IRON METABOLISM


C.M.


This review includes a comprehensive discussion of the iron compounds of the body and their properties, the mechanisms concerned in the regulation of iron absorption by the gastrointestinal mucosa, and the possible abnormalities in iron metabolism which may lead to the development of hemochromatosis. The author's own hypothesis of the regulation of iron absorption assumes the existence of a gradient of reduction in the mucosal cell; e.g., that part of the cell nearest to the lumen of the gut is less reducing for ferric iron and that portion closest to the blood stream has a higher reducing ability. Two regulatory mechanisms, however, are probably involved. One is the determination of the amount of ferrous iron moving into the cell by a mucosal block which is related to the ferritin content of the mucosal cells. The other concerns the reducing ability of the cell wherein the amount of ferrous iron entering the blood stream depends on the relative redox level of the cell which in turn is a function of the amount of oxygen supplied by the blood stream.

Evidence is presented which suggests that the metabolic defect in hemochromatosis does not reside in those factors concerned with the mucosal block but rather is related to a greater reducing tendency of the cell for iron which permits more iron to enter the blood stream. Such a state could arise from either an increase in the effectiveness of reducing enzymes or a decrease in effectiveness of oxidizing enzymes. (See also: S. Fransden, Acta med Scandinav. 128: 186-191, 1947.)

H. W. B.


The author has made investigations especially with ferrous gluconate and ferrous formiate. He found that small peroral doses of iron (44 mg.) did not substantially alter the serum iron level of normal as well as of anemic subjects. Even larger doses of iron very rarely influenced the serum iron level of normal persons. It is the author's opinion that the hydrochloric acid in gastric secretion is of little significance for the absorption of iron preparations, yet that it plays an eminent role in the utilization of the iron in the food. The absorption rate of iron compounds may be assumed only in anemias. In cases
of infectious anemias and of malignant tumors the absorption of iron is inhibited, i.e., we find the same rates as in normal persons. Yet there are some cases of infectious anemias that respond readily to high doses (400 mg. iron). In cases of idiopathic, chronic, hypochromic anemia a well tolerated iron compound is necessary. The ferrous gluconate fulfills this requirement remarkably well.

C.M.

ANEMIA

The Anemic States: Their Causes and Treatment. C. A. Doan and C. S. Wright. From the Division of Medical Research, Department of Medicine, Ohio State University, Columbus, Ohio. M. Clin. North America 33: 541-560, 1949.

The authors briefly discuss normal erythropoiesis and erythrophagocytosis, the anemias of central bone marrow origin, and finally anemias due to excessive peripheral demand (loss or destruction). Under the last subject the views of these authors on 'hypersplenic' syndromes are discussed in some detail with illustrative examples.

G.E.C.


A study of the effect of the parenteral administration of vitamin B₁₂ on the course of 8 patients with Addisonian pernicious anemia was made. Following an initial dose of 25-50 micrograms, all patients exhibited reticulocytosis within 48 hours and peak response at about 96 hours following injection. In only 2 were secondary reticulocyte responses induced by a subsequent injection. Although maximal reticulocytoses as indicated by Isaacs' formula were not obtained, the immediate conversion of megaloblastic bone marrow to a normoblastic picture and the return of erythrocytes and hemoglobin to normal levels within sixty days indicated a satisfactory remission. The authors recommend average maintenance injections of vitamin B₁₂ in the amount of 0.0 micrograms at intervals of one month. Paresthesias and other symptoms relative to early and moderately advanced combined system disease were found to disappear or be ameliorated. In a single case sensitive to refined liver, no sensitivity to vitamin B₁₂ was noted. Preliminary observations on a group of patients whose combined system disease had persisted in spite of large doses of liver extract indicated some subjective but no objective improvement in their condition following the administration of vitamin B₁₂.

W.N.V.

Treatment of Pernicious Anemia with Crystalline Vitamin B₁₂. R. Weiss and E. H. Reisner, Jr. From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Fourth Medical Division, Bellevue Hospital, New York, N. Y. Am. J. Med. 6: 643-650, 1949.

Eleven cases of Addisonian pernicious anemia treated with parenteral vitamin B₁₂ are reported. All showed a satisfactory hematologic remission, and 5 patients with combined system disease showed neurologic improvement. Different, and in several cases amended, dosage schedules were employed, and from these several observations it was concluded that the effective parenteral dose was slightly less than one microgram daily. This approximation of a minimal effective dose is borne out by other similar studies. Any evaluation of the effectiveness of an average daily dose must, however, take into consideration the frequency and size of the individual doses.

H.W.B.


Six patients with macrocytic anemia associated with pregnancy were studied within a few weeks after delivery. The reportedly satisfactory clinical and hematologic response to folic acid is illustrated by one case report.

The author stresses the importance of realizing an association between this type of anemia in the
mother and the development of megaloblastic anemia in the infant, and states that both of these can usually be prevented by treatment of the mother with folic acid during the late stages of pregnancy.

H.W.B.


Two hundred grams of wet feces from a patient with untreated pernicious anemia were subjected to a papain digest and phenolic extraction. \textit{L. lactis} Dorner assay of the extract showed 1 microgram per ml. equivalent of B\textsubscript{12} activity. Five ml. of extract given daily for five days to a second patient with untreated pernicious anemia resulted in an optimal therapeutic response. Chromatography of the extract gave a chromatogram closely resembling those shown by purified liver extracts.

S.C.


Twenty-six rats made anemic by the formation of a cul de sac in the small intestine (see Lancet 2: 404, 1948, Blood 2: 803, 1949) were divided into four groups; a control group, and groups treated parenterally with Anahaemin, pteroylglutamic acid and vitamin B\textsubscript{12} respectively. There was a significant increase in survival time with pteroylglutamic acid but not with Anahaemin or B\textsubscript{12}. Five of 6 animals treated with P.G.A. showed an hematologic remission. Two from each of the Anahaemin and B\textsubscript{12} groups of 7 and 6 animals also had a remission. The impression was that this was not fortuitous, but as spontaneous remissions occurred in the control group, the effect of liver extract and B\textsubscript{12} was not clear cut.

S.C.


A case of nutritional macrocytic anemia in a mentally subnormal woman of 56 is described. The anemia failed to respond to treatment with 2 ml. Anahaemin daily for ten days followed by 4 ml. "Plexan" crude liver daily for five days, but a good response was obtained with folic acid.

S.C.


This is a detailed report of the two cases of celiac disease associated with megaloblastic change in the bone marrow, already briefly described in 1946 (Dalton et al., Lancet 2: 632, 1946). Treatment with folic acid resulted in general improvement with reversion to normoblastic marrow. One child remained well after discharge on 5 mg. folic acid twice weekly, but the other relapsed. A second relapse later led to complicating infection and death.

S.C.


A technic is described for L. Dorner assay of B\textsubscript{12} in liquid medium. (For details the original article should be studied.) An identical shape of dose response curve is obtained with all types of liver extract, crystalline B\textsubscript{12} and Thymidine or a blend of any of these. Digesting liver with papain does not alter the shape of the curve.

S.C.

The Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients Suffering with Chronic Suppurative Infection. J. C. Robinson, G. W. James, III, and R. B. Kark. From the Medical
Nutrition Laboratory, Department of the Army, and the Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois. New England J. Med. 240: 749-753, 1949.

Nine patients with prolonged suppurative infections were treated for two to eleven weeks by the oral administration of 2.0 to 60 mg. of cobaltous chloride daily. This uniformly resulted in a reticulocytosis, an increase in the circulating erythrocyte, hemoglobin and packed red cell concentration of the blood and an increase in the total red cell mass. This is a clean-cut demonstration of the stimulating action of cobalt on the bone marrow as has previously been demonstrated in animals.

The studies of Heilmeyer, Carwright and Wintrobe and others indicate that the primary fault in the anemia of infection is a retarded rate of hematopoiesis. The clinical demonstration that cobalt acts in the opposite direction to counteract this anemia still leaves open the fundamental question: is the anemia of infection harmful to the individual, or is it a useful compensatory device to conserve metabolic energy during a period of emergency? More evidence must be accumulated before it will be possible to pass opinion on the desirability of cobalt therapy for the anemia of infection.

C.A.F.


Cobaltous chloride (CoCl₂ 6 H₂O) was administered to 61 patients by mouth. In 7 convalescent and 8 psychotic patients, consistent reticulocytosis and elevation of hemoglobin and red count above control levels were observed. The average reticulocyte peak on a dose of 350 mg./day was 4.9 per cent and occurred between the fourth and tenth day. This dose of cobaltous chloride was not tolerated by 12 patients with pernicious anemia in remission. A good erythropoietic response was observed in 2 of 3 patients with infection. Five patients with refractory anemia and hyperplastic bone marrow gave no response. Sixteen patients with anemia due to leukemia or lymphoma were treated. There was no response in 13 of the patients. In 3 others, evidence was equivocal because of therapy of the underlying disease. One of 2 patients with hypocromic anemia due to iron deficiency and one patient with Cooley's trait responded, while a patient with the anemia of liver disease was not affected. Two patients with chronic nephritis could tolerate the drug for only a few days but showed no reticulocyte response.

No serious toxic manifestations were observed but gastrointestinal symptoms of nausea and vomiting were present in 37 of the 61 patients.

It is apparent from this and other studies that cobalt provides an additional stimulus to the marrow for hematopoiesis. One might generalize from these observations that the action of cobalt is most conspicuous when the bone marrow is not under a great stimulus before treatment. As stated by the authors, "the possibility that the erythropoietic action depends upon a fundamental alteration of tissue respiration indicates the need for further studies of chronic toxicity in animals. . . ."

C.A.F.

POLYCYTHEMIA VERA

OSLER'S CHRONIC CYANOTIC POLYCYTHEMIA WITH SPLENOMEGALY. M. M. Wintrobe. From the Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah. Bull. Johns Hopkins Hosp. 89: 75-86, 1949.

An excellent discussion of the historical aspects, clinical features, pathologic physiology and pathogenesis of polycythemia vera with particular reference to the contributions of Sir William Osler is presented. Brief mention of available therapy is made. Of particular interest is the critical evaluation of the various concepts of the pathogenesis of the condition and particularly those concepts relating to the role of anoxia. The author, while regarding the subject as an open one, is inclined to favor the view that erythremia is similar in its pathogenesis to leukemia and is not attributable to the influence of anoxia on the bone marrow.

W.N.V.

THE CONTROL OF POLYCYTHEMIA BY MARROW IRRADIATION. A TEN YEAR STUDY ON 172 PATIENTS. J. H.
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Lawrence. From the Division of Medical Physics and Donner Laboratory, University of California, Berkeley, Calif. J. A. M. A. 141: 13-18, 1949.

Of 172 patients with various forms of polycythemia, radioactive phosphorus was used in the treatment of some 121 in whom the diagnosis of idiopathic polycythemia (polycythemia vera) could be made. This report details the results of this form of treatment ten years after its inception.

In general, the results of treatment were very satisfactory, with good relief of symptoms and signs. Of all patients treated, 48 per cent required only one course of treatment; of those treated during the first five years, 28 per cent had only one such course, and some required no further therapy for four to as long as eight years. Among other things, the spleen regularly became smaller or even impalpable following treatment. Some 35 per cent of patients with polycythemia in whom the blood pressure was initially elevated, showed a fall of blood pressure after P32 therapy. Some 70 per cent of patients with initial leukemoid blood counts showed disappearance of this feature following P32.

There was no evidence of an increase of leukemia following the use of P32: of the 11 deaths in this series, 5 (about 4 per cent) were due to leukemia. This complication was no more frequent in this group than in polycythemic patients who are untreated, or treated with other methods (Fowler’s solution, x-ray, etc.).

It was of interest that thromboses seemed to be reduced following the use of P32: they occurred in 4.2 per cent of patients following therapy, as compared with 15 per cent before treatment. Phlebotomies alone did not reduce the incidence of thromboses to this degree.

Finally, the average duration of life following diagnosis was 17 years. The average age at diagnosis in this group was 50.7 years; at death, 67 years. The author points out, therefore, that with this form of treatment, the life expectancy of the newly-discovered polycythemic is as good as that of the diabetic with insulin, or that of the pernicious anemia patient with liver extract. The use of radioactive phosphorus is recommended as the ideal form of treatment of polycythemia vera at the present time.

S.E.

LEUKOCYTES


From the Departments of Medicine and Preventive Medicine and Student Health, University of Wisconsin Medical School, Madison, Wis. Am. J. Med. 6: 311-318, 1949.

Liver function tests were performed at random or in series during the course of infectious mononucleosis in 83 patients between the ages of 17 and 34. Tests included icterus index, qualitative urine urobilinogen excretion, cephalin cholesterol flocculation, thymol turbidity, prothrombin time and bromsulfalein dye retention. One or more of these tests were abnormal in 75 of the cases. The most frequently abnormal test was the cephalin cholesterol flocculation, which became positive early and for a significant length of time in nearly all cases tested in series. Since it was positive more uniformly than the heterophile antibody determination, it was considered a valuable diagnostic aid whenever infectious hepatitis of virus etiology could be excluded. The next most frequently abnormal test was the thymol turbidity. Abnormalities in the icterus index, urobilinogen excretion and bromsulfalein retention were also detected in a significant number of cases.

This and other studies indicate that nearly all patients with infectious mononucleosis will demonstrate abnormal liver function at some time during the course of illness.

The authors comment on the difficulty in differentiation between infectious mononucleosis and infectious hepatitis, the lack of correlation between abnormalities in liver function and duration of symptomsatology in infectious mononucleosis, and the need for further study of these patients, particularly after recovery. Until the clinical significance of these changes in liver function is known, it is suggested that patients with infectious mononucleosis be placed on the same regimen recommended for patients with infectious hepatitis.

H.W.B.

The present investigation was prompted by the finding of numerous mast cells in and about a spontaneous epithelium-like reticulum cell splenic neoplasm in mice. No relationship could be established between neoplastic and mast cells. Miscellaneous neoplasms, with the exception of some luteomas, were in general free from mast cells. Apparently some tumors either stimulate mast cell proliferation or attract mast cells. This may be brought about by some substance present in the tumor or by a metabolite of the tumor cells. These suggest additional experimentation with subcutaneous injections of cell-free extracts of certain tumors. Recent histochemical evidence links mast cell function with production of the ground substance of connective tissue and the blood clotting mechanism.

O.P.J.

EVALUATION OF METHODS OF ENUMERATING STERNAL MARROW EOSINOPHILS. Philip Piolato. From Clinical Laboratory Service, Veterans Administration Hospital, Department of Pathology, Charity Hospital of Louisiana and Louisiana State University School of Medicine, New Orleans, La. Am. J. M. Technol. 14: 215-216, 1949.

The author evaluates the various methods of counting marrow eosinophils—chamber methods, direct smear, stained sections. A combination of the Levy Newbauer chamber method with the use of May-Grünwald propylene glycol as diluent plus the direct smear is recommended. Variations with any method even from a single procedure are appreciable.

W.N.V.


An experimental approach is presented for the study of the antibody content of lymphocytes collected from the thoracic duct lymph of cats. Using the technic described, and typhoid vaccine as an antigen, no antibody could be detected within extracts of washed lymphocytes. Comparative titrations of the relative antibody content of lymph fluid free of cells and lymph containing large numbers of lymphocytes which were artificially lysed in order to release their protein content into the surrounding lymph fluid also failed to indicate the presence of any antibody within the lymphocytes. Exposure of the animals to x-ray did not significantly alter the antibody content of the cell-free lymph fluid. Administration of large doses of adrenal cortical hormones failed to cause any significant alteration in the antibody content of cell-free lymph fluid.

G.E.C.

LEUKEMIA AND MALIGNANT LYMPHOMA


This is an extremely well written, easily readable general discussion on the subject of treatment of chronic forms of malignant lymphomas and leukemias. The author discusses therapy from the simple general approach of (1) the early, strictly localized disease, (2) the intermediate stage of spread of the disease, and (3) the stage of marked generalization of the disease. Individualization of treatment is stressed. Such therapeutic agents as nitrogen mustard, x-ray, urethane, arsenic, radioactive phosphorus, benzol and folic acid antagonists are considered. The author again expresses his encouraging belief that adequate early treatment of a localized early process may offer hope for cure.

G.E.C.


The authors add 64 more cases treated with nitrogen mustard to the literature. They include 14 cases of Hodgkin's disease, 4 of chronic lymphatic leukemia, 2 of chronic myelogenous leukemia, 8 of lympho-
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sarcoma, to carcinomas of the lung and other miscellaneous malignancies. Many of their cases had been treated with x-ray prior to mustard therapy. Data regarding the individual cases is effectively presented in tabular form. Conclusions are essentially the same as reported by others.

C.A.F.


The experimental use of folic acid conjugates and folic acid antagonists in the treatment of neoplastic diseases is briefly reviewed. It is pointed out that, while the status of chemotherapy of malignant disease remains essentially unchanged, a very real step has been made toward our understanding of the pathologic physiology of neoplasms. It is entirely conceivable that with further investigation of nucleic acid metabolism, more effective compounds with a far more selective effect on neoplastic tissue may be found.

H.W.B.

BLOOD COAGULATION AND HEMORRHAGIC DISEASE


In a study of 70 consecutive cases of various forms of liver disease, the authors noted the frequent occurrence of a hemorrhagic diathesis in those patients with parenchymatous liver disease (hepatitis, cirrhosis), whereas hemorrhagic phenomena were rare in non-parenchymatous hepatic disorders (stone, stricture, carcinoma of bile ducts or pancreas). The hemorrhagic manifestations, they found, were not due solely or necessarily to hypoprothrombinemia, but often to thrombocytopenia and to increases in capillary fragility. They therefore studied the occurrence of thrombocytopenia and increased capillary fragility in their 70 cases: of the 29 with extrahepatic jaundice, only 4 showed these abnormalities; of the 41 patients with hepatitis or cirrhosis, 37 showed a reduction in platelets, increased capillary fragility, or both. These findings could not be correlated with hypoprothrombinemia or with jaundice.

Few data, unfortunately, are presented to explain these findings. What bone marrow punctures were done showed "active marrows" and "megakaryocytes in adequate numbers"; there is no note as to platelet formation from the megakaryocytes. No data are given as to other bleeding tests beyond the generalization that, usually, "the bleeding time was prolonged, the coagulation time normal or slightly prolonged, and the clot retraction poor." The authors' comment that the associated hypoprothrombinemia made these tests difficult to interpret is strange. Nor can one accept the statement that the bleeding in liver disease may so often simulate that of idiopathic thrombocytopenic purpura, that every case of the latter disorder should be suspected of being thrombocytopenia secondary to liver disease (even to the point of liver biopsy) till disproven.

The data in this report, however, emphasize that the bleeding of certain patients with liver disease may be due, not to a reduction of prothrombin, but to thrombocytopenia and capillary defects. The mechanism for these alterations in blood and circulatory system, and the possible role of hypersplenism, are not discussed.

H.

HEMOPHILIA-LIKE DISEASE IN WOMEN. J. S. Hewlett and R. L. Haden. From the Division of Internal Medicine, the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, Ohio. J. Lab. & Clin. Med. 34: 151-157, 1949.

Two female patients with a clinical picture of hemophilia are presented. The outstanding characteristic was a prolonged coagulation time of the blood. The coagulation time of recalcified plasma was positive in both patients. When normal citrated plasma was added to blood from one of the patients the coagulation was markedly accelerated. Tiselius protein fractionation revealed a definite abnormality in the alpha-globulins in one patient and suggestive but not conclusive evidence of an abnormality in the
second patient. In these two patients the defect was similar to that found in hemophilia but the authors are careful to call this 'hemophilia-like disease' and suggest that an acquired change in the plasma protein pattern might be the basis for the coagulation defect.

G.E.C.

Changes in the Prothrombin Time Induced by Methylxanthines. Role of the Plasma Cofactor of Thromboplastin. R. Honorato. From the Chemical Laboratory, School of Dentistry, University of Chile, Santiago, Chile. Arch. Biochem. 22: 345-352, 1949.

The influence of caffeine, theobromine, theophyllin and sodium benzoate on the prothrombin time of rabbits was studied, and these substances were found to shorten the prothrombin time. These results can be observed in rabbit plasma only if the latter is diluted to 5-10 per cent. If dilutions are made with human fresh plasma treated with Al(OH)₃ or with fibrinogen solutions, care must be taken to make certain no thromboplastin cofactor is present in the diluent. The authors believe that these results are produced by an increase of the thromboplastin cofactor (? synonymous with Factor V [Owen] and AC-globulin [Seegers]) associated with the administration of these drugs.

W.N.V.


Ninety-nine patients were treated with dicumarol. Fifty per cent of these were treated as outpatients. One stage prothrombin methods (whole plasma, 12.5 per cent and 5 per cent plasma) were compared with the two-stage method. Wide variations between the methods were noted. With the two-stage method it was possible to maintain the prothrombin level accurately within a desired range over a period of months, with a maximum variation of 15 per cent. The one-stage method was found to be of value in estimating the summation of clotting factors in an individual blood, particularly at a time when the prothrombin as measured by the two-stage test was below 10 per cent. Bleeding occurred in 15 of the patients. In 13 of the 15 patients, the prothrombin level was below 11 per cent (two-stage method) when the bleeding became apparent and stopped when the prothrombin rose to between 15 and 20 per cent. In the other 2 cases, bleeding occurred following trauma, the prothrombin being 36 per cent at the time. The results of this study suggest that a range of 10 to 30 per cent (two-stage method) is a safe, efficient level for the maintenance of plasma prothrombin.

G.E.C.

MORPHOLOGY


Literature concerning bone and marrow infarction contains many contradictory reports based, in some instances, on nonphysiologic experimentation. The present series of experiments, conducted on 23 skeletally immature rabbits (2.3-3.3 Kg.), extended over a period of one day to six months. Infarcts were produced by transecting the nutrient artery and in most cases the accompanying vein of the femur. At the termination of the experiments, the femurs were cleaned and roentgenograms taken. Histologic preparations were made from fragments not over 2 cm. in length after decalcification in nitric acid. Tissue changes were detected in both bone and marrow twenty-four hours following infarction and were still evident after six months. In marrow infarcts, the absence of a fibrous cicatrix was striking. Fat released from necrotic cells was engulfed by phagocytic cells. Hematopoiesis was diminished or absent. An unidentified yellow material, presumably lipid, was noted in macrophages. As a rule small areas of necrotic bone were located along the inner margins of the cortex of the shaft.

O.P.J.


For quite some time, the large foamy cells derived from the reticulum and histiocytes in the spleen,
liver, lymph nodes and bone marrow in Gaucher’s disease have been known to contain kerasin, a cerebroside. This substance is composed of lignoceric acid, sphingosine and usually galactose. Such a compound might be expected to produce a positive reaction with the periodic acid-leukofuchsin method. This was confirmed by using pure kerasin isolated from human brain. Microscopic localization of this histochemical reaction in sections from three spleens removed from patients with Gaucher’s disease was made possible by the fact that the altered carbohydrate remains bound to the insoluble components of kerasin. Gaucher cells gave the brilliant rose-purple color of a positive reaction. The periodic acid-leukofuchsin method has differential diagnostic possibilities for lipidic diseases because characteristic foam cells of Niemann-Pick’s disease remain colorless.

RADIATION AND RADIOACTIVITY


This article is a review of experimental data related to the toxic effect of radiation. The radiation syndrome is divided into the initial shock, the acute period, the subacute period and the chronic period. The authors point out how limited our knowledge is, from the problem of how radiation produces cell damage to the interpretation of the many secondary metabolic effects which may be part of the general alarm reaction.


This article deals with the metabolism and tissue localization of products of nuclear fission. To evaluate the potential hazard of these radioactive isotopes, the substances were administered to rats orally, by inhalation and by parenteral injection. There are 14 isotopes of importance and their half life, fission yield, oral absorption, accumulation in the principal organ of retention and elimination are tabulated. Elements such as plutonium deserve special attention due to their skeletal localization and potential danger to the bone marrow. Radioautographs illustrate the osseous and pulmonary localization of some of these elements.


It has been widely recognized that lymphoid tissue is among the most sensitive indicators of damage by roentgen radiation. Further, after large doses of radiation the blood lymphocytes disappear very rapidly from the peripheral blood and are virtually absent in twenty-four hours. In this report changes in the numbers of thoracic duct lymphocytes and rate of flow of thoracic duct lymph in cats receiving a single dose of 1500 r whole body irradiation are recorded. Following this amount of irradiation the number of lymphocytes in thoracic duct lymph decreased rapidly.