NEOPLASTIC LEUKOCYTIC DISEASE

The effects of and indications for the use of triethylene melamine (TEM) are discussed in the light of the authors' experience.

When given intravenously in doses of 2 to 3 mg., TEM rarely produced nausea or vomiting, whereas at higher doses nausea did occur and persisted longer than that caused by HN₂. Pancytopenia was produced as a delayed toxic effect.

Oral administration of the drug in doses of 5 mg. may produce nausea and vomiting eight to fifteen hours later. Maximum marrow depression may not occur until seven to fourteen days after the last dose. The initial dose is thus usually 10 mg. given in two to four days.

Lymphatic leukemia usually responds to small doses, and 5 mg. are given as the initial dose in this condition.

Data are presented for 15 patients with Hodgkin's disease (12 showed some improvement), 4 with chronic myelogenous leukemia (3 improved), 6 with chronic lymphatic leukemia (5 improved) and a variety of allied conditions.

HN₂ is indicated when rapid control is desirable. The oral administration of triethylene melamine produces results qualitatively similar to the effects of HN₂, but the ease of administration, the possibility of maintenance therapy, the lesser nausea and vomiting and the slower and more prolonged form of the oral treatment make it a drug of potential value.

—T.R.T.,Jr.

THE PROTECTIVE EFFECT OF CYSTEINE ON LEUKOPENIA INDUCED BY NITROGEN MUSTARD.

A. S. Weisberger and R. W. Heinle. From the Department of Medicine, Lakeside Hospital and the School of Medicine, Western Reserve University, Cleveland, Ohio. J. Lab. & Clin. Med. 36: 872-876, 1950.

Cysteine hydrochloride injected intraperitoneally into rabbits, in doses of 650 to 1000 mg. per Kg. body weight ten to fifteen minutes before injecting HN₂, 2.5 mg. per Kg. body weight intravenously, resulted in partial protection against leukopenia. There was no such protection when cysteine was injected immediately after HN₂. When 25 mg. of BAL per Kg. body weight was injected intramuscularly one hour before HN₂, no protection against leukopenia was afforded. No statement is made concerning what factors were taken into account in deciding the time intervals so employed. The possibility of clinical application of these findings is considered.—T.R.T.,Jr.

Atrophy of the thymus, spleen and lymphoid tissues as well as hypertrophy of the adrenal cortex after administration of aminopterin had been previously observed in rats by other workers. This and other related findings led the authors to study the excretion of adrenal hormones in 20 patients with untreated acute leukemia, in 8 cases of untreated chronic leukemia and in 6 patients with acute leukemia who received 0.5 to 1.0 mg. of aminopterin daily.

The excretion of urinary corticosteroids in 15 of the untreated patients who had acute leukemia were within normal limits, 4 cases had slightly elevated values and one had a subnormal value. All of the 8 patients with chronic leukemia had normal values.

The urinary excretion of 17-ketosteroids was low in 13 cases of acute leukemia and at the low range of normal in 1 case. Four cases of chronic leukemia had low values.

In 6 cases of acute leukemia the administration of aminopterin led to a marked reduction in urinary corticosteroids in 3 cases and a slight depression in 1 case. In 1 case there was a disappearance of the urinary corticosteroids.

ACTH was given to 1 patient whose output of corticosteroids was markedly depressed as a result of aminopterin therapy with a resulting augmentation of urinary corticosteroid excretion. It is therefore suggested that the adrenal cortex was still capable of responding but that the adrenocorticotropic function of the anterior pituitary was depressed by aminopterin.

No further understanding of the action of aminopterin is provided by this study, but it is at least demonstrated that aminopterin did not cause an increase in adrenocortical function.—T. R. T., Jr.


A group of 12 children, comprising 9 with lymphoblastic, 2 with myeloblastic and 1 with myelocytic leukemia, was treated with parenteral aminopterin, supplemented by frequent blood transfusions and prophylactic penicillin or aureomycin. The effect of therapy was evaluated in the light of serial, usually weekly, bone marrow examinations as well as by the clinical response and the routine periodic hematologic studies.

As to be expected the most satisfactory responses were observed in those patients with acute lymphoblastic leukemia. The marrow changes in 5 of the 9 children in this group were interpreted as showing definite improvement although a true hematologic remission, such as noted in one other briefly mentioned patient under treatment with amethopterin, was not seen in any of these patients. It is of interest that, despite the favorable response, the life span of the patients with lymphoblastic leukemia, compared to that of several untreated groups was not prolonged by aminopterin.

The main purpose of this report is to emphasize the value of the data obtained by frequent bone marrow examination. These findings served not only to evaluate the overall inhibitory effect of aminopterin but also provided a fairly accurate guide to the therapeutic management and avoidance of toxic reactions in these patients.—H. W. B.

THE INHIBITION OF CHICKEN-BONE-MARROW CHOLINE OXIDASE BY AMINOPTERIN IN VIVO. J. S. Dinning, C. K. Keith, P. L. Davis and P. L. Day. From the Department of Biochemistry, School of Medicine, University of Arkansas, Little Rock, Ark. Arch. Biochem. 27: 89-93, June 1950.

No choline oxidase activity was observed in chicken bone marrow after aminopterin administration while control marrow exhibited activity. The authors report a single experiment in which prolonged administration of large doses of aminopterin failed to alter
the general appearance or hemogram of the rabbit, a species whose bone marrow is said to contain no choline oxidase. The authors raise the possibility that the leukopenic effects of aminopterin may be related to its effect on choline oxidase.—W.N.Y.


Aminopterin is a potent inhibitor of the functions of pteroylglumatic acid (PGA). CF (citrovorum factor) is a substance formed from PGA by metabolism in rat liver slices and utilized for growth by Leuconostoc citrovorum. In this organism it has been noted that the inhibition of its growth by aminopterin was counteracted effectively by concentrates of CF derived from liver or urine.

The possibility that aminopterin inhibits the functions of PGA by interfering with either the conversion of PGA to CF or the utilization of CF, or both, is the subject of this paper. The data accumulated show clearly that aminopterin interferes, both in vitro and in vivo, with the conversion of pteroylglutamic acid to the factor(s) which promotes the rapid growth of L. citrovorum. The product of the metabolic alteration of PGA, viz. CF, not only is capable of preventing the toxicity of aminopterin, but also acts as a biologically active derivative of PGA as demonstrated by the growth response of PGA deficient rats which received aminopterin and a concentrate of CF. Inhibition of the conversion of PGA to CF was more complete in liver slices if aminopterin was injected into the rat rather than added directly to the tissue in vitro. The aminopterin apparently competes for the enzymes in vivo and in vitro which accomplish the conversion of PGA to CF.

In addition aminopterin interferes directly with the utilization of CF by bacteria, particularly L. citrovorum. However, in mice and rats, 250,000 units of CF daily completely counteracts the toxic effects of aminopterin. This last observation may afford a means of counteracting the toxic action of aminopterin when it is used clinically in the therapy of acute leukemia in children.—R.B.C.


Liver extracts and fermentation liquors from Streptomyces griseus contain a growth factor for Leuconostoc citrovorum. A microbiologic tube test has been developed for this factor and an arbitrary unit has been defined. The factor is not identical with vitamin B₁₂ or vitamin B₂₅. Concentrates of the factor derived from liver or from fermentation liquors, and containing vitamin B₁₂ have been purified approximately ten times. The factor appears to have no activity against pernicious anemia, but possesses leucocyte stimulating activity.—G.E.C.


The authors have compiled an excellent summary of this subject, and discuss in the light of their own experience the indications and contraindications for therapy in the various types and stages of lymphomatous disease. The use of HN₂, P₃₂, x-ray and triethylene melamine is discussed. The article is useful for orientation of both the student and clinician.—T.R.T., Jr.

DIAGNOSTIC AND THERAPEUTIC ASPECTS OF MULTIPLE MYELOMA. L. R. Limarzi. From the Department of Internal Medicine, University of Illinois College of Medicine, Chicago Ill. M. Clin. North America Chicago number: 189-224, 1951.

This is an excellent comprehensive review of all aspects of multiple myeloma. It is based on 75 cases of the disease and in addition includes an intelligent review of the literature. The article should be equally useful to the student and the experienced clinician.—T.R.T., Jr.

The clinical and laboratory manifestations of 32 cases of multiple myeloma are analyzed and discussed with reference to the reported findings of others.—H.W.B.

CONGENITAL LYMPHATIC LEUKEMIA. R. C. Heen. From the Laboratory of the Milwaukee Hospital, Milwaukee, Wis. Am. J. Dis. Child. 80: 800-802, 1950.

The rare occurrence of lymphatic leukemia in the newborn is reported. Clinical manifestations included multiple purpuric lesions, fever, hepatomegaly, splenomegaly, anemia and lymphocytosis with predominantly mature lymphocytes. The infant died on the forty-second day of life. Autopsy findings revealed widespread cellular infiltration of the skin, liver, spleen, lymph nodes, bone marrow, kidneys and to a lesser extent, other organs. —H.W.B.


A case of congenital myelogenous leukemia verified by autopsy findings is reported. The case is of particular interest because of the unusual feature of multiple cutaneous nodules which showed leukemic infiltration. The course of the disease was unaltered by urethane therapy and the infant died on the fourth day of life.—H.W.B.

THE PRESENCE OF FACTORS IN THE BLOOD OF LEUKEMIC INDIVIDUALS WHICH INFLUENCE THE LEUKOCYTE COUNT IN HEALTHY PERSONS. G. Oliver and C. Tramontana. From the Medical Department of the University of Perugia, Italy. Schweiz. med. Wchnschr. 80: 306-308, 1950.

The authors injected 20 cc. of oxalated plasma from leukemic patients into healthy persons and for twenty-four hours repeatedly counted the leukocytes. In 14 cases the result was a marked increase in neutrophile leukocytes with plasma from myeloid and of lymphocytes with plasma from lymphatic leukemia. Control cases did not show any response. —C.M.

INFECTION MONONUCLEOSIS

NEUROLOGICAL COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS. J. L. Silversides and J. C. Richardson. From the Department of Medicine, University of Toronto and Medical Service, Toronto General Hospital, Toronto, Ontario. Canad. M. A. J. 85: 138-143, 1950.

Three cases of infectious mononucleosis with neurologic complications are reported. In one patient a convulsion and stupor preceded the general manifestations of the disease; a second patient had a severe myelitis and later a relapse with convulsions; the third patient developed facial diplegia after the second week of illness. All 3 patients recovered.

Fifty-nine reported cases in the literature are reviewed and the neurologic complications classified into four main types. In order of frequency these were: (1) lymphocytic (serous) meningitis, (2) encephalitis (meningo-encephalitis, encephalo-myelitis, etc.), (3) Guillain-Barré syndrome and (4) peripheral neuritis. Eight fatalities from neurologic complications have been reported.

While the neurologic manifestations of infectious mononucleosis are extremely variable and the diagnosis rests entirely upon the other clinical features of the disease, this report stresses the importance of keeping the disease in mind when infections of the central nervous system of unexplained or probable viral origin are encountered.—H.W.B.

During the investigation of the hematologic changes associated with exposure to cold, it was noted that many of the blood films revealed abnormal mononuclear cells consistent with a diagnosis of infectious mononucleosis. This prompted a further investigation.

Twenty-six men were observed. There were 5 clinical and 21 sub-clinical cases. The authors discuss the difficulties of diagnosis in these and in other reported cases and point out that at the present time infectious mononucleosis cannot be considered as a well defined entity.—T.R.T., Jr.


In none of 34 cases admitted to the hospital has the right diagnosis been made by the practitioner. Twenty per cent of the patients admitted as diphtheria turned out to be infectious mononucleosis.—C.M.

EOSINOPHILIA


A case is reported of a 2 year old child with chronic eosinophilia, leukocytosis, hyperglobulinemia, pulmonary infiltrations and eosinophilic granulomatous lesions in the liver. In view of the recent reports of this syndrome this case is of unusual interest because larvae of A. lumbricoides were demonstrated within the liver. Several aspects of the case strongly implicate an allergic reaction to ascaris rather than ascaris infestation per se as the underlying mechanism.

While the authors do not suggest that ascaris is the etiologic agent in all cases and agree with the concept that this clinical entity is probably due to a sensitivity to one of several antigenic agents, it is their contention that specific lesions are caused by a hyperergic tissue response to actual antigen contact rather than to a general allergic reaction with the liver or lung acting as a “shock organ.”—H.W.B.


A case of chronic pulmonary infiltration with low grade fever, leukocytosis and eosinophilia in a 48 year old female is reported. Extensive investigative and therapeutic efforts failed to reveal the etiologic mechanism in this patient. An allergic tissue response, however, could not be definitely ruled out, since after a five months' illness, improvement began within several weeks of the institution of desensitization procedures.

The similarities of the case to Loeffler’s syndrome and tropical eosinophilia are discussed. Reference is not made to the recent reports of a somewhat similar syndrome in children. Obviously this entire group of probably related (allergic?) disorders needs continued investigation and elucidation.—H.W.B.


This critical review is written primarily from the point of view of dermatology. However, it is a scholarly discussion of the problem which should be valuable to all clinicians, especially hematologists. The author concludes that the term “eosinophilic granuloma” has outlived its usefulness, and that it should no longer be used. He points out that the term represents a heterogeneous assembly of diseases and that it may obscure the diagnosis rather than clarify it.—T.R.T., Jr.
"MEGALOBLASTIC" ANEMIA


A megaloblastic anemia similar clinically to the megaloblastic anemia of infants was produced experimentally in monkeys fed various milk diets all deficient in vitamin C. In an attempt to determine the specific therapeutic and prophylactic effects of vitamin C, vitamin B12 and pteroylglutamic acid it was found that megaloblastic anemia did not occur regardless of diet if adequate vitamin C was provided but that all the diets devoid of vitamin C resulted in megaloblastic anemia unless sufficient amounts of folic acid were also administered. The megaloblastic marrow could be reverted to normal gradually by vitamin C administration alone and rapidly by either folic acid or the simultaneous administration of vitamin B12 and vitamin C. Vitamin B12 alone, however, did not alter the bone marrow nor did it prevent the development of megaloblastic anemia when given prophylactically. The possibility of other contributory etiologic factors such as inadequate dietary protein, infection and gastro-intestinal abnormalities was ruled out in these experiments.

While one mechanism probably does not account for all cases of megaloblastic anemia in infants, these experiments and certain dietary observations of others indicate that many such cases probably are the result of a vitamin C deficiency which in some way interferes with the metabolism of folic acid and related compounds. It would, therefore, appear reasonable, unless vitamin C deficiency can be safely excluded, to include vitamin C in the therapeutic regime of these infants with megaloblastic anemia, particularly if vitamin B12 is the antianemic agent selected.—H.W.B.


Three cases of Addisonian pernicious anemia were treated by a single intramuscular injection of citrovorum factor. The first 2 given 20 and 40 million units respectively showed a slight but incomplete response. The third given 80 million units showed a good response. One unit corresponds to 0.15 to 0.20 μg. synthetic citrovorum factor, i.e., the effective dose was in the order of 12 to 16 mg. of citrovorum factor.—S.T.C.

VITAMIN B12 IN PERNICIOUS ANAEMIA IN REMISSION. M. F. Beard, S. K. McIttanie and M. Nataro. From the Medical Department, University of Louisville School of Medicine, and the Medical Service, Veterans Administration Hospital, Louisville, Ky. South. M. J. 43: 678-685, 1950.

A preliminary report is made of the observations during a four month period on 18 patients with pernicious anemia in remission who were transferred from 120 units of liver extract per month (30 units per week) to 30 μg of vitamin B12 per month. Six patients who did not have optimal blood levels previously showed symptomatic and hematologic improvement on this dosage of vitamin B12; 5 patients were unchanged or very slightly improved; and the remaining 7 showed a decline in hemoglobin either with or without subjective complaints. The cause of this progressive hypochromia remained unexplained.

It was concluded that there was no apparent consistent relationship between micrograms of vitamin B12 and units of liver extract and that any patient being transferred from liver extract to vitamin B12 therapy needed close clinical and hematologic follow-up. It was also the authors' opinion that vitamin B12 is not a complete replacement for liver extract as maintenance therapy in some patients. Such a conclusion appears premature, however, in view of the many variables in an experiment of this kind; e.g., individuality of response and of storage of liver principle, the relatively small dosage of vitamin B12 used compared to the previously required liver extract dose, variation in potency of liver extracts and possibly of the vitamin B12 concentrates, etc. There appears to be little advantage at the
abstracts

present time, however, in changing the therapy of a patient with pernicious anemia who is well controlled on liver extract.—H. W. B.


This is an interesting report of treatment with penicillin of a single case of megaloblastic macrocytic anemia in an African Negress. The patient had been treated and responded on two occasions to liver extract. In her next relapse treatment with marmite was started but two days later she developed fever and pulmonary congestion and was given penicillin. A good hematologic remission occurred. Seven months later she was seen again in severe relapse and was given penicillin only without marmite. Again a good hematologic remission was seen. The possible mode of action by the penicillin is discussed.—S. T. C.


This is a detailed report of the results of treatment of 2 cases of pernicious anemia with thymidine (the preliminary results were published in Lancet 2: 962, 1949). A total dose of 2 and 2.8 Gm. of thymidine respectively produced a hemopoietic response in both patients with conversion of megaloblastic to normoblastic marrow. Ten to 20 mg. of the thymidine concentrate was equivalent to 1 μg. of crystalline B₁₂ assayed by Leishmania leichmannii. —S. T. C.


This is a supplement to the review recently published (Brit. M. J. 2: 1367, 1949). It describes the characteristics of vitamin B₁₂c and B₁₂d which have been obtained in crystalline form from fermentation liquors of Streptococcus griseus. The new factors appear to be slight chemical modifications of the vitamin B₁₂ molecule rather than conjugates with peptides. Other recent advances in knowledge of the structure of B₁₂ are reviewed.—S. T. C.

Heme pigments


The authors describe a substance in the normal plasma which is able to split up the hemoglobin molecule and liberate the iron atom in vitro. The substance is believed to be a protein of the albumin fraction and can be destroyed by heating, CO and KCN. In cases of nephrosis there was a distinct diminution of the substance.—C. M.

studies of coproporphyrin. Y. the isomer distribution and per diem excretion of the urinary coproporphyrin in cases of cirrhosis of the liver. C. J. Watson, D. Sutherland and V. Hawkinson. From the Department of Medicine, University of Minnesota Hospital, Minneapolis, Minn. J. Lab. & Clin. Med. 37: 8-28, 1951.

The urinary coproporphyrin (UCP) was studied in 88 cases of hepatic cirrhosis. The ratio of the type I to type III isomers was determined in 79 of these cases. Six of these cases had hemochromatosis. Elevated UCP was observed in 83 of the cases. There was no correlation with the level of total serum bilirubin, and the most marked increase occurred in a patient with a normal serum bilirubin. The UCP was more often abnormal than the twenty-four hour urine urobilinogen, the urine Ehrlich test on two hour samples, or the cephalin flocculation or
thymol turbidity tests. The UCP was best correlated with the bromsulfalein retention test, although there were several instances of disagreement.

The type III isomers was preponderant in the alcoholic group and the type I isomer was preponderant in the nonalcoholic group.—T.R.T., Jr.

STUDIES OF COPROPORPHYRIN. VI. THE EFFECT OF ALCOHOL ON THE PER DIEM EXCRETION AND ISOMER DISTRIBUTION OF THE URINARY COPROPORPHYRINS. D. A. Sutherland and C. J. Watson. From the Department of Medicine, University of Minnesota Hospital, Minneapolis, Minn. J. Lab. & Clin. Med. 37: 29-39, 1951.

It was shown in the previous paper that alcoholic cirrhosis is characterized by an absolute increase in the type III isomer of coproporphyrin as contrasted with the increase of type I in most cases of cirrhosis in nonalcoholic individuals. The studies reported were made in an effort to determine the effects of acute alcoholism in individuals without evidence of liver disease. These individuals had all been chronic alcoholics prior to the time of observation.

There was an increase in UCP in most of the individuals studied. This increase was in the main due to the type III isomer, and occurred in some cases “without appreciable evidence of liver functional impairment.”

Large increases of UCP were noted in a group of 5 chronic alcoholic subjects who were given large amounts of alcohol in a short space of time. The increased UCP occurred two to four days after the intoxication. It is concluded that the increase was due to a new formation of porphyrin rather than to a release of porphyrin which had already been formed.—T.R.T., Jr.


“A paper strip, drop-reaction test is described which affords a simple, direct, dependable screening test sufficiently sensitive to detect hyperbilirubinemia.

“The test can be done on 1 drop of serum in one minute. The technique is simple, the easily prepared reagents and paper strips are stable, and no elaborate equipment is required.”—T.R.T., Jr.

HEMOLYTIC ANEMIA


Cabot rings, which can be examined easily with the electronic microscope in partially hemolyzed erythrocytes are considered as folds of the erythrocyte membrane which may contain traces of hemoglobin.—C.M.


The sheep erythrocyte antibodies produced in rabbits cause a marked deformity and a fusion of the red blood cells during their agglutination. These changes could be eliminated if albumin (antispherical factor) or lecithin (spherical factor) was added to the agglutinating serum. On the contrary, several hemagglutinating sera obtained from human infectious mononucleosis do not cause any deformities of the sheep blood cells. The general conception that the hemagglutinins induce invariably a deformation of the agglutinated red cells cannot be maintained. The balance of a spherical and an antispherical factor is more important in the production of red cell deformities than the antibodies themselves.—C.M.

ABSTRACTS

From the Department of Medicine of the New York Hospital, Cornell University Medical Center, New York, N. Y. J. Lab. & Clin. Med. 37: 253-263, 1951.

The authors describe their studies of the blood of a patient "who suffered from sensitivity to cold, Raynaud's phenomenon, bleeding from mucous membranes, retinal hemorrhages, progressive deafness and arthritis, a combination of symptoms which were thought to be attributable at least in part to the presence in his circulating blood of a cold precipitable protein in the remarkably high concentrations of 5.4 to 9.8 Gm. per cent." A diagnosis of multiple myeloma and cryoglobulinemia was subsequently made.

In order to prevent jelling, the blood of this patient was drawn in warm syringes and maintained at 37 C.

Studies were made of the gross and microscopic appearance of the blood on slides at room temperature and at 37 C. The effect of saline dilution was also studied. In 5 patients with cryoglobulinemia the sedimentation rate was found to be markedly increased in all instances. There were a number of detailed observations made of this phenomenon. It was found that the increased sedimentation rate was not due to intrinsic properties of the red cells, that it was due, at least in part, to factors other than fibrinogen, and that a factor was present in the plasma which accelerated the sedimentation rate in undiluted blood and which exhibited acceleration initially with low dilutions and retardation with higher dilutions. The addition of purified cryoglobulin to normal blood profoundly affected the sedimentation rate.

It is suggested that these studies re-emphasize the wisdom of employing either a thirty minute or both a thirty and sixty minute reading when determining sedimentation rates.

The various factors influencing the sedimentation rate in the presence of a cryoglobulin are discussed.—T.R.T., Jr.

SOME NEWER CONCEPTS OF "CONGENITAL" AND "ACQUIRED" HEMOLYTIC ANEMIAS. L. E. Young, R. M. Christian and M. J. Izzo. From the Department of Medicine, The University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial Hospital, Rochester, N. Y. Med. Clin. N. America. 35: 571-585, 1951.

The author has reviewed the cardinal aspects of hereditary spherocytosis and has attempted to discuss another group of hemolytic anemias which he has termed "chronic hemolytic disease with erythrocyte-bound antibody."

In this latter group are included those cases usually known as acquired hemolytic anemia. There is a brief discussion of the recent advances in knowledge as revealed by the Coombs test, as well as a short summary of therapy including splenectomy, transfusion and ACTH.

The article may be useful as a general introduction to this subject.—T.R.T., Jr.


Anti-erythrocyte serum, anti-bone marrow serum and anti-blood serum was fed to newborn rats in the first 18 days of life. A typical hemolytic anemia was observed in all cases which resemble the human erythroblastosis. Older rats did not respond similarly to the same procedure. It is suggested that in human Rh erythroblastosis the clinical picture also is partially due to enteral resorption of antibodies ingested with the mother's breast milk.

—C.M.

NOTICE

It has been suggested to the Editorial Board that the readers' attention again be called to the special subscription rate to the Journal for interns, fellows and residents within the United States. This rate is $9.00 per year.

Anyone falling into one of these categories and also interested in the special rate should write to the publisher giving hospital affiliations.