THE EFFECT OF RADIATION ON HEMOPOIESIS. IS THERE AN INDIRECT EFFECT?

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I. Introduction

Since the discovery of the x-ray by Roentgen, medical science has evinced great interest in elucidating its mode of action. Today, the problem is by no means completely solved. Certain facts, particularly those relating to the results obtained when tissues are subjected to direct radiation, are well established and widely accepted. For example, the aplasia of bone marrow resulting from direct widespread radiation in large doses must be regarded as beyond dispute.

However, there are other observations both of a clinical and experimental nature which are poorly understood and highly controversial. These relate particularly to changes in tissues far removed from the direct site of radiation and have led to the postulation of an "indirect" action of x-rays. For example, many roentgenologists have privately observed, and others have publicly reported, marked involution of lymph nodes involved in a lymphomatous or metastatic process when radiation was given to other areas sufficiently remote as to have precluded any direct exposure of the former. Equally well known is the marked reduction in the blood count of leukemias treated by x-ray and the leukopenia which develops infrequently in similarly treated nonleukemic individuals, even when supposedly very small areas of marrow are subjected to the effects of direct radiation. These effects, at least in superficial appearance, are not unlike those well established for direct radiation. The result has been a welter of interesting but confusing literature which will presently be reviewed.

It is with this possibility of an "indirect" action of roentgen radiation that this report is concerned. The concept of "indirect" action requires further definition. It is inconceivable in an organism whose every cell is bathed in a continuous, circulating fluid medium, and which is interlaced with an intricate network of nervous tissue, that such an agent as x-ray, known to be capable of creating extensive destruction of certain cells, should be without an indirect effect. It is well established that there are "indirect" effects from a thermal burn or mechanical crush. Yet in the case of crush injuries, at least, the only action directly attributable to the causative agent ceases at the time the trauma is discontinued. What occurs in the organism after that must be regarded as strictly nonspecific, even though these events may be of a highly serious nature at times. We, therefore,
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have limited our approach to an effort to demonstrate indirect effects peculiar to radiation. The pertinent question is whether or not radiation results in the formation of specific substances (not merely those liberated by nonspecific cellular injury or death) which when transported to distant areas produce a characteristic indirect effect.

If such distant indirect effects exist, it seems reasonable that the agents mediating them will in all probability be transmitted to their site of action by way of the circulation. The experimental approach has been, therefore, to arrange for the direct passage of a very large volume of blood for a period of several hours from a radiated to a normal animal, and then subsequently to observe the normal animal for evidence of changes which might be interpreted as indirect radiation effects. Cross circulation by way of carotid to carotid anastomoses satisfies the concept of this approach. Parabiosis, in which small circulatory connections undoubtedly exist between the two animals, was felt to be disadvantageous in that only small amounts of blood cross circulate per unit of time. The methods and technics employed will be described in detail below. Important corollary principles are that the radiated animal must receive a relatively large acute dose of radiation in order that any indirect effect present may be made more manifest, and that sufficient experiments must be done to cover all time intervals up to at least a few days after radiation of the one animal. Significant changes in the leukocyte and lymphocyte picture in the normal animal following cross circulation have been selected as the criteria of an indirect effect in these investigations. These criteria were selected because (1) these elements have been shown to be among the most sensitive indicators of damage by radiation, and (2) changes in these elements and their precursors have been repeatedly mentioned by those attributing indirect effects to radiation.

2. REVIEW OF THE LITERATURE

An appreciable amount of medical literature has accumulated concerning the "indirect" effects of x-rays. Particularly in the early 1900's many contributions to the subject were making their appearance, the German investigators being especially active in this field. Much of this early literature is mutually contradictory and largely of historical interest. Dosage of radiation administered was in most instances not accurately known, and the quality of radiation employed varied widely from investigator to investigator. Roentgenology was in its infancy and technical factors poorly understood and poorly controlled. Nevertheless, the field is not one that readily lends itself to experimental investigation, and even with vastly increased knowledge and improved technical control, the same general arguments prevailing soon after the turn of the century are still being debated in the literature of the last twenty years.

Broadly these investigations can be grouped into four main types. (1) The demonstration of, or the failure to demonstrate specific toxins (most frequently "leukotoxins") in the serum of patients or experimental animals exposed to radiation. Both in vivo and in vitro studies of this nature are reported. (2) The demonstration of, or the failure to demonstrate significant histologic changes in tissues...
ordinarily sensitive to roentgen radiation following radiation of some site remote from the tissues studied. The clinical demonstration of significant involution of susceptible tissues far removed from the point of application of direct radiation. A group of miscellaneous investigations chiefly concerned with demonstration of a wide variety of biochemical abnormalities occurring after radiation, and purported to be the mediators of an indirect effect.

Efforts to demonstrate a specific toxin developed as a result of radiation have been particularly numerous. Linser and Helber (quoted by Capps and Smith) found that a leukotoxin was produced in the blood of organisms exposed to x-ray. This leukotoxin when injected into other animals destroyed the circulating leukocytes, and when added to animal exudates containing leukocytes caused loss of motion and degeneration of the cells. Curschmann and Gaupp in 1905 injected into rabbits serum taken before and after radiation therapy from a patient with lymphatic leukemia. A few hours after injection the authors observed leukopenia not present in control animals. This, they concluded, was due to the development of a specific leukotoxin which could also be demonstrated as capable of destroying human leukocytes in vitro. They presented evidence suggesting that such a leukotoxin was inactivated by heat (60° C. for one half hour). The following year Klieneberger and Zoeppritz were unable in their investigations to demonstrate any consistently toxic action of radiated serum on leukocytes in vitro either as to cellular disintegration or as to influence on amoeboid activity. In addition no constant leukopenic effect was observed after injection of radiated serum into rabbits. The authors concluded no toxin could be demonstrated as a result of radiation. Milchner and Wolff observed some decrease in leukocytes in animals after the injection of 5 cc. of serum from a radiated animal of the same species. They also noted some degree of leukopenia when material from a radiated spleen was injected, while injections of normal spleen resulted in leukocytosis. However, they felt that their results were not of sufficiently concrete nature to be strong evidence for the presence of a leukotoxin, particularly in view of wide, physiologic variability in the leukocyte counts of the experimental animals used. Benjamin and co-workers after radiating the ears of rabbits with large doses while shielding the remainder of the animal found leukocytosis and lymphopenia occurring, but the blood picture returned to normal within twenty-four hours. They claimed to have found increased choline formation in animals after intense radiation, and to have noted that this corresponded to the period of leukocytosis. The investigations of Capps and Smith were interpreted as favoring the concept of a leukotoxin. These authors found leukopenia to result from the injection of a few cc. of radiated serum from one animal into the abdominal wall of another. This serum was also said to cause abnormal destruction of leukocytes in hanging drop preparations. With this view Harris concurred, though presenting no experimental evidence of his own.

In 1918 Dorn reported that testicular and ovarian atrophy and leukopenia of considerable duration resulted from the injection of enzytol, a borate of choline. The author felt that the effects of radiation were exactly reproduced by this substance and that this offered strong support to the concept of choline as the toxic cause of radiation effects. Walterhofer likewise considered indirect effects of
radiation to result from some toxin, possibly choline. In 1922, Billings in discussing his experiences with the treatment of leukemia by roentgen ray, stated that the application of radiation to any cutaneous surface resulted in the appearance of a leukolytic substance in the blood. The serum of a treated patient dissolved white blood cells in vitro, while the serum of an untreated patient had no such effect. In the same year, Murphy, Liu and Sturm were forced to conclude that their experiments failed to show any evidence of the presence of a lymphotoxin, even when exposures large enough to effect almost complete destruction of lymphoid tissue were employed. Zacherl four years later, as a result of experiments with radiation of single and parabiotic rats, felt that some toxic substance capable of causing sickness and death of the animals must have been produced. Szilárd in 1927 could demonstrate no autolytic effect on leukocytes in the serum of radiated leukemias, nor could any such autolysin be demonstrated by complement fixation tests. He could find no increase in choline in the blood or urine of leukemias under x-ray therapy. This author postulated none the less that perhaps electrons circulating in the blood exerted deleterious effects on distant sensitive cells.

Strumia's studies led him to conclude sweepingly in 1929 that 'radium emanations, as such, are carried by the blood or that they act through the production of leukotoxins, which are produced by the direct effect of the radium emanations upon the white cells of the blood in superficial vessels, or perhaps upon fixed cells of the reticulo-endothelial system.' He further stated, "The direct action of radiation upon hemopoietic foci is altogether unimportant. In all cases, the blood acts as a carrier of radiations, either as such or modified, to the hemopoietic foci where its main action takes place."

Woenckhaus felt that leukopenia observed in normal rats after injection of serum from strongly radiated rats was due to products of proteolysis in the injected serum. However, he also found that when one member of a parabiotic pair was radiated and the other shielded, a leukocytosis and not leukopenia occurred in the non-radiated parabiont. In 1932, Zwer heavily radiated skin flaps in small laboratory animals. The remainder of the animal was shielded, yet if the pedicles connecting the skin flap to the animals remained intact, they uniformly died in two to nine days, and exhibited varying degrees of leukopenia and lymphopenia. The latter, however, were not of the order of magnitude uniformly seen in animals who have received enough generalized radiation to result in death. Zwer concluded that the effect of roentgen rays on the white blood cell picture is not a direct action on the blood forming organs and probably not on the circulating blood. Rather, he believed, the decomposition of cells gives rise to toxins which in turn damage the hemopoietic system.

Macht in more recent years has attacked the problem by phytopharmacologic methods, examining blood and serum obtained both before and after radiation from a variety of animals. His method, briefly, consists of studying the growth of roots of Lupinus albus seedlings in standard physiological solutions as compared with the growth of similar seedlings in similar solutions to which blood or serum had been added. This investigator concluded that there is a toxic substance present in radiated but not in normal serum, and that it reaches its maximum titer twenty-four to forty-eight hours after treatment, disappearing in a few days.
Osgood in 1941 conducted in vitro experiments designed to determine if indirect radiation effects on cells of bone marrow could be demonstrated. He set up four human marrow cultures identical in every respect except one received no radiation, in one both cells and medium (35 per cent human serum and 65 per cent balanced salt solution) were radiated, in one only the medium was radiated, and in one only the cells were radiated. Quantitative hematologic studies indicated no indirect action of radiation on marrow cells suspended in the radiated medium.

A number of histologic studies have also been made in which tissue remote from the direct site of radiation has been examined for evidence of indirect damage. Nakahara and Murphy found identical changes in both deep and superficial lymphoid tissue following small doses of soft x-ray. Since 96.8 per cent of the rays did not penetrate beyond a depth of 1 cm, it was felt these changes in deep tissue could not be the result of direct action by the rays. Jolly and Ferroux in histologic studies made on lymphatic structures outside the field of direct radiation were of the opinion that there was grave doubt that the slight changes noted were due to an indirect, toxic action of radiation. Rather it was their inclination to attribute such slight changes as might exist to diffused or secondary radiation. Akaiwa and Takeshema exposed popliteal lymph nodes of rabbits to various amounts of radiation, leaving one side as a nonradiated control. The changes in lymphoid tissue on both sides were noted at a variety of intervals after radiation. The authors concluded that in the control nodes histologic changes identical with those in the radiated nodes occurred, but that the reaction was much less intense and much slower on the nonradiated side. In 1940, Hsü and Ma radiated one femur only of rats with doses varying from 1000 r over a four day period to 5000 r over a forty day period. The day after the course of radiation was complete animals were sacrificed and the bone marrow of radiated and nonradiated femurs, the submaxillary lymph nodes, and the spleen of each were examined. In the nonradiated hemopoietic tissues changes of a hyperplastic nature interpreted as compensatory, were noted. Le Blond and Segal found large doses of roentgen rays produced secondary changes in well shielded organs far distant from the point of impact. These consisted of constant thymus and generalized lymphatic atrophy and adrenal hypertrophy and frequently of fatty infiltration of the liver and ulcerations of the stomach. Such lesions were considered part of a general intoxication following radiation and were felt to be similar to those described by Selye as occurring in the nonspecific "alarm reaction" developing after the application of a wide variety of injurious stimuli. It is interesting (as has been noted with other noxious agents capable of eliciting an "alarm reaction") that thymus and lymphatic atrophy was suppressed by adrenalectomy but the gastric lesions and general lethal effects of the rays increased. Barnes and Furth in 1943 using single and parabiotic mice reported an extensive series of investigations. These authors examined bone marrow, lymph nodes, and spleen in unexposed areas of mice radiated with anywhere from 400 r to 7000 r. Some histologic changes were observed, but these were slight and regarded as probably the result of products of damaged tissue transported by way of the circulation. The degree of change depended on the dose of radiation and probably on the volume of tissue radiated. The authors observed similar histologic
changes in mice burned under anesthesia with the actual cautery over the chest and abdomen, and in the lymph nodes of two mice dying of iodoacetic acid poisoning. In addition, the effect on the hematopoietic tissue and lymph nodes of normal mice whose parabionts had been subjected to radiation was studied. Histologic changes similar to but much less extensive than those found in the radiated animal were observed in the tissues of the nonradiated parabiont. These were considered nonspecific. Densted,\textsuperscript{9} likewise in 1943, reported on a large number of examinations of bone marrow and peripheral blood in patients being treated with x-ray. Control specimens were obtained before treatment. The majority of the patients were suffering from malignant disease, and x-ray dosages, while variable, were for the most part cancericidal in magnitude. Marrow specimens were obtained a considerable distance away from the sites exposed to direct radiation. Twenty-eight patients developed no granulocytopenia (below 3000 granulocytes per cubic millimeter). In these there was no abnormality of the nonradiated marrow either as regards total quantity of cells or differential values. In 20 patients the granulocytes of the peripheral blood fell below 2300 per cubic millimeter. In these cases, the cellularity of the nonradiated marrow remained normal, but adult polymorphonuclear leukocytes in the marrow decreased from an average of 16 per cent in control groups to 6.5 per cent in granulocytopenic groups. The promyelocytes were questionably increased. For these reasons, the author concluded there is in certain patients some degree of maturation inhibition in myelopoiesis, and that this is probably due to some toxic or anaphylactic factor. He considers this to be an indirect effect of roentgen and radium rays on hematopoiesis and suggests it may occur more readily in patients who are in poor condition.

While many roentgenologists have observed phenomena suggestive of an indirect radiation effect, relatively few have seen fit to publish these clinical observations. However Langer\textsuperscript{25} has stated that he had observed indirect radiation effects on several occasions. He cites the case of a boy treated with x-ray for verruca simplex of both hands. Although only one hand was treated the warts gradually disappeared from the untreated hand. He refers also to a case reported by Baensch in 1921, where, in a patient with primary carcinoma of the breast, regional nodes disappeared even though shielded with lead rubber during radiation. Scott\textsuperscript{41} has reported to have observed frequently in cases where large areas were radiated the disappearance of lymphosarcomatous glands in regions receiving no radiation. In one case, he states, this was manifest within half an hour after therapy.

In addition to the above, a miscellany of diverse mechanisms have been postulated as the mediators of indirect radiation effects. In 1905, Musser and Edsall\textsuperscript{32} concluded that the effect of x-ray is not direct but is dependent on a reaction of the body subsequent to exposure. They felt that the increased catalysis observed after radiation was a response in the form of an increased fermentative process, and concluded that favorable results to x-ray therapy could occur only when the body was capable of such response. Demiéville\textsuperscript{8} concluded that an indirect effect of radiation, probably conditioned through decomposition products, was exhibited in the blood forming organs. Petersen and Saelhof\textsuperscript{38} in 1921 demonstrated increased serum titers of several enzymes after radiation and speculated whether some remote effects of
radiation may not be due to enzyme mobilization. Hussey found an uncompensated alkali excess in rabbits exposed to x-rays and suggested alteration in acid-base balance may be an important factor in their action. Opitz suggested that toxins produced by x-rays may be agglutinated by tumor cells, thus impairing tumor growth. Rahm and Koose assumed chemical changes are initiated in the dead interstitial substances of the body and that these may be responsible for the end effects seen. V. Pannewitz observed acidosis followed by slowly increasing alkalosis which persisted for several days after radiation. Kluge and Zwerg have suggested that mobilization of hormones, particularly those of the hypophysis, are important in producing the observed effects of radiation. Selye in an extensive review of general adaptation phenomena has pointed out that many of the metabolic changes described after radiation such as hyperglycemia, decrease in blood cholesterol, increase in ketone bodies in the blood, elevation of the NPN, and disturbances in acid-base balance are seen with equal frequency as a response to many injurious stimuli such as traumatic shock, exposure to cold, burns, drugs, and solar rays. This author feels such things represent nonspecific systemic phenomena elicited by injurious stimuli to which the organism is qualitatively or quantitatively not adapted. Very recently Dougherty and White have proposed that roentgen radiation exerts both a direct and indirect effect on lymphocytes and that the indirect action can be explained on the bases of the increased pituitary—adrenal cortical activity caused by radiation.

It is readily apparent that the literature weighs heavily on neither side of the question.

3. Experimental Technic and Methods

The experimental animal employed was the cat and the chief experimental device cross circulation by way of carotid to carotid anastomoses. In the twenty-six successful cross circulation experiments which form the basis of this report, a normal animal was in each instance cross circulated with a radiated animal. The latter received its radiation either during the actual time of cross circulation or at varying intervals prior to its establishment. A control group in which normal cats were cross circulated had already been established in this laboratory in connection with experiments previously reported.

The technic of establishing cross circulation was as follows. The animals were anesthetized with nembutal administered intraperitoneally. The operative site was prepared, and the carotid artery of each on one side isolated and dissected free. A small rubber covered clamp was placed at the proximal and distal ends of the freed vessel and the artery divided midway between the two clamps. Both segments were then washed free of blood with isotonic citrated saline solution. In each animal, the proximal arterial segment was cannulated by threading it through a Monel cannula, evverting the cut end of the vessel over the outside of the cannula, and tying with fine 5-o catgut. The two animals were next brought together in such a way that the proximal arterial segment of each was directly adjacent to the distal segment of the other. They were conveniently supported in this position by the use of small sandbags. A bed for the anastomoses was readily formed by sutur-
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ing together the strap muscles of the two animals. Following this, the distal arterial segments were drawn over the outside of the cannulated proximal segments and tied about the cannula. Clamps were then released and cross circulation allowed to function from two to ten hours. The cross anastomoses thus established afforded a continuous endothelial pathway by which the blood from each cat supplied one side of the head of its partner and vice versa. Figure 1 diagrams the method of anastomosis.

The volume of blood traversing an anastomosis of this type, will, if uncompensated, result in the exsanguination of an animal within a few minutes. At the conclusion of the period of cross circulation the patency of each connection was always tested in situ by reapplying the clamps, dividing the anastomoses distal to each cannula, and releasing the clamps for a brief instant.

Prior to an experiment, control hematologic studies consisting of hemoglobin determinations and a total and differential white blood cell count were made. Only animals which were clinically well and which showed no gross hematologic abnormalities were used. During the period of cross circulation leukocyte counts and smears were made at approximately hourly intervals. In each instance blood was obtained from the marginal ear vein. The hematologic follow-up of the non-radiated animal consisted of a minimum of daily (except Sunday) total and differential white blood cell counts for a period of two weeks and similar studies made every other day for a period of approximately an additional two weeks. All counts were made with Bureau of Standards certified pipets. All blood smears were made by the coverslip method and stained with Wright's stain.

The radiation to which one member of each cross circulated pair was subjected was kept constant and subject to the following factors:

- Total Dosage: 1500 r whole body radiation
- Milliamperage: 15
- Target Distance: 22 inches to center of cat
- Filter: Aluminum parabolic plus 1/4 mm. copper
- Half Value Layer: 2.1 mm. copper
- Rate of Administration: Approximately 15 r per minute with slight variation.

![Diagram of anastomosis](image-url)
This amount of radiation invariably results in the death of cats within four to seven days.

In the majority of experiments, one animal was radiated at some interval prior to cross circulation. In seven experiments, however, cross circulation was first established and then one animal radiated while the other was shielded. Shielding was accomplished by means of an appropriately shaped wooden frame covered with one-fourth inch of lead plate. An ionization chamber placed under the frame recorded the small amount of scatter radiation which escaped the shielding. This varied in different experiments from a minimum of 2.0 r to a maximum of 43 r.

It was customary to administer isotonic saline subcutaneously to both animals during cross circulation and at its conclusion. In some instances, penicillin in saline was also administered.

4. Presentation of Data

In all, twenty-six successful cross circulation experiments were performed. Of these, all the normal animals except one were followed hematologically for a period of approximately twenty-eight days after return to their own circulation. Cat number 153 had to be sacrificed about two weeks after cross circulation because of a wound infection. With one exception, each cross circulated team consisted of one radiated and one nonradiated member. The experiment involving normal cat number thirty-six who was cross connected in series with two radiated animals simultaneously constituted this exception. In such a circuit, blood from the normal animal passed to one radiated animal, which in turn was connected to a second radiated animal, which likewise in turn supplied blood to the normal cat.

The data pertinent to these experiments are especially suited for presentation in graphic and tabular form and this has been the mode of presentation selected.

Figure 2 shows in graphic form the duration of cross circulation and the interval after radiation of one member of the team that cross circulation was established. It can readily be seen that in the majority of experiments the duration of cross circulation was in the neighborhood of eight hours. A few animals were cross circulated as long as ten hours, one for as little as two hours and seven minutes. The group of animals in which radiation of one partner took place at the time the cross circulation was functioning were connected for approximately three to five hours. More experiments were performed during or shortly after the radiation of one member because it was felt that logically the most profound effects on the normal partner could be expected under these circumstances. Nevertheless, all the time intervals after radiation up to eighty-two hours were covered.

Table I presents detailed hematologic data from each experiment and indicates the total leukocyte and absolute lymphocyte count of each normal animal before and at varying intervals after cross circulation with a radiated partner. The intervals selected were done so arbitrarily with an eye to conserving space without sacrificing a comprehensive and representative presentation of the data. In addition, in the experiments in which one animal was shielded and the other radiated during the period of cross circulation, the amount of radiation recorded by the
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ionization chamber under the shield has been indicated. In every experiment of this type a small amount of scatter radiation escaped the shielding.

Tables 2 and 3 give the means and standard deviations for total lymphocyte and leukocyte counts respectively of the normal animals for the same time intervals before and after cross circulation as given for the individual animals in table 1.

The figures are divided into three groups: those applying to the shielded group of normals, which were cross circulated at the time of their partner’s radiation, those applying to the non-shielded group which were cross circulated with a previously radiated partner, and those applying compositely to the group as a whole. It will be noted that the number of animals for which data are presented varies somewhat on different days in the tables. This is due to the fact that counts were made but six

days a week so that at any specified interval after cross circulation it is possible that counts are not available for every member of the group.

Figure 3 indicates graphically a composite picture of the average leukocyte and lymphocyte counts of the entire group during the period of follow-up. In addition, the same data on the seven shielded animals are graphed separately, both because these animals unavoidably received small amounts of radiation, and because this type of experiment was considered the most critical of the group.

5. Results

Analysis of the data indicates few or no detectable hematologic abnormalities in the normal cat at any time after its cross circulation with a radiated animal.
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<th>Cat No.</th>
<th>Duration of x-circ. in hrs.</th>
<th>Amt of Radiation</th>
<th>Prior to x-circ.</th>
<th>First After x-circ.</th>
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<th>2 days</th>
<th>3 days</th>
<th>5 days</th>
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EFFECT OF RADIATION ON HEMOPOIESIS

Table 1—Continued

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<td>2,250</td>
<td>2,220</td>
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<td>2,768</td>
<td>1,976</td>
<td>1,989</td>
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* = Total Leukocyte count.
† = Absolute Lymphocyte count.
‡ = Shielded animals.

Table 2.—Means and Standard Deviations for Absolute Lymphocyte Counts of Normal Cats Following Cross Circulation with Radiated Animals

<table>
<thead>
<tr>
<th></th>
<th>Shielded Group</th>
<th>Non-shielded Group</th>
<th>Entire Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>S.D.</td>
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<tr>
<td>Prior to x-circ.</td>
<td>7</td>
<td>2642.3</td>
<td>1063.1</td>
</tr>
<tr>
<td>First after x-circ.</td>
<td>6</td>
<td>2093.3</td>
<td>1145.2</td>
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<tr>
<td>1 day after x-circ.</td>
<td>7</td>
<td>1383.9</td>
<td>734.8</td>
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<tr>
<td>2 days after x-circ.</td>
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<td>1386.3</td>
<td>665.1</td>
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<td>3 days after x-circ.</td>
<td>7</td>
<td>1804.3</td>
<td>1159.5</td>
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<tr>
<td>5 days after x-circ.</td>
<td>7</td>
<td>1721.0</td>
<td>1017.4</td>
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<tr>
<td>7 days after x-circ.</td>
<td>7</td>
<td>2157.4</td>
<td>974.4</td>
</tr>
<tr>
<td>10-11 days after x-circ.</td>
<td>7</td>
<td>2155.3</td>
<td>1279.2</td>
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<tr>
<td>14-15 days after x-circ.</td>
<td>6</td>
<td>2160.1</td>
<td>1321.8</td>
</tr>
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<td>21-22 days after x-circ.</td>
<td>6</td>
<td>2357.5</td>
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<tr>
<td>End of Experiment</td>
<td>6</td>
<td>1551.7</td>
<td>1056.8</td>
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</tbody>
</table>

N = Number of animals on which counts are available at the time specified in column 1.

The average leukocyte count for the entire normal group and for the critical group in which cross circulation was established at the time of radiation of their partner remains throughout the entire approximately twenty-eight day period of follow-up actually somewhat higher than the pre-cross circulation control level. In not even a single animal did evidence of significant leukopenia develop at any time during the experiment — this despite the fact animals received for a period of several hours the full volume output of the carotid artery from a radiated partner. As would be expected, well marked leukocytosis was present in many instances for a few days after the operative procedure. Its duration varied rather widely from
J. S. Lawrence, W. N. Valentine and A. H. Dowdy

Table 3.—Means and Standard Deviations for Total Leukocyte Counts of Normal Cats Following Cross Circulation with Radiated Animals

<table>
<thead>
<tr>
<th></th>
<th>Shielded Group</th>
<th>Non-shielded Group</th>
<th>Entire Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>Prior to x-circ.</td>
<td>7</td>
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<tr>
<td>First after x-circ.</td>
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<td>1 day after x-circ.</td>
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<td>2 days after x-circ.</td>
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<td>3 days after x-circ.</td>
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<td>5 days after x-circ.</td>
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</tr>
<tr>
<td>7 days after x-circ.</td>
<td>7</td>
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<td>4988.9</td>
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<tr>
<td>10-11 days after x-circ.</td>
<td>7</td>
<td>19737.1</td>
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<td>14-15 days after x-circ.</td>
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<tr>
<td>21-22 days after x-circ.</td>
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<td>13572.7</td>
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N = Number of animals on which counts are available at the time specified in column 1.

Fig. 3. Average leukocyte and lymphocyte counts per cubic millimeter of the whole group of animals for the entire period of the experiment are indicated. The average leukocyte and lymphocyte counts for the critical shielded group are graphed separately.

animal to animal. Of some interest is the very striking degree of leukocytosis developing at the time of cross circulation in certain animals whose partners had received their radiation at the time of or shortly before cross circulation. Whether these more striking instances of leukocytosis are due to the passage of leukocytotic
metabolites resulting from tissue breakdown as a result of radiation cannot be said with certainty. The leukocyte counts in question were markedly in excess of those developed in a normal control group, however.

Individual lymphocyte values found in normal animals after cross circulation show a moderate amount of variation. As would be expected during the period of marked leukocytosis during the few days immediately following cross circulation, a drop in the absolute lymphocyte count was noted. Lymphopenia is a well known companion of neutrophilic leukocytosis and in this instance, it was presumably accentuated by the fact some animals had been cross circulated with partners who had no circulating lymphocytes at all. To be sure, the average lymphocyte level for the entire group remained throughout slightly lower than that found before cross circulation and this trend was slightly more apparent in the critical shielded groups as a whole. In view of the physiologic variations in lymphocyte counts, in view of the persistence of some increase in the average total leukocyte counts throughout the experiment, and more particularly in view of the fact that the reduction in lymphocyte count was relatively slight and not at all of the order of magnitude associated with direct radiation, there is grave question that any significance can be attached at all to this finding. At no time did the average per cent of lymphocytes fall below 4.9 per cent of the leukocytes present even in the shielded group, and this figure was obtained only for the first day after radiation. In all other instances it was appreciably higher than this.

6. Discussion

It is apparent that under the conditions of our experiments, no specific "indirect" effect of radiation has been demonstrated. It is also felt that if significant indirect effects peculiar to radiation are dependent upon the circulation, they should have been readily demonstrated by the experimental setup employed. However, it cannot be denied that had it been possible to maintain cross circulation for much longer periods—say forty-eight or seventy-two hours instead of eight to ten hours—indirect effects too slight for demonstration during the shorter period might have become manifest. The possibility of an indirect radiation effect mediated solely by the lymphatics has also been considered but discarded as highly unlikely. Any lymphatic disseminated agent would in all probability soon reach the venous and arterial tree and would be expected to manifest itself in the blood. Further, if in some devious manner it should be removed from lymph before reaching the blood, indirect effects of radiation would exist purely in the regional lymphatic drainage area of that portion of the body directly radiated. The existence of such a purely localized regional indirect radiation effect is supported by no evidence and, in fact, is contrary to whatever evidence there is suggestive that such indirect effects exists.

It is also apparent that there is no satisfactory evidence for a characteristic indirect radiation effect presented in the medical literature. Such evidence as is presented is of dubious character and refuted for the most part by contrary results obtained in similar types of experiments by other investigators. Nor has there been more than a desultory attempt on the part of investigators of indirect radiation effects to
differentiate body reactions common to a variety of damaging stimuli from those specific to radiation. This is a fundamental differentiation, particularly in view of Selye's now well supported observations that an identical, nonspecific systemic reaction (at times severe enough to result in death) occurs as a response to many unrelated injurious stimuli. Still, it is undoubted that leukopenia develops in a certain number of individuals treated with roentgen radiation even when the amount of marrow directly exposed to radiation is thought to be minimal. It is also highly likely that involution of and histologic changes in normal and abnormal lymphoid tissue remote from the site of direct radiation as observed by many roentgenologists and research workers is real and not apparent. It would seem wise to examine these considerations more closely to see if it is necessary to assume they are peculiar to radiation and if they can be accurately described as specific attributes of radiation per se.

Kornblum and his associates in an extensive series of clinical observations concluded that therapeutic radiation tended to lower the leukocyte count. However, in approximately one-half of the patients studied there was no decrease in the number of neutrophils and in the great majority of the remaining cases depression was of slight degree. In but 7 cases out of 120 were the neutrophils reduced below 2000 per cubic millimeter. The effect of therapeutic radiation on the lymphocytes was more striking, a definite decrease in their numbers being the rule. In most cases the drop in count was relatively slight but in some instances it was very pronounced. It is thus seen that leukopenia of appreciable degree is an inconstant feature of radiation therapy applied to areas where there are no or minimal amounts of hematopoietic tissue. While the area treated, the volume of tissue radiated and the total amount of radiation are, in our opinion, all of importance as regards the production of leukopenia, yet it is impossible to predict accurately in most instances of local radiation over essentially non-hematopoietic areas which individuals will and which will not develop leukopenia. On the other hand, one can always anticipate the development of leukopenia when radiation is given over any appreciable amount of hematopoietic tissue such as in total body irradiation. Further, leukopenia associated with total body irradiation is more marked than when no or minimal amounts of hematopoietic tissue are radiated. Thus radiation over large amounts of active bone marrow can be expected to produce marked leukopenia, whereas radiation over non-blood forming areas produces mild, if any, leukopenia. Still another difference between the results of radiation over hematopoietic and nonhematopoietic areas is to be found in the morphological appearance of the bone marrow. With radiation directly over the bone marrow, hypocellularity and/or aplasia result, whereas the marrow shows normal cellularity or it may even be hyperplastic when other tissues are exposed and it is excluded.

Three possible explanations for these differences arise. First, they may be only quantitative, the so-called indirect effect actually being a direct effect resulting from inclusion of larger amounts of hematopoietic tissue in the field of radiation than generally considered to be the case. It should be noted in this connection that the exact amount of hematopoietic tissue exposed to radiation is not known in
many instances where an indirect effect is said to occur. It may well be that the amount of blood producing tissue radiated in these cases is sufficient to reduce the output of blood cells to a point where their normal level cannot be maintained. In particular, one must consider the possibility that in debilitated patients the reserve for production of blood cells may be distinctly lower than in the normal. If this is true, the inclusion of even small amounts of hematopoietic tissue in the radiated field in patients receiving radiation therapy would be of much greater significance than ordinarily considered since most of such patients are suffering from malignancy or some other serious disorder which is associated with debilitation. As a further indication that the effect may be due to inclusion of hematopoietic tissue in the radiated field is the well established fact that the leukopenia practically never results from radiation of the head in which case radiation can be given without inclusion of more than minimal amounts of active bone marrow.

Second, a specific indirect effect of radiation may exist, i.e., some substance or substances may be produced directly and characteristically by radiation and then transmitted to parts of the individual that were not exposed to radiation. Our experiments have failed to reveal such a situation. Third, a nonspecific effect of radiation may occur, that is, radiation over a local area may produce certain nonspecific changes in the tissues exposed. As a result of these nonspecific effects histological changes may develop in some unexposed tissues and leukopenia possibly be produced also. It is again possible here that the nonspecific effects may be greater in a debilitated than in a normal individual. Our experiments have failed to show the presence of any nonspecific substance capable of producing leukopenia. We have not examined the tissues histologically but feel that the evidence in the literature is sufficient to justify the assumption that these nonspecific histologic changes did occur at least in the normal animals which were being cross circulated at the time their partner was irradiated.

Substantial involution of lymphoid tissue not itself directly injured has been frequently observed as a nonspecific response to a wide variety of injurious agents. Bardeen in studying visceral changes occurring in patients dying of superficial burns noted striking histologic changes of a degenerative nature in lymphoid tissues and commented on the similarity of these changes to those found experimentally after injection of ricin or diphtheria toxin. These widespread alterations in all the lymphoid organs of the body following burns have been amply confirmed by other investigators. Similar changes and transient leukopenia and lymphopenia have been observed in mice subjected to dry heat in nonfatal exposures. Selye in what he has chosen to term the "alarm reaction," has described striking involutionary and degenerative changes in all the lymphatic organs as a nonspecific response to a variety of insults (cold, heat, surgical shock, drugs). Nonspecific damage apparently may result in atrophy of the spleen beginning in the center of the Malpighian corpuscles, marked loss of weight of thymus and lymph nodes, and, at times even complete disappearance of ger.inal centers in the latter. Zechwer noted similar changes after injuring subcutaneous tissues by injection of formalin. It is interesting that this involution of lymphoid structures does not occur in the adrenalectomized animal—particularly in the light
of recent investigations suggesting that lymphoid structures and possibly the lymphocytes may in some way be affected by the administration of adrenal cortical hormone. In view of the above observations, it is possible that x-ray is merely one of many injurious agents capable of producing generalized involution of lymphoid tissue as a nonspecific response to local injury. This, of course, is not to be confused with local involution and degeneration of lymphoid tissue directly exposed to radiation.

The question of whether or not a specific indirect effect of radiation exists must be regarded as unsettled. It is our feeling that leukopenia, when it results from radiation, is probably due at least in part to direct exposure of some of the hematopoietic tissue. Other factors which may be operative are the general physical status of the patient, nutritional disturbances resulting from the effects of radiation to the gastrointestinal tract, general radiation sickness, and the amount and degree of total body irradiation resulting from scattered radiation. We also feel that morphologic changes occur in certain nonexposed tissues (e.g., lymph nodes, and thymus). We are not convinced, however, that these nonspecific changes produce leukopenia.

7. Summary

1. The general aim of the investigations here reported has been to obtain evidence for or against "indirect" radiation effects.

2. To this end, twenty-six successful cross circulation experiments (carotid to carotid anastomoses) have been performed between normal cats and radiated cats.

3. Cross circulation was established in most instances at some specified time interval after the radiation of one partner. All intervals up to eighty-two hours after radiation of one partner were covered.

4. In seven experiments cross circulation was established and then one animal radiated while the other was shielded. These were considered the most critical experiments of the group.

5. Detailed data on leukocyte and lymphocyte counts in the normal animals obtained during an approximately twenty-eight day period of follow-up are presented.

6. These data are not considered to support the thesis of indirect effects peculiar to radiation. A trend toward slightly lowered absolute lymphocyte counts in normal animals after cross circulation was not considered significant, and in no instance did leukopenia develop in the normal animal.

7. The literature is reviewed and discussed.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the assistance of Mr. Morey J. Wantman and the Division of Statistics for the statistical analyses and the valuable assistance of Miss Wilma Kurowski in translating the foreign literature.

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THE EFFECT OF RADIATION ON HEMOPOIESIS. IS THERE AN INDIRECT EFFECT?

JOHN S. LAWRENCE, WILLIAM N. VALENTINE and ANDREW H. DOWDY