the changes produced in the bone marrow.

A detailed study suggested that the reticulocyte response curve was determined by the degree of hyperplasia of the marrow, the potency of material given in relation to the patient’s requirements, the degree of immaturity of the reticulocytes when they enter the blood stream and their rate of ripening. Because of this complicated relationship, the reticulocyte response curve is not an ideal guide to potency of extracts.—S.C.
MEGALOBLASTIC ANEMIA OF PREGNANCY: RESPONSE TO PTEROYLGLUTAMIC ACID AFTER FAILURE TO RESPOND TO LIVER EXTRACT AND VITAMIN B₁₂. V. Ginsberg, J. Watson and H. Lichtman. From the Department of Medicine, Kings County Hospital, Brooklyn, N. Y. J. Lab. & Clin. Med. 36: 238-241, 1950.

A case of megaloblastic anemia of pregnancy is presented, which failed to respond to refined liver extract and vitamin B₁₂, and which then responded maximally to pteroylglutamic acid.—G.E.C.


Euglena gracilis variet Bacillaris was used for microbiologic assay of vitamin B₁₂ in serum, urine and cerebrospinal fluid.

With sera, but not with urine or C.S.F., the amount of growth obtained varied with the degree of heating before inoculation. Heating to 70 C. for half an hour gave 20-350 μg. B₁₂ equivalent per ml. in serum from 40 patients with a variety of conditions. Twelve similar sera heated to 100 C. for half to one hour gave 350-750 μg. B₁₂ equivalent per ml. Heating longer at 100 C. reduced activity as did heating at pH 10.

The B₁₂ equivalent found in C.S.F. was nil to 18 μg. per ml. and in urine nil to 200 μg. per ml.

No activity was found in sera heated at 70 C. from 4 cases of pernicious anemia. Two sera retested after heating to 100 C. showed some activity but less than normal serum. Urine from one case showed no activity.

Sera from two patients with pernicious anemia, taken after an intramuscular injection of B₁₂, showed marked activity, declining over several weeks after injection. Heating these sera was necessary for full activity.—S.C.


In this paper, confirmation of some of the earlier observations on intrinsic factor is reported, using vitamin B₁₂ as extrinsic factor.

Intrinsic factor is heat-labile. It retains its activity in gastric juice when stored at pH 1.7 at a temperature of 5 C. for three months. The activity is apparently destroyed by 95 per cent ethyl alcohol.

The intrinsic factor action of various extracts of stomach and duodenum of swine have been investigated. The materials have been tested by Bethell and associates for their ability to bind vitamin B₁₂ and make it nonavailable for microbial growth (as shown by Ternberg and Eakin). The highest binding activity was shown by the water-soluble non-dialyzable fraction of duodenal mucosa. It is suggested that this method may help in concentration and purification of intrinsic factor. However, evidence is given that binding activity may not always parallel clinical activity.

It is suggested that intrinsic factor may (1) alter B₁₂ so that it more readily traverses the intestinal barrier, (2) protect B₁₂ from destruction by digestive secretions, or (3) prevent removal of the vitamin by micro-organisms. In support of (3), the interesting observation of Lichtman, Ginsbert and Watson is mentioned. They have shown hematopoietic responses in cases of pernicious anemia in relapse given 3 Gm. aureomyein and 3 μg. vitamin B₁₂ daily by mouth.—S.C.


The authors urge the combined use of vitamin B₁₂ and specific coordination exercises in the effective and rapid treatment of the posterolateral sclerosis of pernicious anemia.
ABSTRACTS

They give a regimen of coordination exercises, graduating from the use of individual muscle groups with the patient recumbent, to the training of the patient to rise from sitting position, and then to walk. The use of these exercises themselves, they found, increased the ability to coordinate; but the addition of vitamin B₂ to the exercise regimen (in an experimental patient) caused a marked increase in the rate of the patient's progress. The use of vitamin B₂ by itself, without exercises, arrests or reverses the neurodegenerative changes, but does not accomplish return toward normal as rapidly as when exercises are added. The use of such exercises is stressed.

Analysis of the authors’ results showed a gratifying restoration of most of the treated patients to normal or, in some cases, incomplete improvement. —S.E.

I. ABBSENCE OF INTRINSIC FACTOR FROM INTESTINAL JUICE OF PATIENTS FOLLOWING TOTAL GASTRECTOMY. M. Paulson, C. L. Conley and E. S. Gladsden. From the Gastro-Intestinal and Nutrition Clinic and the Division of Clinical Microscopy, Department of Medicine, The Johns Hopkins University and Hospital, Baltimore, Md. Am. J. M. Sc. 200: 310-312, 1950.

Intestinal juice aspirated from the jejunum of patients following total gastrectomy and incubated with beef muscle failed to produce a hematologic response when administered in large quantities to a patient with pernicious anemia. This indicates that intrinsic factor, if present in intestinal secretion, is in too low a concentration to be detected by this method. Thus, failure of pernicious anemia to occur following gastrectomy still remains unexplained. —G.E.C.

MORTALITY FROM, AND RISK OF GASTRIC CARCINOMA AMONG PATIENTS WITH PERNICIOUS ANAEMIA. J. Mosbech and A. Videbaek. From the Bispebjerg Hospital, Medical Department B, Copenhagen, and the University Institute of Human Genetics, Copenhagen, Denmark. Brit. M. J. 2: 390-394, 1950.

A series of 301 patients with pernicious anemia (219 females and 82 males) were followed up during the period 1928 to 1949.

Mortality did not exceed expected values. In 222 patients followed up more than ten years, the life expectancy of the 168 female was the same as for normal females. The 54 males showed a slightly but not significantly higher mortality than normal males.

The causes of death were investigated. The incidence of all forms of cancer was not found to be excessive but there was a high incidence of gastric carcinoma (5 per cent as compared with the expected 1.7 per cent). It is suggested that achlorhydria is the common etiologic factor in pernicious anemia and cancer of the stomach. —S.C.


One hundred forty-six injections of saccharated oxide of iron in doses of from 100 mg. to 600 mg. were given to 18 subjects.

Reactions to injection were infrequent and for the most part mild. They consisted of (a) pain, venous spasm, and occasionally thrombophlebitis at the injection site and (b) generalized cramping pains in the lower extremities and back. In 2 subjects, general reactions were of such severity that further injections were not given. The incidence of reactions rose significantly with single doses over 300 mg.

Reticulocytosis averaging 8.5 per cent on the fifth to ninth day was observed in 8 to 9 persons with severe hypochromic anemia. There was no relationship between reticulocytosis and initial hemoglobin levels. Rates of hemoglobin regeneration in these 9 persons averaged 0.215 Gm. per 100 ml. per day and were without relationship to initial hemoglobin levels. —G.E.C.

Five female patients and one male patient were found to have a hypochromic anaemia refractory to treatment with 10 grains of ferrous sulphate thrice daily for a period of at least eight weeks. Three also received 300 mg. ascorbic acid daily without effect. Infection, renal failure and excessive blood loss were excluded in each case. All 6 were shown to have defective fat absorption and a "deficiency pattern" in the x-ray of the small bowel. A good response was obtained with treatment by intravenous iron. Five subsequently developed macrocytosis.

In the authors' series of over 200 cases of steatorrhea, 13 patients showed a persistent hypochromic anaemia. One responded normally to iron, 6 with slow and irregular rise, and the remaining 6 were the reported refractory cases.

It is concluded that a high proportion of patients with refractory iron deficiency anaemia have associated steatorrhea. The good response to intravenous iron indicates that hemoglobin synthesis is normal in such patients.—S.C.


The rate of destruction of transfused red cells was determined by the Ashby technic in a small group of patients with anaemia associated with chronic infection, carcinoma, leukaemia and allied disorders. Previous investigation by the author (J. Path. & Bact. 56: 81, 1944) has shown that, when the number of surviving erythrocytes is plotted against time, at least two types of hemolytic mechanisms may operate in some cases of anaemia: (1) a simple increase in the normal or linear decay curve; (2) an abnormal type of hemolysis as shown by considerable curvature in the decay curve as well as a reduction in the average life of the red cell. Results can be expressed numerically by use of an equation which has been developed.

In the present study there was evidence of excessive hemolysis in nearly all cases despite the absence of reticuloerytosis, hyperbilirubinemia, and increased excretion of fecal urobilinogen. Although in the majority, including all cases with chronic infection, the increased hemolysis was of the linear curve type, abnormal and rapid hemolysis was noted in a sufficient number of cases to be deemed significant.

It was suggested that excessive hemolysis occurs more frequently and is of greater significance in cases such as these than is generally supposed. The degree of importance of such a hemolytic factor in the pathogenesis of these anemias must await further investigation. Too, the validity of this method as a measure of the rate of destruction of the patient's own erythrocytes remains to be determined.—H.W.B.

HEMOLYTIC DISEASE


In this discussion, R. R. A. Coombs (Department of Pathology, University of Cambridge) drew attention to several of the factors in the pathogenesis of the human disease which are imperfectly understood, such as the protective mechanisms against isoimmunization in heterospecific pregnancies, the varying antigenicity of Rh antigens, and the factors influencing the varied clinical manifestations of the disease. He also described studies made in collaboration with other workers, and independently in America on hemolytic disease of the newborn occurring in newborn mules and foals of thoroughbred horses. Finally he reviewed briefly some of the experimental laboratory investigations on prob-
lems such as the distribution of the Rh substance in the body and attempts at isolation of the Rh hapten.

Dr. C. A. Holman (Lewisham Hospital) gave an analysis of 164 cases of Rhesus iso-immunization in women attending local antenatal clinics during the past two years.

Dr. Dorothy H. Heard (Department of Pathology, Cambridge) reported that in a stock of rabbits, some of whose young were born dead or moribund, showing marked edema, no antibodies were detected in the does' sera after three pregnancies. However, later 9 does who had been injected with whole blood from bucks to which they were subsequently mated developed antibodies. The red cells of the young from these matings were sensitized but the baby rabbits were not affected clinically.

Dr. Lavinia S. Mynors (Department of Pathology, Cambridge) reported failure to produce isoimmunisation in guinea-pigs by mating and injecting blood from the mate.—S.C.

SICKLE CELL ANEMIA IN THE WHITE RACE: STUDY OF A FAMILY WITH A REVIEW OF GENETIC THEORIES. R. A. Guyton and R. W. Heinle. From the Department of Medicine, Lakeside Hospital, and the School of Medicine, Western Reserve University, Cleveland, Ohio. Am. J. M. Sc. 220: 272-275, 1950.

A case of sickle cell anemia in a white Sicilian girl is presented with a family study, showing that the sickling trait was present in 5 of 9 available members of her family. Possible theories of the genetics of sickle cell anemia are reviewed and the authors' conclusions are as follows. None of the previously widely accepted theories fully explains the genetics in all reported cases. It is certain from study of reported cases and their families that transmission as a simple mendelian dominant is an impossible explanation in many instances. It is suggested that the homozygous-heterozygous theory is probably correct, but that failure of one or both parents of a sickle cell anemia patient to show sickling is the result of incomplete penetrance of the trait-producing gene. This explanation does not necessitate the assumption that much data previously accumulated are based on incorrect laboratory procedures.—G.E.C.


This is a clinical report of a family of seven in whom the father and three of the children had a hemolytic crisis within a month. The blood findings were characteristic of familial spheroctic anemia. The mother and two unaffected members of the family showed no abnormality. There was evidence in the case of the father that the crisis was due to a temporary marrow failure rather than increased hemolysis, as in cases reported by Owren.—S.C.

LEUKEMIA AND MALIGNANT LYMPHOMA


The author comments on his experience in aminopterin treatment of acute leukemia in 10 adults and 14 children. None of the adults showed a good response but some of the children, notably those with lymphoblastic leukemia, had remissions, 4 being alive as long as six months to a year after starting treatment. The drug was given in a dose of 0.5 to 1 mg. daily with maintenance therapy even during remission. In some children the blood and bone marrow appeared to return to complete normality. In an attempt to prevent ultimate relapse, Innes is now supplementing treatment with an oral nitrogen mustard preparation (R 48), but there is no indication as yet whether this will be an improvement on aminopterin alone.—S.C.

ABSTRACTS

Aminopterin was used to treat 5 cases of myeloblastic and one of monocytic leukemia in adults and 3 cases of myeloblastic and 4 of lymphoblastic leukemia in children. As others have observed, the effect of treatment was most striking in the children, all of whom showed a temporary remission, whereas only 2 of the adults showed a temporary remission.

The aminopterin was given in interrupted courses, treatment being suspended when the patients were in remission. Where there was a good response the peripheral blood and bone marrow approached normal, but leukemic cells never completely disappeared from the marrow.—S.C.


This report analyzes the data collected over a five year period on 95 cases of lymphomas and leukemias, including 57 cases of Hodgkin’s disease, treated with nitrogen mustard. The clinical response of each case was evaluated according to a classification which included the duration of remission after single courses of treatment, the duration of effective nitrogen mustard therapy, and the period of survival and normal activity from the initiation of nitrogen mustard therapy. The results in general conform with the experience of others in indicating the value of nitrogen mustard therapy in Hodgkin’s disease, lymphosarcoma and chronic lymphatic leukemia.

Of particular interest is the discussion of the relationship of nitrogen mustard to irradiation therapy. It is the authors’ belief that nitrogen mustard should not be used as the sole therapeutic agent in lymphomas and that treatment should consist of relatively intensive irradiation to local tumor masses for as long as feasible with early institution of nitrogen mustard therapy at appropriate intervals to restrict multicentric foci.—H.W.B.


The blood volume was determined with $^{14}$-labeled red blood cells in 24 cases of chronic lymphatic and 17 cases of chronic myelogenous leukemia. The variation of the total red cell volume for a given volume of packed red cells was so large that it was of little or no value for the prediction of the total red cell volume in either normal subjects or patients with chronic leukemia. Normal plasma volumes were present in 80 per cent of the patients with chronic lymphatic leukemia. Eleven of the 13 patients with myelogenous leukemia who had palpable spleens had high plasma volumes but had normal total red cell volumes. —G.E.C.


The incidence of leukemia as a cause of death in nonradiologic physicians for the 5-year period 1944 to 1948 inclusive was 0.72 per cent (113 in 15,637). The incidence of leukemia in radiologists during this period was 4.84 per cent (6 in 124). These percentages approximate those reported for the preceding 15-year period in both nonradiologic physicians (0.44 per cent) and radiologists (4.57 per cent). The combined figures for the two decades 1929 to 1948 inclusive become: 65,922 nonradiologic physicians died, of whom 334 died of leukemia (0.51 per cent). During this same period 299 radiologists died, of whom 14 had leukemia (4.68 per cent). Thus, leukemia has occurred more than 9 times as frequently in radiologists as in nonradiologists. This figure has the statistical validity that there is one chance in a billion of this observed increased incidence rate being coincidental.—G.E.C.

Three cases of carcinoma, five of leukemia and two of lymphosarcoma are reported.

Two of the patients with cancer were treated with cortisone, with some general improvement but no alteration in the actual neoplasm. One cancer patient treated with ACTH showed a striking improvement and diminution in size of his squamous carcinoma of the lip.

The leukemic patients were all treated with ACTH. One died on the fourth day of treatment. One with myelogenous leukemia had great clinical and moderate hematologic response but developed hallucinations. The other three with lymphatic leukemia showed good but temporary remissions.

Cortisone in the two patients with lymphosarcoma also produced good but temporary remissions.—S.C.

Uric Acid Excretion in the Course of Chemotherapy of Leukemia. L. Défer, M. Hrubíško and J. Hružík. From the 1st Medical Clinic, Slovak University, Bratislava, Czechoslovakia. Čas. 16k. čes. 88: 1419, 1949.

An increased excretion of endogenous uric acid was observed in patients with chronic leukemia treated with urethane or nitrogen mustard (TS 160). This excretion was higher after the second drug and ran proportional to the rate at which the proliferating system decreased in size. This was partly reflected in the leukocyte count. The factors influencing the rate of uric acid excretion were (1) potency of the cytostatic drug determined by its chemical composition, responsiveness of the proliferating system and the frequency of mitotic divisions; (2) the total mass of the hyperproliferating system which is parallel within certain limits to the initial leukocyte count; (3) the dose and mode of administration of the cytostatic; (4) the initial purine metabolism.

The greatest fall of leukocytes and the highest figures for urinary uric acid were encountered with the usual nitrogen mustard administration (TS 160, 0.1 mg./Kg body weight in two to four doses given every second day). The leukocyte fall is more protracted and the excretion of uric acid is slightly after a single dose of nitrogen mustard or when smaller doses are given (1 mg. twice daily for ten days) or with the usual doses of urethane. No conclusions about a different mode of cytostatic effect of these two drugs can be drawn from these results. The differences are due to a different mode of administration of a similar principle.—M.N.


The authors report a case of a 46 year old male with Hodgkin’s disease, treated with x-ray and nitrogen mustard during a five year period, who developed marked ascites, generalized anasarca and pleural effusion prior to death. The most significant postmortem finding was amyloidosis involving the spleen, liver, kidneys and adrenals. Evidence of Hodgkin’s disease, however, was minimal.

Twenty-nine other reported cases of coexistent amyloidosis and Hodgkin’s disease were tabulated with respect to the findings pertinent to the diagnosis of amyloidosis. It was concluded that the most reliable antemortem differential criteria for determining the presence of amyloid in Hodgkin’s disease were the presence of proteinuria and a significant absorption of congo red from the blood.—H.W.B.