period of 14 days, injected with progesterone in daily doses of 50 mg for 7 days and 100 mg for 7 days, and observed during a final control period of 14 days. These doses of progesterone caused significant exacerbation of the glycosuria.

Discussion. Very large doses of progesterone are diabetogenic in the partially depancreatized, force-fed rat. The diabetogenicity of this hormone is enhanced by 11-oxygenation. The diabetogenic action of 11-ketoprogesterone is evident in the absence of the adrenal glands, thereby invalidating the hypothesis that it must be converted to an adrenal cortical hormone by the adrenal cortices before it is biologically active.

Progesterone and 11-ketoprogesterone are each capable of causing partial atrophy of the adrenal glands. The hypothesis was considered that it should be possible to cause some degree of adrenal cortical insufficiency by the administration of these compounds. Since there is a striking amelioration of diabetes in the adrenally insufficient rat we looked for signs of suppression of glycosuria in these experiments. There was a small decrease in the level of glycosuria in some of the rats given 2 to 16 mg daily of progesterone. This small change may or may not have represented suppression of adrenal cortical function. There was no significant suppression of glycosuria by any dose of 11-ketoprogesterone.

Summary. Partially depancreatized force-fed rats were injected with 1 to 100 mg per day of progesterone and 1 to 32 mg per day of 11-ketoprogesterone. Very large doses of progesterone caused exacerbation of the diabetes and 11-ketoprogesterone was found to be significantly more potent in this respect. The diabetogenicity of 11-ketoprogesterone is manifest in either the presence or absence of the adrenal glands.

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Received February 5, 1953. P.S.E.B.M., 1953, v82.

Hematologic Studies on Dogs Receiving Low Doses of Total Body Irradiation.* (20134)

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Most studies on the effect of either total or fractional body irradiation on the hematopoietic system have been performed with the application of relatively large doses. The use of such doses produced a multiplicity of changes which probably obscured some of the more basic effects. Therefore, the alteration in the level of circulating granulocytes was not considered to be a satisfactory indicator of the cellular activity in the bone marrow. Accordingly, a detailed study of both bone marrow and peripheral blood cell patterns was made to ascertain the effect of low doses of total body irradiation in both situations.

Method and material. As experimental animals, one- to 2-year-old thoroughbred cocker spaniels and beagle dogs, male and female, weighing from 7 to 11.3 kg were used. These animals were subjected to a total body irradiation of 100 roentgen, given either in single or divided doses. The allocation of the animals to the different groups is shown in Table I. Three cc of cephalic venous blood was drawn into an oxalated 5 cc syringe and transferred at once to a clean test tube. Red and white counting pipets were immediately loaded and counts made in a Neubauer counting chamber. Kingsley stained peripheral blood smears were

* This work was done under contract with the U. S. Atomic Energy Commission.

TABLE I. Allocation of Animals to Experimental Groups.

No. and type dog	r/dose (group)	Doses	Factors kv.	Factors ma.	Filtration	HVL, mm Cu	r/min.
8 cocker	10	10	175	5	None	0.24	12.5
8 "	25	4	"	"	"	"	"
8 "	50	2	"	"	"	"	"
4 "	100	1	"	"	"	"	"
4 beagle	100	1	"	"	.25 mm Cu 1.0 mm Al	0.83	6.7
6 cocker	Non-irradiated control group						

Avg distance from target 66 cm.

TABLE II. Normal Blood Counts for Cockers and Beagles.

Type of dog	No. of Dogs	No. of Counts	Avg Rbc, mill./mm³	Total Wbc, thous./mm³	% neutrophiles (seg.)	% neutrophiles (band)
Beagle	28	36	5.5	13.8	52.0	5.7
Cocker	69	153	5.8	15.6	52.0	7.4

made and most differential counts made by 2 or 3 persons; 200 to 300 cells were counted on each slide. In all irradiation groups blood was drawn 6 hours prior to exposure. Animals in the 10 and 25 r groups were bled 18 hours after each irradiation. Blood samples were obtained 6 and 18 hours after irradiation from the dogs in the 50 and 100 r groups. The control group was bled at the same hour at weekly intervals and was subjected for a period of 3 weeks to similar experimental procedures as that of the other animals but without exposure to x-ray. Blood was drawn 18 hours following such a procedure. From each group, except the control and the 10 r groups, an average of 3 dogs was selected for pre- and post-irradiation bone marrow biopsies taken with a modified Turkel needle(1) from the 6th, 7th or 8th ribs. Both control and treated marrows were obtained from the same animal. Pre-irradiation biopsies were taken approximately one week prior to the initial irradiation. The post-irradiation biopsies were taken 18 hours following completion of 100 r total body irradiation. This biopsy material was fixed with Zenker's acetic acid solution, cut into sections of 5 mμ thickness and stained according to the Kingsley method.

Results. The normal levels for red blood cells, lymphocytes, segmented and band neutrophiles were first determined in both cocker spaniels and beagles (Table II). The effect of irradiation on the peripheral blood pattern is given in Fig. 1-4. The counts in the control groups are given in Fig. 1. Line A represents the total white count; Line B the total neutrophile count; Line C the lymphocytes, and Line D represents the band neutrophiles. This graph shows clearly the small variations occurring during different weeks.

The behavior of the total white, neutrophile or lymphocyte count (Fig. 2) after irradiation with 100 r is similar to what has been previously described. The 50 r group also presented a leukopenic pattern very much like that seen in mice subjected to this dose(2). The 50 r dose appears to be the smallest dose which resulted in this form of sensitivity. The most significant findings were in the 10 and 25 r group. The total and differential counts taken at weekly intervals have been plotted (Fig. 3). The solid lines in this graph connect the average of counts taken 6 hours prior to irradiation while the interrupted lines connect average of counts taken 18 hours following irradiation which was given at weekly intervals for 10 consecutive weeks. Line A shows the total white count which shows only slight variation. The total neutrophile count is indicated by Line B, which shows an elevation during this period of irradiation. The lymphocytic count (Line C) remains fairly constant. The principal change (Line D) is the marked increase of the band neutrophiles in the peripheral blood. This shift to the left is more clearly demonstrated in Fig. 4, in which the band neutrophiles are plotted in the control group, in the 10 r group and the 25 r

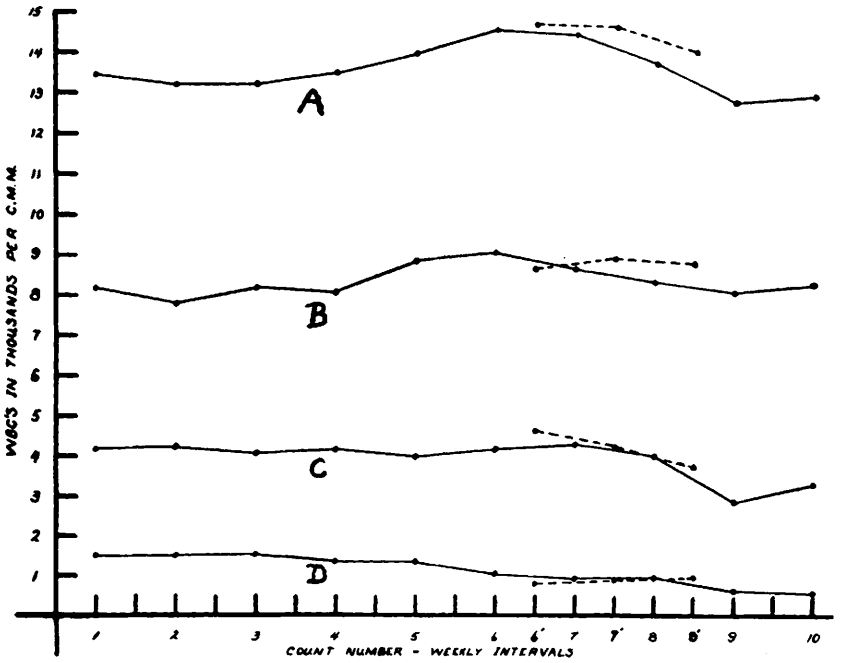

FIG. 1. Blood counts, control group. A. Total white counts. B. Total neutrophile counts. C. Total lymphocyte counts. D. Band neutrophile counts.

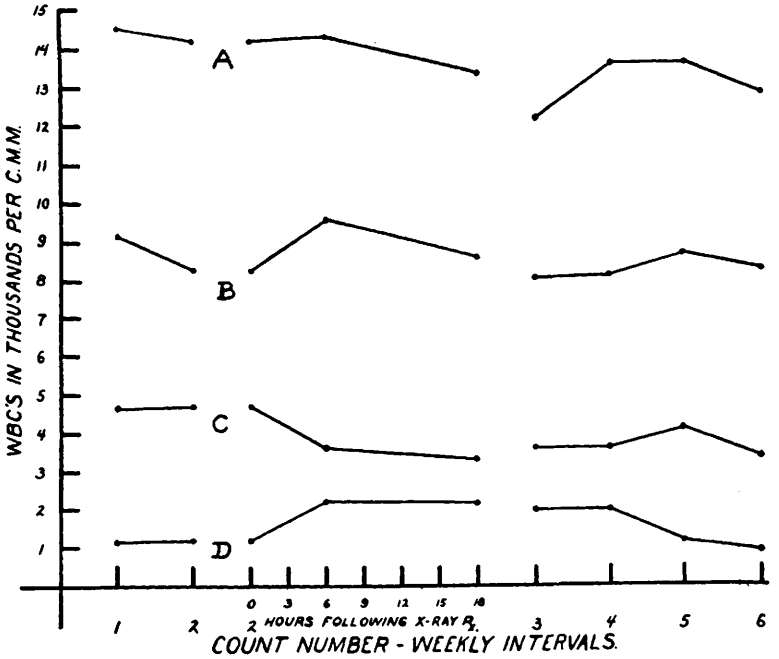

FIG. 2. Blood counts, 100 R group. A. Total white counts. B. Total neutrophile counts. C. Total lymphocyte counts. D. Band neutrophile counts.

group. This graph shows a definite increase of band forms during the irradiation period reaching its maximum in about 8 weeks and followed by a rapid drop to normal. This same increase of band neutrophiles was observed in the bone marrow. A comparison

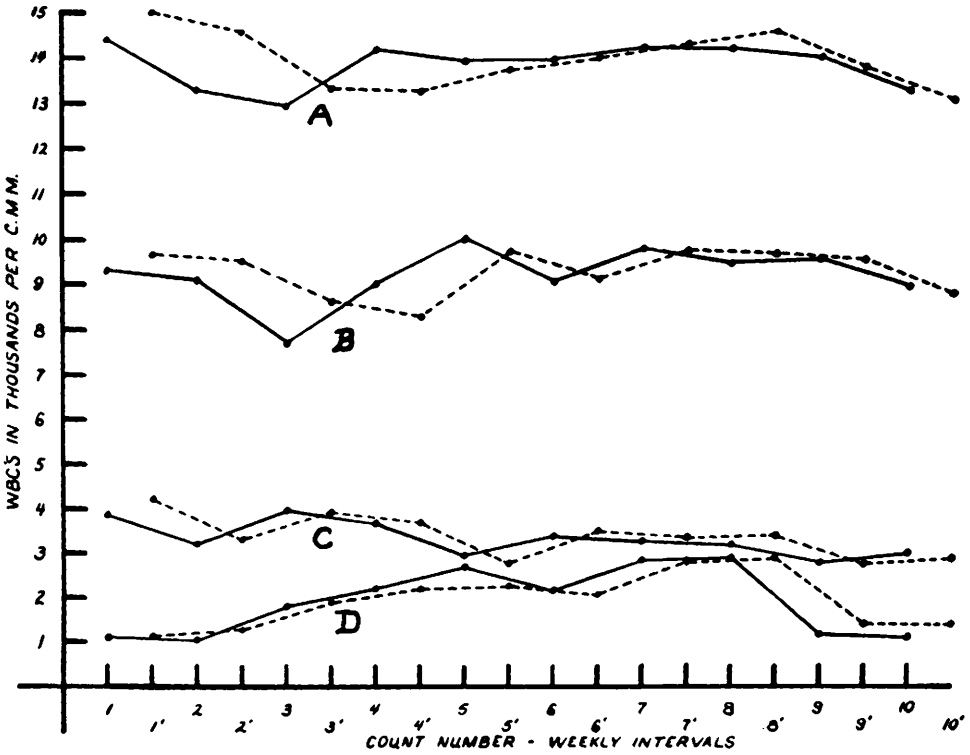

FIG. 3. Blood counts. 25 R group. A. Total white counts. B. Total neutrophile counts. C. Total lymphocyte counts. D. Band neutrophile counts.

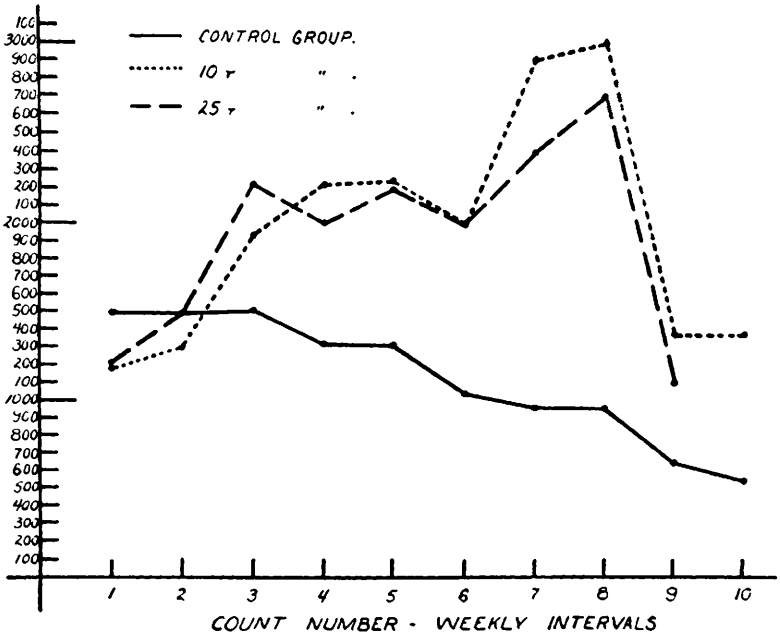

FIG. 4. Band neutrophile count.

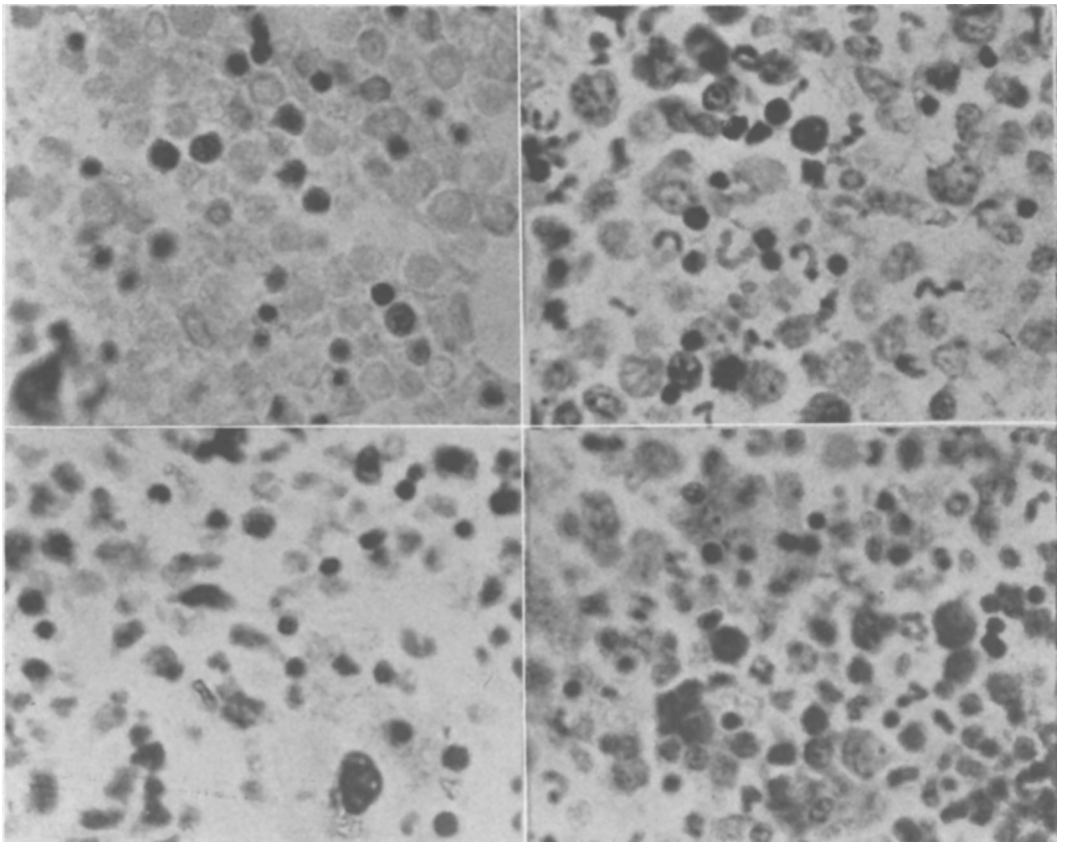

FIG. 5. Bone marrow sections. A, B (left top and bottom). Before irradiation. C, D (right top and bottom). 18 hr after irradiation.

between the pre- and post-irradiation marrows demonstrated an increase in the more mature granulocytes, band as well as segmented forms (3). Bone marrow specimens (Fig. 5) taken from 2 of the dogs before irradiation are compared with specimens taken 18 hours after completion of a total body irradiation of 100 r. The increase in band and segmented granulocytes in the marrow is very pronounced. This change was observed in all 6 animals on which bone marrow specimens were taken before and after irradiation. This increase in the bone marrow occurred at the same time that these cells were markedly increased in the peripheral blood.

Total leukocyte counts taken on the control group 18 hours following simulated irradiation showed a maximum deviation of 200 cells when compared with the counts taken 6 hours prior to this procedure. The total leukocyte counts for both groups during this interval ranged from 13,800 to 14,700 per cu mm. This is within the limit of errors inherent in the method of leukocyte counting(4). It is unlikely, therefore, that the manipulation of the animals in this experiment influenced in any way the data found after exposure to x-ray.

Neither single nor divided administration of this dose in total body irradiation produced any significant changes in the erythrocytes. The results of these counts are summarized in Table III.

Discussion. Our experiments were designed to demonstrate changes in the hematopoietic system at low doses, both single and divided, of total body irradiation. In reviewing the literature, special attention was given to descriptions of early increase in band neutrophiles in the peripheral blood following irradiation in relation to bone marrow activity(5). We felt that such a response could best be studied by parallel samplings of the bone

TABLE III. Red Cell Counts before and after Irradiation.

Period	No. of dogs	No. of counts	Avg Rbc count in mill./mm³
Pre-irradiation	38	75	5.79
Irradiation interval	32	157	5.87
Post-irradiation	21	84	5.83

marrow and peripheral blood. Our results showed that there was a qualitative and quantitative variation in response to 100 r total body irradiation when given in single or divided doses. When 100 r was given in a single dose or in 2 doses of 50 r, the order of decreasing radiosensitivity of leukocytes in the circulation was lymphocytic to granulocytic. However, when 100 r total body irradiation was given in divided doses of 10 to 25 r, this order was reversed. This increase of immature granulocytes in the peripheral blood occurred without evidence of any accompanying leukopenia. The comparison of pre- and post-irradiation bone marrow biopsies showed an increase in band cell granulocytes after exposure in every instance. It is evident, as might be expected, that an increased maturation in the marrow occurs at the time of the elevation of immature band forms of granulocytes in the peripheral blood. Circulating blood may be valuable as an indicator of bone marrow activity following irradiation.

In spite of different opinions in previous articles, we believe that the study of blood and bone marrow samples taken concurrently is an indispensable technic in studying results of irradiation. Experiments in which low dosages of total body irradiation are used offer possibilities for studying reactions of various components of the hematopoietic system which cannot be observed when large doses are employed.

Summary and conclusions. 1. Data showing qualitative and quantitative differences in the peripheral blood and bone marrow of the dog following administration of single or divided doses of 100 r total body irradiation are presented. 2. The accepted pattern of leukocytic radiosensitivity (lymphocytic > granulocytic) is observed after administration of 100 r in one dose or in 2 doses of 50 r. 3. Administration of 10 or 25 r per dose shows a reversal of this sensitivity apparent in the occurrence of an increased number of granulocytes in the blood and bone marrow in the absence of a lymphocytopenia. 4. The increase in band forms in the post-irradiation biopsy specimen indicates an increase in maturation in the bone marrow. 5. The study of the peripheral blood may be valuable as an indicator of bone marrow activity when only small doses of x-ray are used.

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Received February 5, 1953. P.S.E.B.M., 1953, v82.