ABSTRACTS

JOSEPH F. ROSS, M.D., Editor

ABSTRACTERS

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LEUKEMIA AND MALIGNANT LYMPHOMA


The clinical and roentgenologic findings in 72 children with leukemia have been analyzed. X-ray evidence of bone involvement was obtained in over 70 per cent of cases studied, by far the most common abnormality being the appearance of a transverse band of diminished density in the metaphyses of the long bones. This band was the first sign of skeletal disease in the majority of patients, and the sole osseous change in almost half of the cases exhibiting x-ray changes. Roentgenographic signs, when present, invariably included evidence of involvement in the knee area, in view of which it is suggested that routine roentgen examination of this region might provide a helpful screening technic in the investigation of all suspected cases of leukemia, perhaps obviating the necessity of more extensive skeletal surveys.

C. P. E.


The life duration of patients with chronic leukemia is summarized from the literature by the authors. The frequency of remission, effect of infection and treatment is discussed. The hematologic data of 31 patients with lymphogenous and myelocytic leukemia chosen from 190 cases of the authors because of their long survival are tabulated.

C. A. F.

OBSERVATIONS IN GUINEA PIGS FOLLOWING INJECTION OF SPECIFIC HEMATOPOIETIC SUBSTANCES DERIVED FROM BEEF LIVER. L. M. Meyer and A. Sawitsky. From the Department of Therapeutics, New York University, College of Medicine, New York, N. Y. Am. J. Path. 24: 835-855, 1948.

The authors report pathologic changes observed in guinea pigs receiving repeated intramuscular injections of extracts prepared from normal beef liver as follows:

An ethanol extract of dried liver, after concentration and saponification, was repeatedly extracted with ether before and after treatment with carbon dioxide and hydrochloric acid. After successive extractions with petroleum ether and methanol, the material was treated with lead, and the acidified ether-insoluble lead salts were crystallized at minus 2.0 degrees C. in acetone. The noncrystalline material in the mother liquor having been concentrated (B-acids), it was separated by succination into carbinols and noncarbinols.

Nine animals received B-acid extracts derived from 200-800 grams of beef liver. Seven of this series
developed Hodgkin's-like lesions in cervical nodes, spleen, liver, adrenal and kidney. The bone marrow exhibited myeloid hyperplasia in 6, lymphoid hyperplasia in 1 and no changes in 2 animals. Myeloid metaplasia of the cervical nodes and spleen were noted in 1 guinea pig. The carbinol fraction was injected into 12 guinea pigs, in 9 of which a lymphoid reaction developed, myeloid changes being noted in another of this series. Of 18 guinea pigs receiving the noncarbinol fraction, 13 exhibited varying grades of myeloid reaction, 5 others presenting evidence of a mixed myeloid and lymphoid stimulation; definite myeloid hyperplasia resulted in 13 animals of this series.

It is concluded that beef liver extracts of the "carbinol" type stimulated lymphoid hyperplasia and infiltration, and those of the "noncarbinol" type, myeloid hyperplasia and infiltration when injected into guinea pigs. The resultant lesions were clinically and pathologically dissimilar to spontaneous leukemia. A reciprocal relationship between myeloid and lymphoid tissues, with respect to their reactivity to hemopoietic stimulation and relative rates of proliferation, appears to have been confirmed.

C. P. E.


Guinea pigs were injected with urine extracts including the carbinol fractions of urines from patients with lymphoid leukemia, and noncarbinol fractions derived from the urine of patients with myeloid leukemia. Although the resultant lesions were clinically and pathologically dissimilar to those characteristic of spontaneous leukemia, the results suggested that the urines of leukemic patients contain materials which are extractable and separable by the methods described, carbinol fractions inducing a specific lymphoid hyperplasia and infiltration, and the noncarbinol fractions inducing a myeloid response.

C. P. E.

In summarizing their own and other reported material on skeletal lesions of Hodgkin's disease, the authors stress the underlying marrow involvement. They have studied by sternal aspiration 59 patients with proven Hodgkin's disease and reviewed pathologic material on 20 patients, looking for marrow involvement. One is impressed by the nonspecificity of changes in differential cell counts of the marrow which include (1) a shift to the left in neutrophile series with a relative decrease in segmented neutrophiles and an increase in bandforms; (2) increase in eosinophilic myelocytes. There also appeared to be increased megakaryocytes in several instances. It would have been interesting to determine how frequently a specific diagnosis could have been made on aspirated pieces of marrow prepared by fixation and sectioning. In this respect, the authors indicate only that in 11 of 20 autopsied cases, Hodgkin's disease was found in the marrow sections reviewed. The difficulty of morphologic differentiation between reticulo-endothelial cells, Sternberg-Reed cells and megakaryocytes is not discussed.

C. A. F.

DIAGNOSIS OF PRIMARY HODGKIN'S DISEASE OF THE STOMACH. E. L. Pirke and S. M. Roberts. From the Department of Radiology, University of Louisville School of Medicine, Louisville, Ky. Radiology 52: 757-78, 1949.

To the 22 cases of primary Hodgkin's disease already in the literature, the authors add one of their own. Interest in this diagnosis stems from the fact that, so far as published reports go, if the patient survives the operation of gastrectomy, complete cure is likely. The usual preoperative diagnosis, based on x-rays, is extensive infiltrating carcinoma of the stomach. The authors suggest, however, that the characteristic of Hodgkin's disease is polyp-like masses along the involved gastric area on the x-ray, an appearance which is relatively constant in all these cases, although there may be no other symptoms or signs or laboratory findings to suggest Hodgkin's disease.

Although the authors' patient did not survive postoperatively, autopsy failed to reveal Hodgkin's disease anywhere except in the operative specimen. The authors' data suggest that a radiographic diagnosis of "extensive carcinoma of the stomach," in the absence of metastases, should not preclude attempt at operative treatment, since the diagnosis may be wrong and, apparently, removal of a stomach involved by primary Hodgkin's disease may result in cure.

S. E.


From an analysis of the literature relative to pregnancy in the course of Hodgkin's disease, 3 cases of which are described in detail by the author, it is concluded that this disease has no demonstrable influence on ovulation, fertility, or the obstetric aspects of gestation, parturition or the puerperium. The disease was transmitted from the mother to the fetus across the placenta in 9 per cent of reported cases. No evidence was obtained to indicate that x-ray therapy results in injury to the shielded fetus. Artificial interruption of pregnancy, on the basis of coexisting Hodgkin's disease, appears, therefore, to be unwarranted.

C. P. E.


The chemotherapeutic value in malignancy of microbial products, antireticular cytotoxic serum, folic acid conjugates and antagonists, stilbamidine, urethane, androgens, estrogens and nitrogen mus-

This paper presents a concise historical review of chemotherapy in the proliferative disorders of the white cells and summarizes the author's experiences with nitrogen mustard (described in Blood 4: 338, 1949) and with certain folic acid antagonists, including aminopterin, a-methopterin, amino-an-fol and a-ninopterin. Of 21 cases of acute or subacute leukemia who survived more than four days after initial therapy, remissions occurred in 9. The most pronounced drug toxicity and greatest efficacy were demonstrable in the patients receiving aminopterin, which proved to be as effective, and toxic, when administered orally as when given parenterally. It was apparently necessary to produce definite toxic manifestations in order to achieve a remission. Therapeutic complications included ulceration of tongue and mucous membranes, nausea, upper abdominal discomfort and diarrhea. Vascular purpura and an enhanced bleeding tendency were also observed.

It was concluded that the folic acid antagonists possess, in varying degrees, the capacity to induce remissions in about one-third of the cases of acute and subacute leukemia, both in adults and in children, and in both leukemic and leukopenic forms. Clinical, hematologic, and at least partial marrow remissions occurred most commonly in lymphocytic, and least often in monocytic leukemia. Although by no means curative, these agents were therapeutically effective to a degree suggesting that, with increasing knowledge of cellular enzyme systems and their inhibitors, great improvement in the treatment of leukemia may be anticipated and that the successful control of this disease may ultimately be achieved.

C. P. E.

EFFECTS OF FOLIC ACID ANTAGONISTS INOCULATED IN EMBRYONATED EGGS. P. F. Wagley and H. R. Morgan.
From the Thordike Memorial Laboratory, Boston City Hospital, Boston, Mass. Arch. Path. 46: 441-450, 1948.

Since 1928, when Sabin first reported that fraction R of liver extract would influence the development of primitive erythroblasts of living chick blastoderms, contradictory results have been obtained by various investigators. Muller (1932) and Hays, Last and Koch (1942) obtained negative results. Reimer (1938) observed nonspecific degenerative changes in the liver. More recently, Riggio (1942) has observed that chick embryos incubated 32-33 hours responded to liver extract in three ways, viz., reversal of the ratio of erythroblasts and micromegaloblasts, reduction in percentage of histioid cells and an increase of mitoses in prophase. The present article by Wagley and Morgan is important because it shows that when some folic acid antagonists are injected into the yolk sac of chicks incubated for six to eight days hematopoiesis is definitely influenced. Blood islands are decreased in size and number, nuclei exhibit pyknosis, karyolysis and karyorrhexis. The larger doses of antagonists shortened the time for survival of the embryos. It was possible to protect against this effect by using relatively large doses of folic acid but not...
possible with the dosage of liver extract and vitamin B_{12} used. In this connection it should be noted that Rusznýk, Lőwinger and Lajtha (1947) reported that folic acid acts directly on megaloblasts in tissue culture. Methyl 4-aminopteroylglutamic acid was not as potent as 4-aminopteroylglutamic acid and N\textsuperscript{10}-methylpteroylic acid had no effect in relatively large doses. Experiments like this should be encouraged and extended.

O. P. J.


The present experiments reinvestigate on dogs experiments of a similar nature previously conducted on rats. Although the data are of a similar nature, better information concerning the daily changes in the blood picture were obtained. The material consisted of 17 dogs and the vesicants used were bis (2-chloroethyl) sulfide dissolved in thiodiglycol, the hydrochlorides of ethyl-bis (2-chloroethyl) amine and tris (2-chloroethyl) amine dissolved in isotonic sodium chloride solution just before being injected into the saphenous vein. The results indicate that not only are vesicants rapidly acting specific poisons, but that they have a slower more general intoxicating effect. Secondary pathologic changes occur in the organs which are believed to interfere with their proper functioning.

O. P. J.

MULTIPLE MYELOMA. ITS CLINICAL AND LABORATORY DIAGNOSIS WITH EMPHASIS ON ELECTROPHORETIC ABNORMALITIES. W. S. Adams, E. L. Alling and J. S. Lawrence. From the Departments of Medicine and Radiology, University of Rochester School of Medicine and Dentistry, and the Medical Clinics of the Strong Memorial Hospital and the Rochester Municipal Hospital, Rochester, N. Y. Am. J. Med. 6: 141-161, 1949.

Sixty-one cases of multiple myeloma were analyzed and emphasis was placed on the most common and characteristic clinical and laboratory findings. A large section of this presentation is devoted to the electrophoretic study of the plasma protein abnormalities. These studies were considered of particular value in the differential diagnosis of this disease.

Of the 30 cases of multiple myeloma studied electrophoretically, 21 showed major abnormal patterns with tall, narrow peaks; 8, without such peaks, presented slight but significantly irregular pattern abnormalities, and 1 case of solitary myeloma of the antrum with chronic infection showed patterns consistent only with infection.

The association of Bence Jones protein with multiple myeloma is discussed. It was observed that the incidence of Bence Jones proteinuria was low in the group with large abnormal peaks in their electrophoretic patterns but high in those patients with only small abnormalities. It is suggested that these small abnormal peaks were due to Bence Jones protein in the plasma and the Pence Jones proteinuria occurred in these patients because of the absence in the plasma of a protein of high molecular weight capable of forming complexes with Bence Jones protein.

Undoubtedly, electrophoretic studies will prove of great value in the future in our objective evaluation of the beneficial effects in this disease of the various chemotherapeutic agents.

O. P. J.

RADIATION EFFECTS


The exposure of rats to large single or repeated doses of beta rays from P_{32} externally placed resulted in the appearance in the rats, some ten to twelve months later, of a large variety of tumors of the skin and subcutaneous connective tissue. Rats were exposed either to single doses of beta irradiation from plastic materials containing radioactive phosphorus; or to repeated daily doses for a period of months. If the dose was sufficiently low, there were no effects of the irradiation. When single doses of 4,000 to 6,000 "rep" (roentgen equivalent physical) were given, typical changes occurred as follows: In one week,
acute skin erythema was followed by desquamation, alopecia, ulcers, and, in some rats, death in four weeks. Rats which survived showed healing of ulcers, blindness, falling off of the ears, alopecia, telangectasia of the skin, and, ultimately, neoplasms. The neoplasms were of all varieties seen in the skin and connective tissue, and were malignant. Certain nonmalignant changes (production of extra claws; soft tissue papillomata) also occurred.

These changes were less marked at single doses of 8,000 "rep," suggesting an "optimal" range for their production. They were much less marked in certain of the animals exposed to small daily doses over a period of months. Tumors did not occur in control males, and were much less frequent in control females.

No conclusions are drawn which might relate to human usage of internal beta irradiation (i.e., in clinical application of PIII therapy). The range of dosage in the authors' experiments was extremely large ('rep' is the amount of ionizing radiation produced in one gram of tissue by 1 roentgen) and outside the clinical range. The conclusion, however, that this type of irradiation resulted in a change in the destiny of certain cells, is obviously tenable and of great interest in questions of growth.

S. E.

BONE MARROW


Several interesting and logical, although admittedly controversial, concepts are presented in this excellent discussion of normal bone marrow physiology and the functional disturbances associated with various disease states.

Normal hemopoiesis involves three distinct functions: (1) multiplication of precursor cells by mitosis; (2) maturation of cells; and (3) release of mature elements. Mitosis and maturation are considered as opposing although finely integrated tendencies in the development of the marrow cells. While both processes normally occur in nearly all stages of cellular development, mitosis predominates in younger cells and maturation in the more highly developed cells with a fairly even balance between the two in the intermediate stages. In various pathologic states the functions of multiplication and maturation become dissociated. Thus, if mitotic function is lost in the more highly differentiated cells, the number of immature cells increases markedly due to the depletion of the more mature cells and to the predominance of mitosis over maturation at primitive levels. Maturation of such cells is, therefore, scanty, slow and abnormal.

Perhaps the most controversial point in the discussion is the concept that all immature red and white cells which appear in the peripheral blood in abnormal conditions (e.g., leukemia) come from extramedullary foci of hemopoiesis rather than from the bone marrow. Several observations are cited to support this viewpoint. In certain conditions in which extramedullary hemopoiesis can be demonstrated or assumed, this is easily conceivable, but there would appear to be noteworthy exceptions. The answer must await a more thorough understanding of the mechanism of release of cellular elements from the bone marrow.

H. W. B.

STUDY OF FIXED TISSUE SECTIONS OF STERNAL BONE MARROW OBTAINED BY NEEDLE ASPIRATION. III. METASTATIC CARCINOMA IN STERNAL BONE MARROW. A. S. Weisberger and R. W. Hemle. From the Department of Medicine, Lakeside Hospital and the School of Medicine, Western Reserve University, Cleveland, Ohio. Am. J. M. Sc. 177: 263-268, 1949.

Of 50 selected patients with malignant tumors, 7 were found to have metastatic lesions in the sternal bone marrow as demonstrated in tissue sections of particles obtained by needle biopsy. Sternal marrow metastases were found only in the case of those tumors which have a tendency to metastasize to bone. Metastatic lesions were found in the marrow in 2 patients after operations for carcinoma of the lung and breast respectively. In one patient a metastatic lesion in the marrow was the only positive antemortem evidence of carcinoma. This would indicate that the procedure might be of benefit preoperatively in cases of carcinoma which are likely to metastasize to bone, and as a diagnostic tool in selected cases.

G. E. C.
ANEMIA


Prepartum fetal roentgenographic findings in erythroblastosis are described in 4 cases. These changes include increased bone density, zones of decreased density in the long bones at the cartilagenous juncture, soft tissue edema, evidence of fetal death.

It would be desirable to have information on a much larger number of cases before any possible value of these changes in anticipating erythroblastosis can be evaluated.


It had previously been noted that, although the macrocytic anemia associated with certain cases of coeliac disease responded favorably to pteroylglutamic acid, other types of anemia in such cases did not show any response to the material. The authors treated 22 children in whom they were able to establish a diagnosis of coeliac disease. None of these children apparently had fibrocystic disease of the pancreas. None of these cases had macrocytic anemia.

For a preliminary period of one to two months, treatment consisted of a low-fat high-protein diet with added liver extract and vitamins. After this period, pteroylglutamic acid was added to the regimen for a comparable period of time. The dose of folic acid was 20 or 10 mg. daily for one to two months. There was no particular change in the laboratory or clinical status of the patients on folic acid, and the author concluded that this material had no effect on coeliac disease in cases in which a macrocytic anemia (and megaloblastic marrow) were absent.


The subject of this report was pale at birth and showed, at the time of initial examination at the age of 18 months, pallor, slight hyponutrition, mental retardation, and ptosis of one eyelid (which was present congenitally). The liver, spleen, and lymph nodes were normal. The red cells numbered 1,300,000 per cu. mm., with a hemoglobin of 20 per cent (1.8 Gm.); the white cells and platelets were normal; reticulocytes were virtually absent; and a bone marrow aspiration showed a marked reduction of erythroid activity. A subsequent bone marrow biopsy showed "absence of red cell precursors." Treatment was of no avail, except blood transfusions, which were necessary and sufficient to maintain the child's blood at reasonable levels.

According to the authors, there are very few reports of pure red cell anemia in the literature, perhaps 6 in children and 7 in adults. This report therefore is the seventh in a child. Of importance, state the writers, is possible spontaneous remission following repeated blood transfusion over a long period of time; hence continued treatment, although without optimism, is indicated.


Ten cases with necropsy findings are presented in which profound sickling of the red cells was the outstanding and often the only significant finding. None of the patients had active sickle cell disease. In several cases ischemic lesions were seen in the spleen, kidney or brain, although thrombus formation was not demonstrable in the vessels supplying these areas.

The question is raised as to whether vascular obstruction is produced primarily by the masses of agglutinated sickle cells observed histologically or whether sickling and agglutination are merely secondary phenomena under conditions of stasis and anoxemia. Regardless of which is the initiating factor,
these cases do emphasize the potential hazard of sicklemia in conditions producing lowered oxygen tension such as shock, anesthesia, fever and congestive failure.

H. W. B.


Two patients with pernicious anemia in relapse, taking 30 and 50 mg. of pteroylglutamic acid daily, developed acutely sore tongues with mucosal atrophy during the third month of therapy. The lingual mucosal atrophy of 5 patients with untreated pernicious anemia responded in five to seven days to injection of vitamin B12. The authors mention that in 6 of their patients treated with pteroylglutamic acid, whose lingual responses were poor or who later relapsed, the blood levels remained below normal; neurologic disease progressed in one, and the red cell count fell significantly in another. They state in conclusion: "The therapeutic limitations of pteroylglutamic acid in pernicious anemia relate to all manifestations of the disease—anemic, neurologic, and lingual—rather than to merely the neurologic."

G. E. C.


Studies, using *L. casei* and *St. faecalis*, of the fate of pteroyltetraglutamic acid in human subjects indicated that two hours after intramuscular injection approximately two-thirds of the dose was present in the circulation. Of this total, about two-thirds was present as the monoglutamate, one-third as the triglutamate. Subsequently, the concentration of the monoglutamate declined more rapidly than the triglutamate. Different individuals showed considerable variations from the average metabolic pattern.

G. E. C.


A case is reported of a girl who at 12 months developed severe anemia following enteritis. She responded to treatment with liver and iron, but relapsed after a further attack of diarrhea and vomiting, and was readmitted to hospital at 17 months. On investigation, the anemia proved to be megaloblastic and responded to folic acid treatment.

S. C.


The authors present a thorough review of the literature and report 3 additional cases of Marchiafava-Micheli syndrome, bringing the total reported at the time of writing to 76. The review emphasizes the abnormality in the erythrocytes which undergo lysis by a thermolabile component of normal serum. Hemolysis is inhibited by sodium citrate, potassium oxalate, potassium cyanide, and heparin. The possible efficacy of pilocarpine nitrate in treatment is mentioned, a favorable influence on hemolysis apparently being observed in one case. The drug in this instance had to be discontinued because of undesirable side effects. Splenectomy is ineffective and is accompanied by a 40 per cent operative mortality in the cases where it has been attempted. Since hemolytic anemia without hemoglobinuria may dominate the clinical picture, the necessity of performing the specific serologic tests for this disease in any obscure hemolytic anemia is apparent.

W. N. V.


Three forms of anemia are seen in myxedema: (1) The uncomplicated myxedemic anemia (endocrine type); (2) the hypochromic anemia (endocrine type plus sideropenia); (3) (very rare) the hyperchromic form similar to pernicious anemia.
NEWS AND VIEW

The author gives a description of a typical case of the third form. The following characteristics differentiate the myxedematous pernicious anemia from the typical pernicious anemia: (1) unusually high color index (not treated 1.9); (2) inhibition of hemolysis; (3) inhibition of bone marrow activity; (4) course free from fever and relative bradycardia despite severe anemia; (5) normal or slightly reduced basal metabolism.

The endocrine disturbance prepares the way for pernicious anemia.


Mixed solutions of benzene and its derivatives as used in ‘intaglio’ damage the leukopoietic system and cause a moderate anemia of the hyperchronic type. This anemia is characterized by a slight increase of the average diameter of the red cells. Investigations based on 10 cases illustrate the diagnostic importance of this hyperchromic anemia as an early symptom.


In the past, the many studies of pernicious anemia marrow during relapse have reported a decrease in megakaryocytes in general, and alterations in nuclear segmentation and lack of azurophilic granules in some instances. In the present study, marrow was aspirated from 5 patients before therapy was begun and again after the reticulocyte response had occurred. The number of megakaryocytes was estimated in terms of a million nucleated cells within about 20 oil-immersion fields. Two general classes of megakaryocytes were recognized, viz., the mononuclear group and the group containing multiple nuclei in a single cytoplasmic mass. The latter are referred to as polykaryocytes of which there may be young, intermediate and mature forms. During relapse, the percentage of polykaryocytes was high and that of the mononuclear megakaryocytes low. After remissions were induced by liver extract therapy, the ratios were reversed. Whole blood and red cell concentrate transfusions did not produce this reversal. In other words, the megakaryocytic system in pernicious anemia during relapse needs something other than an increase in the oxygen-carrying capacity of blood.

O.P.J.


A family with methemoglobinemia is described in whose case, contrary to former observations, heredity was not recessive but dominant. Furthermore the pigment was not the usual methemoglobin but a new modification with a maximum absorption band at 602mμ. The author believes that this variation is due to a specific change in the globin component of the hemoglobin molecule.

C.M.