

EXPERIMENTS ON THE LEUKOLYTIC ACTION OF  
THE BLOOD SERUM OF CASES OF LEUKÆMIA  
TREATED WITH X-RAY AND THE INJECTION  
OF HUMAN LEUKOLYTIC SERUM IN  
A CASE OF LEUKÆMIA.

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Since the discovery of the remarkable effects of X-ray upon the blood, spleen, and glands in leukæmia, numerous attempts have been made to explain its action. Experiments for this purpose have been fruitful, but they have been, for the most part, restricted to animals. Human experiments are obviously preferable to animal ones, whenever they can be carried out, for the reaction of a healthy animal to X-ray is not necessarily the same as that of man in disease. In such an investigation as the present one it is desirable to work with human material, since leukæmia is rarely found in animals, and it has not been produced artificially.

For the purpose of observation we were fortunate in having at our disposal four cases of leukæmia, three of which were of the lymphatic and one of the splenomyelogenous variety. These cases exhibited many phases of reaction to X-ray treatment. One patient gave a favorable therapeutic result; another, a fair result; a third,

a slight improvement only; a fourth, a good result, followed by a relapse.

Finally, we were able to inject the blood serum of the patient who was most improved directly into a patient who was not under the influence of the X-ray.

I. THE EFFECT OF THE BLOOD SERUM OF LEUKÆMIC PATIENTS  
EXPOSED TO X-RAY UPON THE LEUKOCYTES OF  
INJECTED ANIMALS.

It was first pointed out by Heineke<sup>1</sup> that lymphoid cells are very susceptible to X-ray. Linser and Helber<sup>2</sup> after numerous animal experiments concluded that X-ray destroys not only the lymphoid cells of the glands and spleen, but also the leukocytes of the circulating blood, attacking first the young mononuclear forms. They found, furthermore, that following the treatment a new substance, a leukotoxin, was produced in the blood, that when injected into animals destroyed the circulating leucocytes, and when added to animal exudates containing leukocytes, caused loss of motion and degeneration of the cells.

A series of animal injections was carried out by us on similar lines to those of Linser and Helber, except that we used human instead of animal serum. The leukocytes of the animals treated were counted before the injection, and at intervals of about two, five, eight, twenty-four, and forty-eight hours afterward. The maximum effect was usually seen in twenty-four hours, but was sometimes delayed until forty-eight hours. The count made at the expiration of the first twenty-four hour period was used for comparison with the normal.

A. *Normal Human Serum.*

*Experiment 1.*—Blood drawn from the veins of a healthy man (C.) with Luer syringe was defibrinated and centrifuged under aseptic conditions. 3 c.c. of serum injected into rabbits caused in twenty-four hours an increase of about 10 per cent. in the number of leukocytes.

*Experiment 2.*—5 c.c. of the same serum caused in the same time an increase of 12 per cent. in the number of leukocytes.

*Experiment 3.*—3 c.c. of serum taken from a healthy man (S.) injected into

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<sup>1</sup> Heineke, *Munch. med. Woch.*, 1904, li, 785.

<sup>2</sup> Linser and Helber, *Cong. für innere med.*, 1905, xxii, 143.

rabbits caused in twenty-four hours an increase of 5 per cent. in the number of leukocytes.

*Experiment 4.*—3 c.c. of the same serum injected into guinea-pigs caused in twenty-four hours a rise of 15 per cent. in the number of leukocytes.

### B. *Leukæmic Serum.*

*Experiment 5.*—The blood was obtained from a case of lymphatic leukæmia (Eich.) before the X-ray treatment was begun. 2.5 c.c. of the serum were injected into a rabbit and caused in twenty-four hours a rise of 25 per cent. in the number of leukocytes.

*Experiment 6.*—2.5 c.c. of the same serum injected into a guinea-pig was followed by a rise of 5 per cent. in the number of leukocytes.

*Experiment 7.*—The blood was obtained from a case of splenomyelogenous leukæmia (Butcher). 2.5 per cent. of the serum injected into a rabbit was followed in twenty-four hours by a rise of 50 per cent. in the number of leukocytes.

*Experiment 8.*—2.5 c.c. of the serum injected into a guinea-pig was followed in twenty-four hours by a rise of 20 per cent. in the number of leukocytes.

*Experiment 9.*—The blood was obtained from a case of lymphatic leukæmia (Knox) which had not been under treatment for three months. 3 c.c. of the serum injected into a rabbit was followed in twenty-four hours by a rise of 56 per cent. in the number of leukocytes.

*Experiment 10.*—2.5 c.c. of the same serum injected into a guinea-pig was followed in twenty-four hours by a rise of 20 per cent. in the number of leukocytes.

### C. *Leukæmic Serum from a Patient under X-ray Treatment.*

*Experiment 13.*—The blood was obtained from a case of lymphatic leukæmia (Fifield) which had been under regular X-ray treatment for eighteen months, and which showed, at the time of bleeding, glands and spleen of almost normal size, and a leukocyte count of less than 10,000 per c. mm.

2.5 c.c. of the serum injected into a rabbit was followed in twenty-four hours by a decrease of 35 per cent. in the number of leukocytes.

*Experiment 14.*—2.5 c.c. of the same serum injected into a guinea-pig was followed in twenty-four hours by a decrease of 60 per cent. in the number of leukocytes.

*Experiment 15.*—The blood was obtained from a case of lymphatic leukæmia (Knox) under regular X-ray treatment for two months, which had been much improved, but in which the glands and spleen were still enlarged, and the leukocytes varied from 30,000 to 50,000 per c. mm. 3 c.c. of the serum injected into a rabbit was followed by a fall of 40 per cent. in the number of leukocytes.

*Experiment 16.*—3 c.c. of the same serum injected into a guinea-pig was followed by a decrease of 12 per cent. in the number of leukocytes.

*Experiment 17.*—The blood was obtained from a case of splenomyelogenous leukemia (Butcher) which had been under regular X-ray treatment for three months. The spleen was about one-half as large as at the beginning of the treatment, and the leukocytes varied from 40,000 to 60,000 per c. mm. 2.5 c.c.

of the serum injected into a rabbit was followed in twenty-four hours by a fall of 20 per cent. in the number of leukocytes.

*Experiment 18.*—2.5 c.c. of the same serum injected into a guinea-pig was followed in twenty-four hours by a fall of 10 per cent. in the number of leukocytes.

*Summary.*—The injection of normal human serum in rabbits and guinea-pigs is followed in twenty-four hours by a slight increase in the number of leukocytes.

The injection of serum from cases of leukæmia is followed by a more marked rise in the number of leukocytes.

The injection of serum from cases of leukæmia which have been treated by X-ray causes within twenty-four hours a distinct fall in the number of leukocytes. The fall is greatest with the serum of patients who have shown the most decided improvement under X-ray treatment. The fall is least with the serum of patients who have received the slightest benefit from the treatment. We are, therefore, warranted in concluding that the amount of leukolytic substance present in the blood of these cases probably varies directly with the degree of clinical improvement observed in the cases.

Differential leukocyte counts of the blood of animals injected with the serum showed that the mononuclear cells are more influenced than the polynuclear ones. Hence the leukolytic action is, to a certain extent, selective.

## II. THE EFFECT OF X-RAY ON PHAGOCYTOSIS.

In these experiments on phagocytosis the following method was employed: The blood to be tested was defibrinated and placed in two tubes, one of which was exposed to the X-ray for twenty minutes, while the other was kept as a control. To both of these was added a definite amount of a twenty-four hour culture of anthrax bacillus or staphylococcus, after which the tubes were well shaken. At intervals of thirty minutes, one hour, and at intervals of from two to four hours, a drop was taken from each tube, spread on a slide with rice paper and stained with Leischman's stain. A large number of leukocytes, never less than fifty, was then counted, and the percentage of leukocytes containing bacteria was noted. By comparing these results with those observed in the controls one could say whether X-ray treatment increased or diminished phagocytosis.

The blood of two healthy men, and of one case of splenomyelogenous and one of lymphatic leukæmia, was treated in this way. As it was thought that the glass of the test tube might cut off many of the X-rays, most of the experiments were repeated, using a shallow vessel with a cotton covering for the blood. In this case the rays were applied from above. The results were practically identical with the test tube experiments.

In normal blood and in lymphatic leukæmia the X-ray did not materially alter the number of phagocytes or the number of bacteria in the leukocytes. In splenomyelogenous leukæmia, phagocytosis was slightly impaired. These results are easily interpreted when one considers that the polynuclear cells are the only leukocytes capable of phagocytosis, whereas the cells influenced chiefly by the X-ray are the mononuclear ones and the myelocytes, the polynuclear cells being most resistant. In other words, the X-ray may destroy large number of myelocytes or mononuclear cells without materially affecting the phagocytic power of the polynuclear cells.

In the light of these observations it is difficult to understand the assertion of Quadrone<sup>3</sup> that X-ray, by stimulating the phagocytic power of the leukocytes, increases the resistance of animals to disease. He injected various pathogenic bacteria into mice and guinea-pigs, and found that the animals which had been exposed several times to X-ray resisted the infection better than the control animals.

### III. THE EFFECT OF THE SERUM OF LEUKÆMIC PATIENTS EXPOSED TO X-RAY ON THE HUMAN LEUKOCYTES AND ERYTHROCYTES, AS OBSERVED IN THE HANGING DROP.

The technique was as follows: The leukocytes used in each experiment were obtained by centrifuging a tube of freshly defibrinated blood; from the top of this tube a platinum loop was filled and placed on a cover-glass. This drop was made up of a large number of leukocytes mixed with a good many red corpuscles. A loop of the serum which was to be tested was added to the drop, and the two were thoroughly mixed on the cover-glass. The cover was placed on a hollow-ground slide and the edges were rimmed with vaselin to prevent drying. The effect of the serum on both the

<sup>3</sup>Quadrone, *Cent. für innere Med.*, 1905, xxvi, 521.

leukocytes and erythrocytes was observed and compared with the controls.

All of the experiments in the table were repeated with leukocytes which had been washed free of red corpuscles and serum with normal salt solution. The behavior of the leukocytes was essentially the same as in the unwashed specimens.

It will be noted that the three cases of leukæmia which were employed represent entirely different clinical reactions to the X-ray treatment. The first (Eich) responded only slightly; the second (Butcher) improved considerably; and the third (Fifield) was improved to the extent of being quite free from subjective or objective symptoms of the disease. Experiments 14 and 15 were intended to show whether the serum of Butcher, which responded only partially to X-ray, had any neutralizing effect upon the strong leukolytic serum of Fifield. The results on this point were not conclusive.

*Summary.*—1. Leukæmic serum which has not been treated has no leukolytic action on normal blood nor on other leukæmic blood. It has little or no agglutinating action on normal erythrocytes or on the erythrocytes of other leukæmias.

2. The serum of cases of leukæmia which has been treated with X-ray has a decided leukolytic action on normal blood and on other leukæmic blood, and this effect is in direct ratio to the clinical reaction of the patient to the X-ray, as shown by symptomatic improvement.

3. The leukolytic action is selective, showing a marked preference for the mononuclear cells and the myelocytes.

4. The serum of leukæmia which has been treated with X-ray agglutinates the erythrocytes of normal blood and other leukæmic blood. The degree of agglutination corresponds roughly to the degree of leukolysis present.

#### IV. THE EFFECT OF HEAT ON LEUKOLYTIC BLOOD.

According to Linser and Helber, the leukolytic substance is destroyed by heating the serum to 55° or 60° C. Experiments 9 and 10 with the hanging drop (see Table) and the experiments repeated with the washed leukocytes showed only an impairment of leukolytic action of the serum of leukæmia treated with X-ray after

EXPERIMENTS ON THE EFFECT IN THE HANGING DROP OF SERUM OF X-RAYED LEUKEMIA UPON HUMAN BLOOD.

No. Exp.	Mixture of One Loop Each.		Effect Upon.	
	Leukocytes with Many Red Cells.	Serum.	Red Cells.	Leukocytes.
1	Normal (Coles).	0.9% NaCl sol.	No rouleaux; no clumps.	No swelling in 60°; no fragmentation in 20°.
2	Normal (Coles).	Normal (Thomas).	Rouleaux formation; no clumps.	Swelling in 6°; no fragmentation in 18°.
3	Normal (Thomas).	Normal (Coles).	Moderate rouleaux; no clumps.	Only swelling in 10°; no fragmentation in 20°.
4	Normal (Thomas).	Lymph. leuk. (Eich) <sup>4</sup> before x-ray.	No tendency to clump.	No swelling in 4°; no fragmentation in 20°.
5	Normal (Thomas).	Same after x-ray in vivo.	Moderate degree of clumping.	Swelling in 4°; fragmentation slight in 10°.
6	Normal (Thomas).	Same after x-ray in vivo and also in vitro.	Same degree of clumping.	Swelling in 4°; fragmentation moderate in 10°.
7	Normal (Thomas).	Sp. myel. leuk. (Butcher) x-ray in vivo. <sup>5</sup>	Moderate amount of clumping.	Swelling in 3°; fragmentation in 8°.
8	Normal (Thomas).	Same x-ray in vivo and also in vitro.	Same amount of clumping.	Swelling in 3°; fragmentation more marked in 8°.
9	Normal (Thomas).	Same heated 60° C. for 30'.	Same as above.	Swelling and fragmentation slight; less marked.
10	Normal (Thomas).	Lymph. leuk. (Fifield) x-ray in vivo. <sup>6</sup>	Clumping very marked and immediate.	Swelling and clearing in 2°; fragmentation in 4°, very marked.
11	Normal (Thomas).	Same heated 60° C. for 30'.	Same.	Less marked, but still considerable.
12	Sp. myel. leuk. (Butcher).	Normal (Coles).	No clumps; rouleaux present.	No swelling in 6°; no fragmentation in 20°.
13	Lymph. leuk. (Fifield).	Normal (Coles).	No clumps; rouleaux present.	No swelling in 6°; no swelling in 20°.
14	Normal (Thomas).	1 loop (Butcher) + 1 loop (Fifield).	Clumping marked.	Swelling and fragmentation less marked than X; swelling and fragmentation same as VII.
15	Normal (Thomas).	2 loops (Butcher) + 1 loop (Fifield).	Clumping fairly marked.	Swelling and fragmentation less marked than XIV.
16	Lymph. leuk. (Fifield).	Sp. myel. leuk. (Butcher).	Moderate clumping.	Swelling in 3-4°; fragmentation in 6°, especially myelocytes.
17	Sp. myel. leuk. (Butcher).	Lymph. leuk. (Fifield).	Clumping very marked and immediate.	Swelling in 2-3°; fragmentation in 3-4°, especially myelocytes.
18	Sp. myel. leuk. (Butcher).	Same heated 60° C. for 30'.	Same.	Considerably less swelling and fragmentation.

<sup>4</sup> Eich—lymphatic leukæmia; only slight reaction to X-ray; leukocytes = 300,000.

<sup>5</sup> Butcher—splenomyelogenous leukæmia; considerable improvement under X-ray; leukocytes = 40,000.

<sup>6</sup> Fifield—lymphatic leukæmia; very marked improvement under X-ray; leukocytes = 8,000.

being heated for thirty minutes to 60° C. The agglutinating effect of the serum upon the erythrocytes was not altered by the heat. However, we consider these experiments inconclusive as to whether the leukolytic substance is thermolabile or thermostabile. For, if the leukolytic substance is made up of amboceptor and complement, and the complement is destroyed by heat, fresh complement is supplied by the test leukocytes in the hanging drop. The same objection exists to injecting the serum, after heating, into animals, for fresh complement may be furnished by the blood of the animals.

We attempted to obtain anticomplement, which, by replacing the destroyed complement, would render the leukolysin inert; but the animal injected for this purpose died during the process of immunization.

#### V. THE EFFECT OF X-RAY UPON THE BLOOD OF LEUKÆMIC PATIENTS IN VITRO.

##### A. *Normal Blood.*

*Experiment 1.*—2 c.c. of normal defibrinated blood (S.) were exposed for twenty minutes to X-ray in a test tube, at a distance of four inches. Under the microscope, no swelling nor fragmentation of the leukocytes were seen. When a loop of serum was added to a loop of normal leukocytes (C.) and examined in the hanging drop, within ten hours no leukolysis was observed.

*Experiment 2.*—The above experiment was repeated, using normal blood (C.) for the X-ray exposure, and normal leukocytes (S.) for the test leukocytes. The results were identical.

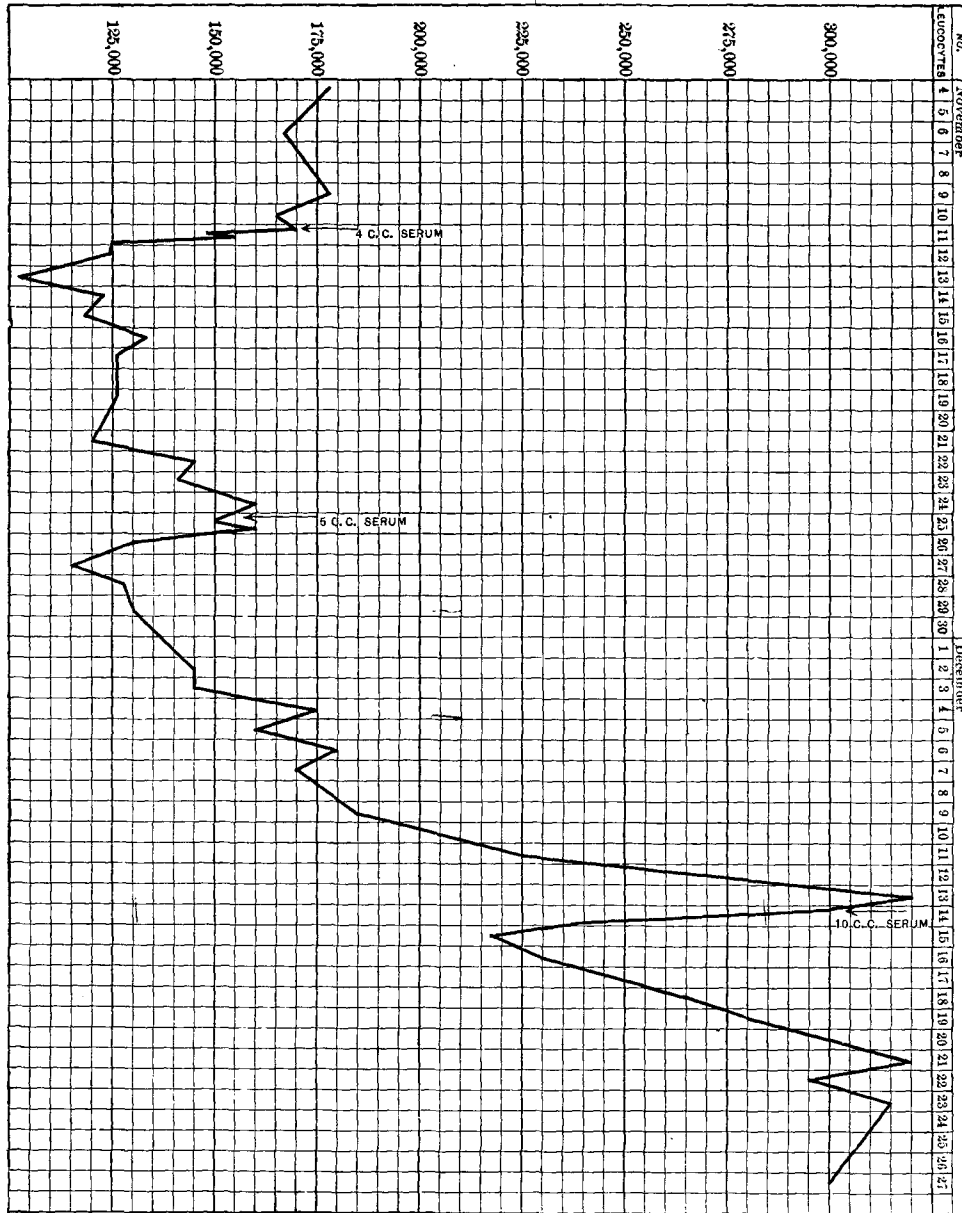
##### B. *Leukæmic Blood.*

*Experiment 3.*—In a case of lymphatic leukæmia (Eich.) which had been treated four times with X-ray, the serum of which is slightly leukolytic, the leukocytes numbered about 300,000. After a thirty-minute exposure in a test tube to X-ray, the leukolytic action of the serum was increased, and the leukocytes showed, in the next twelve hours, more swelling and fragmentation than those in the control tubes.

*Experiment 4.*—A case of splenomyelogenous leukæmia (Butcher) which was under X-ray treatment most of the time for twelve months, showed only moderate reaction. The leukocytes numbered about 50,000 and the serum was moderately leukolytic. After X-ray treatment for thirty minutes, in the course of the next ten hours the leukocytes gave evidence of greater disintegration than the control leukocytes. The myelocytes were the most affected, and the serum became more leukolytic.

*Experiment 5.*—A case of lymphatic leukæmia (Knox) at first improved under the X-ray treatment and then relapsed. The leukocytes numbered about





40,000. Before treatment, the serum was not leukolytic, and after being treated in a tube for thirty minutes, it was not leukolytic to any extent. The leukocytes in the exposed tube showed a slight swelling and an earlier fragmentation than those in the control tube.

*Summary.*—Single direct exposure to X-ray of normal blood in the test tube causes no appreciable destruction of the leukocytes, nor is the serum leukolytic to any extent. Direct exposure of leukæmic blood produces varying degrees of fragmentation of the treated leukocytes and imparts, in some cases, a leukolytic property to the serum. The development of leukolytic substance seems to be greatest when the leukocytes are most abundant, and slight or absent when but few leukocytes are present. It is probable that in normal blood too few leukocytes are present to produce any considerable amount of leukolysin.

#### VI. THE EFFECT OF X-RAY UPON THE BLOOD OF LEUKÆMIC PATIENTS IN VIVO.

##### *Single Exposure.*

*Experiment 1.*—A patient with splenomyelogenous leukæmia (Butcher) had taken no X-ray treatment for twelve weeks. The leukocytes numbered about 36,100. After vigorous treatment with X-ray for thirty minutes over the spleen and liver, three hours later, the leukocytes numbered about 29,800; six hours later, they numbered 26,000; twelve hours later, 28,000; thirty hours later, 26,000. A differential count made it evident that the decrease had been chiefly in the myelocytes. Before the X-ray treatment, about 5 per cent. of the leukocytes were fragmented; twenty-four hours after treatment nearly 20 per cent. were fragmented.

*Experiment 2.*—A case of lymphatic leukæmia (Knox) had been given no X-ray treatment for over a month. The glands of the neck and spleen were then exposed to the X-ray for thirty minutes. Before the treatment, the leukocytes numbered about 106,000; six hours after, they numbered 112,000; twenty-four hours after 94,000; and forty hours after, 84,000.

In a drop of blood taken forty hours after the X-ray exposure, a larger number of free nuclei were to be seen than in the blood taken before the treatment was administered.

##### *Repeated Exposures.*

Four cases of chronic lymphatic leukæmia were exposed to X-ray over periods varying from four months to two years. In every case there was a steady fall in the number of leukocytes, until the count was normal or nearly so. The rate of decrease depended upon the frequency and length of duration of the exposures, but it also varied

with the individual. —When the patient suffered a relapse the response to the treatment was slower, and after a time failed altogether. The mononuclear cells suffered relatively far more than the other cell types. Two cases of chronic splenomyelogenous leukæmia reacted to X-ray treatment in a similar way, with the exception that the myelocytes were destroyed more than any other cells.

This selective action of the X-ray in animals was first demonstrated by Linser and Helber.<sup>7</sup> Bozzolo<sup>8</sup> states that several hours after treatment the leukocyte count in splenomyelogenous leukæmia rises rapidly and then sinks again. Other observers, including Hoffman,<sup>9</sup> have failed to find such an increase. After long continued treatment, the X-ray may lose its effect upon the glands, spleen and blood. This indicates that the individual may acquire immunity to the X-ray.

VII. THE INJECTION OF A STRONG LEUKOLYTIC SERUM FROM A LEUKÆMIC PATIENT EXPOSED TO X-RAY INTO AN UNTREATED CASE OF LEUKÆMIA.

The serum in this case was obtained from a patient suffering from lymphatic leukæmia (Fifield), who had been under X-ray treatment at regular intervals for nearly two years. The serum, which had been tested upon leukocytes in the hanging drop and by means of animal injections, was found to be leukolytic to a high degree. The subject for the injection was a case of lymphatic leukæmia, which, for three months, had not been treated in any way and had been getting steadily worse, as was indicated by the increasing number of leukocytes, and the enlarging glands and spleen. The blood was obtained under aseptic precautions, and after being defibrinated and centrifuged the serum was drawn off and injected into the abdominal wall of the patient.

The accompanying chart illustrates the rapid fall in the number of leukocytes after each injection of the serum. The decrease was greatest at the expiration of the twenty-four to forty-eight hours following the injection. After the first injection of 4 c.c. of the

<sup>7</sup> *Loc. cit.*

<sup>8</sup> Bozzolo, abstract from *Reforma Medica*, 1905.

<sup>9</sup> Hoffman, *Cong. f. innere Med.*, 1905, xxii, 125.

serum the leukocytes decreased in forty-eight hours by 64,000. After the second injection of 5 c.c. of the serum, in forty-eight hours the leukocytes decreased by 34,000. After the third injection of 10 c.c. of the serum, in twenty-four hours the leukocytes decreased by 82,000. It will be observed that the leukocytes attained the original count or a higher one in periods of thirteen, nine, and six days, respectively, after the injection. Although the amount of serum injected was increased, the effect was more transitory each time. Here again is indicated a partial immunity to the leukolytic serum similar to the immunity to the X-ray itself, which may be acquired by a patient. The destruction of the leukocytes was selective, the mono-nuclear cells being the ones chiefly attacked.

In this connection may be cited the interesting experiments of Flexner<sup>10</sup> and of Bunting<sup>11</sup> upon the influence of myelotoxic and lymphotoxic sera upon the blood and blood-forming organs. These sera cause first a leukopenia, then a leukocytosis, and, finally, a return to the normal. The lymphotoxic serum caused, at first, a lymphopenia and, afterwards, a lymphocytosis, and its injection was followed by hypertrophy of the lymphatic glands.

#### VIII. THE NATURE OF LEUKOLYSIN AND THE MANNER OF ITS PRODUCTION.

Leukolysin is probably formed by the destruction of the leukocytes by the X-ray. This action is seen in the experiments with the leukæmic blood in test tubes exposed to X-ray, where both the fragmentation of the leukocytes and the formation of the leukolytic serum can be demonstrated. In the living subject the leukocytes in the circulating blood and the spleen may alone be the source of leukolysin; or this function may be shared by the lymphoid cells of the glands and spleen. The latter seems to us the more probable, because the formation of leukolysin and evidences of leukocyte destruction are much more marked after a given exposure of the spleen and glands to X-ray than after an exposure of the blood in the test tube. Moreover, we know that lymphoid cells, like the leukocytes, are susceptible to X-ray.

<sup>10</sup> Flexner, *Univ. of Penna. Med. Bulletin*, 1902, xv, 287.

<sup>11</sup> Bunting, *Ibid.*, 1903, xvi, 200.

The nature of this leukolysin remains in doubt. It may be an amboceptor-complement complex or a true toxine.

*General Conclusions.*—1. The X-ray produces in leukæmia a disintegration of the leukocytes, affecting especially the young forms, viz., the myelocytes and the non-granular mononuclear cells. A similar action, but one of less degree, takes place in leukæmic blood exposed to X-ray in vitro.

2. The serum of a leukæmic patient who has improved under the X-ray treatment, when injected into animals, causes leukopenia; when added in the hanging drop to the leukocytes of another individual it disintegrates the cells. This leukolytic action is selective, destroying first the mononuclear cells. The strength of the leukolytic action seems to be proportional to the degree of clinical improvement of the patient under the X-ray treatment.

3. The serum of a case of leukæmia which has been exposed to X-ray has a marked agglutinating action on normal red corpuscles and on other corpuscles. The degree of agglutination varies roughly with the degree of leukolysis present.

4. X-ray treatment of normal or leukæmic blood in vitro does not materially alter the phagocytic power of the leukocytes.

5. The injection of a strong leukolytic serum from a patient suffering from lymphatic leukæmia under X-ray treatment into another individual with lymphatic leukæmia, not under the treatment, caused a decided and rapid fall in the number of leukocytes. The mononuclear cells were principally affected. With repeated injections a partial immunity to the serum was established.

We take this opportunity of acknowledging our indebtedness to Drs. Billings, Bevan and Herrick for clinical material, and to thank especially Drs. Hektoen and Ricketts for their many helpful suggestions.<sup>12</sup>

<sup>12</sup>Read at the meeting of the Association of American Physicians, Washington, D. C., May 15-16, 1906.