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Hematology

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PROGRESS REPORT

1. THE INFLUENCE OF COBALT STIMULATION ON THE SENSITIVITY OF THE HEMOPOIETIC SYSTEM OF RATS AND GUINEA PIGS TO X IRRADIATION AND P^{32}

A pilot experiment in which X radiation or P^{32} was administered to rats having a cobalt-induced polycythemia has been completed and a larger series of rats has been prepared for an experiment which is now in progress.

Attempts are being made at the National Cancer Institute and in our laboratory to induce cobalt polycythemia in the guinea pig. Thus far, using equivalent dosages to those which are effective in the rat, there has been no evidence of polycythemia after 3 months of treatment. The purpose of this attempt to induce polycythemia in the guinea pig is to determine whether the precipitous anemia produced by daily exposure to 8.8 r total-body X radiation can be prevented or significantly modified by the prophylactic administration of cobalt.

2. THE SIGNIFICANCE OF ECTOPIC BLOOD FORMATION IN SR^{89} INTOXICATION

In previous experiments on mice it was found that the administration of Sr^{89} in a dosage of 2.2 μc per g of body weight produced no anemia in intact male and female mice. The same dosage produced a marked and sustained anemia in mice which were splenectomized prior to the injection. It was shown that the failure of anemia to develop in intact mice after this dosage of Sr^{89} was due to the fact that ectopic erythropoiesis developed so rapidly in the spleen that complete compensation for the bone marrow destruction resulted. Perhaps

of more fundamental interest in this experiment than the prevention of anemia was the fact the lymphatic nodules in the spleens of Sr^{89}-injected animals were depleted by three days after the Sr^{89} injection and remained so depleted for more than 60 days. The lymphatic tissue elsewhere in the body (lymph nodes and thymus) was not appreciably affected. Because ectopic blood formation in the spleen of these animals was so extensive, the possibility that lymphatic depression may be on a mechanical basis (crowding) has to be considered. We are therefore doing some experiments with mice and are studying the effect of mechanical crowding. This is being done by the administration of phenylhydrazine thereby forcing the spleens of the experimental animals to develop extensive ectopic hematopoiesis. We know from experiments on rabbits that this crowding factor is of no significance insofar as alteration in lymphatic tissue is concerned. Experiments are in progress in which intact rabbits, guinea pigs, and mice, as well as splenectomized animals of these species, have been given Sr^{89}. The purpose of the extension of this experiment to the guinea pig and rabbit is to determine whether 1) ectopic blood formation is a significant factor in the alleviation of Sr^{89} toxicity in mammals other than the mouse; 2) to determine whether there is selective depression of lymphatic tissue in the spleen of these species; 3) to determine the rapidity with which major hematopoietic activity is transferred to the spleen; and 4) to study the mechanism of the stimulation of erythropoiesis under these circumstances. This latter aspect is of great fundamental importance since the transfer of the bone marrow erythropoiesis to the spleen of Sr^{89}-injected animals occurred in the absence of appreciable reduction in the circulating erythrocytes. Therefore, it would appear that some mechanism

for the stimulation of erythropoiesis other than the accepted reduction in erythrocytes or reduced amount of circulating oxygenated hemoglobin must be postulated if these observations are valid.

3. THE QUANTITATIVE DETERMINATION OF FIBRINOGEN IN RABBITS HAVING A NITROGEN MUSTARD INDUCED COAGULATION DEFECT

A great deal of time has been spent in perfecting the technique of running quantitative fibrinogen on rabbit plasma in order to rule out the factor of fibrinogen reduction in the prolonged whole-blood clotting time (Lee-White) which occurs in rabbits after nitrogen mustard treatment or X irradiation. These studies indicate that no significant reduction in the fibrinogen occurs in the presence of the coagulation defect produced by these toxic agents but it appears as though a definite increase occurs.

4. CLINICAL STUDIES ON THE TREATMENT OF LEUKEMIA, HODGKIN'S DISEASE AND RELATED DISEASES WITH VARIOUS DOSAGES OF RADIOARSENIC

Nineteen patients with tumors of the hematopoietic system have been given As^{76} prepared by pile irradiation of arsenic trioxide and cacodylic acid. As^{76} has a half-life of 26.8 hours and energetic β and γ radiations. Dosages of As^{76} ranged from 1 to 80 mc with 3 to 10 mg of stable arsenic and were administered intravenously as the trioxide. Preliminary studies indicated that each mc was approximately equivalent to 1 r of total-body irradiation. In 4 previously untreated patients with chronic myelocytic leukemia, single injections of this radioisotope produced clinical and hematologic remissions. One of these patients is still in remission after 11 months. However, no significant clinical response was produced by the isotope in 2 patients with chronic myelocytic leukemia who no longer responded to conventional irradiation therapy. One patient having an acute myelocytic leukemia failed

to respond. One patient having a subacute myelocytic leukemia had clinical and hematologic remissions of about 2 months after each of 2 injections. However, this latter case required frequent transfusions, and an osteomyelitis of the femur failed to heal in spite of chemotherapy and surgery.

Three patients with chronic lymphocytic leukemia treated with less than 30 mc were not benefited. One aged male, previously insensitive to nitrogen mustard and needing massive transfusions, responded with a decrease in lymph node enlargement and splenomegaly, an increase in subjective sense of well-being, as well as a depression of the white count for about 2 months.

Two patients with acute lymphocytic leukemia were treated with 70 and 60 mc, respectively. One had a temporary and incomplete remission; the other, a definite clinical and hematologic remission of approximately 8 weeks.

Two patients with polycythemia rubra vera were treated with radioarsenic. A relatively brief remission was produced in one of these patients who was given a dosage of 45 mc. The other patient received essentially a tracer dosage. Four patients with Hodgkin's disease received less than 13 mc of As^{76} each. The clinical effect of the isotope on the course of these 4 patients was essentially insignificant. Likewise, 2 patients with multiple myeloma failed to respond favorably to the radioisotope.

The huge liver of a patient with metastases from a carcinoma of the stomach decreased about 5 cm in size following 80 mc of As^{76} in two dosages. Nevertheless, his clinical condition continued to deteriorate and he died within 2 weeks.

Serial biopsies have been obtained from the liver, spleen, and bone marrow of many of these patients before and after treatment with radioarsenic. A complete report on these hematologic and histologic studies in in progress.

Chronic External Irradiation

Dr. Egon Lorenz
Miss Margaret Sutton

PROGRESS REPORT

The work of this group during the past quarter may be summarized as follows:

Studies are being made of the effects of long-continued exposure of mice, guinea pigs, and rabbits to γ radiation. The data accumulated since April 1946 (the time at which the last complete reports were made) are being tabulated and analyzed for a final report which should be finished some time next year.

A series of new experiments, started since the beginning of the year, is under way, and parts are nearing completion. Some of the experiments are repetitions of previous ones (already reported). They cover the following problems:

1. Incidence of lung tumors following single exposure of newborn mice.

2. Incidence of lung tumors following total-body or lung irradiation only.

3. Incidence of mammary tumors following single exposures of newborn C_3H (b) mice.

4. Possible effects of continued as well as single exposures on the spontaneous gastric hyperplasia of strain I mice.

5. Anemia in inbred guinea pigs (family 2) induced by chronic exposures to 8.8 r, 4.4 r, 2.2 r, and 1.1 r.

6. Comparison of the breeding behavior of mice following single total-body exposures or single exposures to the ovaries only.