SOME PHASES OF RADIUM ACTION WITH SPECIAL REFERENCE TO THE HEMATOPOIETIC SYSTEM

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HISTORICAL

Although a great deal of work has been done in demonstrating the effects on the hematopoietic system of exposure to the various radioactive substances, most of the conclusions reached have been based on the results of experiments on the lower animals, chiefly mice, guinea-pigs, and rabbits. The pioneers in this work were German. Thus, Heineke (2) first demonstrated the profound changes brought about in the spleen and lymph-nodes of mice and guinea-pigs by exposure to the Roentgen rays. No attempt, however, will be made to give a complete review of the voluminous literature: a good summary of all work done prior to 1913 has been provided by Gudzent (1). Suffice it to say that the chief results obtained have been from observations of Roentgen-ray effects, which may be summarised as follows:

1. Destruction of lymphoid cells and deposit of pigment in the spleen (2). The earlier of these effects is explosive in character, and precedes effects on any other group of body cells.

2. Destruction of all forms of bone-marrow cells in situ (3).

3. Primary rise of polymorphonuclear count, followed by a drop to a point below normal (4).

4. Steady decline in lymphocyte count (5).

5. Resistance of the red cells to radiation (5).

Although something is known in a vague way among the medical profession about blood-changes in roentgenologists, close
analysis shows that very few other investigations have been made in man, and deductions have sometimes been drawn from an altogether insufficient number of blood-counts. Allen (6), however, was able as early as 1903 to show an immediate slight leucocytosis following x-ray treatment without any appreciable effect on the red cells. Kolde and Martens (7), using mesothorium, demonstrated a primary drop in the red count followed by a return to normal on the fourth day. The most recent work is that of Schweitzer (8), who studied the effect of mesothorium treatment on the blood of patients suffering from cancer of the cervix uteri or vagina. The dosage used was from 2600 to 7700 milligram-hours. His counts were made daily at the same hour and are, therefore, strictly comparable. No counts were made immediately after the application of the mesothorium. His findings may be summarised as follows:

1. Primary leucocytosis followed by a drop to below the original level within twenty-four hours. This subnormal level was maintained until eight weeks after the last treatment.
2. Primary drop in lymphocytes, followed by lymphocytosis.
3. Absence of effect on the red blood cells.
4. Changes in the eosinophile count similar to those in the lymphocyte.

It was this paper which stimulated us to attempt a somewhat more elaborate study of the effects of radium in similar cases, in the hope of throwing some light on the mode of action of the radioactive substances. Schweitzer attributes these blood changes to the action of a supposed "Roentgen-toxin" or to the production of toxic substances of unknown origin, and regards the leukopenia as an unfavorable effect.

INTRODUCTORY

The object of the following study was to determine the immediate and remote effects of radium on the activity of the blood-forming organs, as demonstrated by the numbers of the various formed elements found in the circulating blood at definite stated intervals after the radium application, and with special reference to changes in the leucocytes.
For this purpose, ten patients were chosen who had squamous-cell carcinoma of the cervix uteri and vagina, some hitherto untreated, others with recurrences after a previous operation. The number of applications varied in the different cases, as did also the intervals between applications. Some of the patients received x-ray treatment in addition to radium. In view of this fact, the remote effects of treatment may be due to the cumulative effect of both x-ray and radium. The immediate changes, however, following radium application may be ascribed to this agent alone, especially since these changes were present in most marked degree in those patients who had had no previous x-ray treatments.

TECHNIQUE

The radium was applied directly to the tumor mass in a brass cylindrical applicator, which, for purposes of cleanliness, was wrapped in a rubber finger cot. No further screening was used. The applicator was introduced through a speculum and packed in place with cotton. In applications to the vaginal wall the healthy sides were protected by placing the applicator in a half-cylinder of lead 2 mm. in thickness, adhesive plaster and rubber being used to absorb the secondary rays.

The dose employed was 50 mgm. radium element in the form of radium bromide. The time used was thirty hours for each application whose immediate effects were studied, with two exceptions (case I, August 4, 1916, eighteen hours, and case VIII, November 20, 1916, twenty-six hours). Applications whose immediate effects were not studied varied from three to forty-eight hours in duration. The interval between treatments varied from twelve to sixty-two days, the usual interval being two to three weeks.

The patients were kept in bed during the whole course of the treatment. On the first day of the application the blood was counted in the early morning, between 5 and 9 a.m., usually at 5.45 a.m. The radium was applied immediately afterwards and

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1 The brass cylinder was the usual type distributed by the Radium Chemical Company of Pittsburgh, Pa., and styled "Universal Applicator, Type B."
counts were then made at the following intervals: \( \frac{1}{2} \) hour, 1 hour, 2 hours, 4 hours, 6 hours, 9 hours, 12 hours, and then daily. The patient was given no breakfast, and took a light luncheon after the 6-hour count, and supper after the 12-hour count, so that there was always two and one-half hours between any meal and the next following blood-examination. The daily counts were made between 10 a.m. and 11 a.m., three or four hours after breakfast. The following counts were made on each occasion: Total white count and differential count (stained smear or unstained specimen used for white count\(^2\)); in five cases a red cell count was also made (nos. VI, VII, VIII, IX, and X) and in three a platelet count (nos. VI, IX, and X).

Observations on any given series were made as far as possible by a single individual in order to eliminate individual differences in technique.

**TREATED PATIENTS**

The following changes were found to take place in the period immediately following the radium application.

**A. Total white count**

1. A drop in the total white count. This usually was found to occur within the first half-hour, but sometimes did not reach its lowest point until six hours after the radium application. In one instance no drop was recorded, but here the half-hour count was not taken (case IX). Counts made on this patient during a subsequent treatment showed a primary drop during the first half-hour. In two cases (VIII and X) the drop was preceded by a slight temporary rise. In one case (V) the primary drop was succeeded after a temporary rise by a secondary drop, which reached its lowest point six and fifteen hours after the application during two successive treatments.

\(^2\) It was found by careful comparison of several simultaneous counts that there was usually no difference worth consideration between results obtained from stained and those from unstained specimens. Occasionally the difference was fairly distinct, but this did not occur more frequently than it does in counting two separate hundreds in one stained specimen.
2. A return of total white count to approximately its former level. This occurred on nine occasions within the first six hours, on seven occasions between six and twelve hours, and on two occasions between twelve and nineteen hours after the application.

3. A compensatory rise of the total white count, in some instances to a point considerably higher than before the radium application. This phenomenon occurred as follows:

   Twice, two to three days after the application.
   Three times, twenty-four to twenty-six hours after the application.
   Four times, twelve to twenty-four hours after the application.

![Chart 1. Early Changes in Total White Count](image-url)
Twice, within twelve hours after the application.
Seven times, no such rise occurred.
Another striking point that comes out on study of the charts is
that in cases where the early response to radium application is not
altogether typical, for example, when the primary drop in total

**Charts 2a and 2b. Atypical Reaction Repeated During Subsequent Treatment**

Note preliminary rise before usual fall.

**Charts 3a and 3b. Modified Reaction of Total White Count During Subsequent Treatment**
white count is delayed, or unusually well sustained, or preceded by a temporary rise, the same behavior is noted during a later application (see cases V, VIII, and X).

Finally, it is also worthy of note that in one case (case I) the response of the polymorphonuclears to the radium application was not so marked following the later application as it was following the first. It would seem in this case that the power of the hematopoietic system to react to what would usually be an efficient stimulus had been diminished, either by frequent radium applications in the past or by the advance of the disease itself.

Observations on the stained smear, which will be considered later, seem to show that this failure to react is due to lasting damage to the hematopoietic system from the primary radium application.

B. Total polymorphonuclear count

This ran throughout so closely parallel to the total white count that all that has been said above in regard to changes in the total count applies also to changes in the polymorphonuclear count.

C. Total lymphocyte count

1. No characteristic change was found to occur in the total lymphocyte count immediately after the application of radium. There was more frequently a drop than a rise, but the degree of change in either case was usually so slight and the duration of the change so variable that it need not be considered.

2. No characteristic change in the total lymphocyte count could be demonstrated to occur during the first two weeks following treatment. The largest drop was from 7800 to 1000 (case IV) at the end of nine days, the largest rise being from 1200 to 4200 at the end of thirteen days (case VI).

3. In most cases, the total lymphocyte count varies to some extent in harmony with the variations of the total white count. This behavior is most noticeable, as a rule, when the variations in the total white count are considerable (cases III and IV), although it is sometimes noticed when variations are rather small.
CHART 4. SHOWING EARLY CHANGES IN TOTAL LYMPHOCYTE COUNT COMPARED WITH CHANGES IN TOTAL WHITE COUNT
(case V). There are exceptions, however, to this general statement, as for instance in case VI, where the variations in the total white count are distinct, while the total lymphocyte count shows only a slight variation from one time to another.

**D. Total large mononuclear count**

No constant variations were found in the total mononuclear count.

**E. Percentage values of the various cells**

These were studied in stained smears made during and after nine radium treatments in five patients. In all these cases the blood showed some pathological findings before treatment was begun, as, for instance, absence of eosinophiles, immature forms of white and red cells, and changes in the form of the red cells. In two patients the percentage of polymorphonuclears and lymphocytes was within normal limits; in the other three there was pronounced neutrophilia and lymphopenia.

1. *Neutrophiles.* In eight out of the nine treatments there is first a drop in the neutrophilic curve, preceded in five instances by a brief preliminary rise lasting from one-half hour to nine hours after the radium application. This drop lasts from one to twelve hours after the beginning of treatment, and is immediately followed by a rise to a point which is always above the level noted before the treatment was begun, in some instances as high as 93 per cent. This rise usually attains its highest point within forty-eight hours after the time of application, though in one instance this was not reached until the third day. During the days that follow there is a gradual return of the curve to its normal level, which is usually reached by the fifth to the eighth day. In one patient (case X) the drop continued until the second treatment was begun (eleven days) and then continued still further until well below the normal level.

In one treatment no definite change in the neutrophile percentage could be demonstrated. This case showed a very pronounced neutrophilia and lymphopenia.  

Φ
To summarize, the following points may be made:

1. There is a drop in the neutrophile percentage, sometimes preceded by a temporary rise. This drop is not below the lower limit of normal.

2. After twelve hours, there is a compensatory rise to a point above the upper limit of normal.

3. The curve returns to the normal level in five to eight days.

Of interest in this connection is the behavior of the myelocytes and of those neutrophiles which are in the transitional stage between the myelocyte and the polymorphonuclear form—the so-called "metamyelocytes" of Pappenheim (9). These latter cells could be demonstrated in the blood of all the patients before treatment was begun, indicating, probably, some irritation of the bone-marrow due to the toxins resulting from the disease. During radium treatment, however, they showed a decided increase simultaneous with the rise in neutrophile percentage. In cases VII and X the rise in metamyelocytes preceded and heralded the rise of neutrophiles. The myelocytes, likewise, were observed to increase in numbers. In four out of the five patients these were demonstrated in the blood in small numbers before treatment, but during treatment they were found much
more frequently. This was especially the case in case X, who, during her second treatment, showed 2 per cent myelocytes in the blood. It would seem, then, that the radium has a definite irritant action on the bone-marrow.

The behavior of the neutrophile count during subsequent treatments is somewhat modified. Four out of the five patients were given several treatments. Of these case IX showed simply an irregular drop in neutrophiles during the second treatment. Case VI, who was treated five times, and whose blood was studied during the first and fourth treatments, showed no appreciable change in the neutrophile curve during the fourth treatment. It is fair to state in this connection that at this time she showed a marked neutrophilia (93 per cent) and lymphopenia (5 per cent). In case X the effect on the curve was not quite so marked during the second as during the first treatment.

In general, then, it may be said that the radium effect is more marked during the first application than during later treatments.

2. Lymphocytes. These likewise showed a constant percentage curve in eight out of the nine treatments studied. In case X no such response could be demonstrated, although even here
the curve has one thing in common with those of the other cases, namely the drop in relative lymphocyte count at the end of the 30-hour treatment. The changes noted in the other eight instances are as follows:

(1) An increase in the count, reaching its maximum in from two to twelve hours, and preceded in five instances by a brief preliminary drop. In the two cases which showed a normal percentage before treatment the count rose to 30 per cent, while in those which had showed marked lymphopenia the highest point never exceeded the upper limit of normal, and in some instances did not reach the normal level at all.

(2) After from four to twelve hours there begins an irregular drop, which in seven instances reaches its lowest point before the end of the treatment (thirty hours). In one instance, the lowest point is not reached until the next day, while in the ninth instance (case IX) the drop continues for eight days. In every instance the low point is well below the lower limit of normal. In those patients who showed a normal blood picture before treatment the percentage fell as low as 9 per cent, while in those with previous lymphopenia it even reached 4 per cent. In one case the low point was still slightly above the level noted before treatment (case VI, second treatment), but the blood in this case was highly abnormal, showing an extreme lymphopenia (5 per cent) before treatment.

It seems reasonable to infer that this drop in the percentage of lymphocytes is an expression of actual damage done to the lymphatic system, a supposition which is borne out by the finding of numerous pyknotic and vacuolated lymphocytes in the blood-smears taken during this period. These degeneration forms first appear six to ten hours after the beginning of treatment and remain in the smear until its end (thirty hours), an observation which agrees with those of Heineke (2).

(3) Immediately or shortly after this period of depression there is a secondary rise in the lymphocyte curve, even in those cases which had showed a marked lymphopenia. In six instances this rise continues to a point slightly above the level noted before treatment, once to a point just below it. In one case only (case VI) it is impossible to demonstrate this rise.
To sum up, the lymphocyte curve is approximately the reverse of the neutrophile curve, and shows:

1. A rise, sometimes to a point as high as 30 per cent, and preceded occasionally by a preliminary drop.
2. A sharp drop after four to ten hours to a point well below the normal level.
3. A return to the original level after several days.

Charts 7A and 7B. Early Changes in Lymphocyte Percentages Immediately Following Application

Charts 8A and 8B. Changed Reaction of Lymphocytes During Subsequent Treatment
As in the case of the neutrophiles, the lymphocytes show a modified reaction to repeated treatments. More than one treatment was given in cases VI, VIII, IX, and X.

In case VI, five treatments were given and the blood was studied during the first and fourth. The influence of the fourth treatment was much less marked than that of the first.

In case VIII the curve showed about the same course during both treatments, although the difference between highest and lowest points is less during the second than during the first.

In case IX, however, the influence of the second treatment was more protracted and intense than that of the first. The difference between high and low points was greater during the second treatment, the figures being 32 vs. 8 as opposed to 27 vs. 9 during the first treatment. After the first treatment the original level was again reached after forty-eight hours and the following weeks showed a rise in average lymphocyte count, while after the second the normal level was not reached until the twelfth day, and the average count of the following weeks (21 per cent) was less than the average count of the weeks following the first treatment (24 per cent). In this case, however, constitutional effects must be taken into consideration, because twenty-one
days after the second treatment there appears a terminal sharp drop in relative lymphocyte count.

![chart](chart10a.png)

**Chart 10A. Intensified Reaction of Lymphocytes During Subsequent Treatment**
First treatment

![chart](chart10b.png)

**Chart 10B. Intensified Reaction of Lymphocytes During Subsequent Treatment**
Second treatment
In case X the reaction of the lymphocytes to the treatment is decidedly stronger during the first application than during the second, as evidenced by these figures:

<table>
<thead>
<tr>
<th></th>
<th>First treatment</th>
<th>Second treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>31</td>
<td>24</td>
</tr>
<tr>
<td>Lowest</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

As in case IX, however, the effect is more protracted after the second treatment than after the first, the original level being again reached on the second day after the first treatment and not until the seventh day after the second. In the period following these treatments the count rose to 24 per cent after the first, and 26.7 per cent after the second.

In general, then, it may be said that the lymphocytic reaction, numerically considered, is less marked with subsequent treatments than with the original one, although the "depressor" effect may be more lasting after the later treatments. This fact seems to indicate a permanent damage to the lymphopoietic system from the first treatment, rendering it incapable of its normal reaction to a given stimulus and slower to recover from the effects of that stimulus. In cases VI and X there were
greatly increased numbers of pyknotic and vacuolated lymphocytes during the later treatments, which may be taken as confirmatory evidence of the increased damage to the lymphopoietic system.

3. Large mononuclears. During seven treatments there was noted a preliminary rise of the large mononuclear percentage, the highest point being reached four to twenty-six hours after the application. In three instances during a first treatment and once during a later treatment the figure rose above the upper limit of normal, but in all other instances the percentage remained within normal limits. This rise was followed by a drop which persisted until the end of the treatment on the day following. In two instances it continued to the third and fourth day respectively. Twice this secondary drop occurred without any preliminary rise. In all cases the curve fell to a point well below normal, once even getting down to 1 per cent. This drop
in turn was followed by a rise to the original level or above, lasting from one to nine days after treatment.

Repeated treatments showed absence or diminution in intensity of this effect. The curve of the large mononuclears follows so closely that of the lymphocytes as to favor the theory of their lymphatic origin.

4. Eosinophiles. Prior to treatment all patients showed an absence or decrease in number of the eosinophiles. During treatment there was noted in three cases a rise at varying periods, in one instance as high as 6 per cent. In the other cases no definite influence was demonstrable. These findings are directly contrary to those of Schweitzer (8), who noted a disappearance of eosinophiles during and after treatment, with reappearance two to three weeks later.

F. Platelet count

The platelets were counted during four treatments on three patients (VI, IX, and X). In three instances there was an immediate drop; in two of these the drop was distinct and
lasted two and six hours respectively; in the third case the drop was very slight, lasting only an hour, and was succeeded by a slight steady rise for the succeeding two days. In one instance there was practically no change, although there was a slight steady drop for the first nine hours followed by a return to normal.

Charts 14a and 14b. Early Changes in Platelet Count

In general, then, it may be said that the platelets, like the polymorphonuclear cells, show a tendency to an immediate though often a slight decrease in absolute numbers.

G. Hemoglobin

This was estimated on four occasions (cases VI, VIII, IX, X) during treatment, but showed no change of any importance.

H. Red cell count

The red cells were counted during seven treatments in five cases; in every instance there was considerable fluctuation in the figures. All cases, however, showed a definite increase in the count, at some period within the first three days following the time of application, to a level well above that of the count taken before the radium was applied. Thus:
In five out of the seven instances there was a preliminary drop in the count, lasting from one-half hour to four and one-half hours in the different cases. This was especially marked in case X, which did not show so evident a secondary rise as the other cases.

<table>
<thead>
<tr>
<th>CASE</th>
<th>BEFORE TREATMENT</th>
<th>LENGTH OF TIME</th>
<th>HIGHEST COUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>3,250,000</td>
<td>3 days</td>
<td>4,000,000</td>
</tr>
<tr>
<td>VII</td>
<td>4,300,000</td>
<td>22 hours</td>
<td>5,350,000</td>
</tr>
<tr>
<td>VIII</td>
<td>5,000,000</td>
<td>33 1/2 hours</td>
<td>6,100,000</td>
</tr>
<tr>
<td>VIII</td>
<td>4,900,000</td>
<td>12 hours</td>
<td>5,600,000</td>
</tr>
<tr>
<td>IX</td>
<td>4,150,000</td>
<td>12 hours</td>
<td>5,000,000</td>
</tr>
<tr>
<td>IX</td>
<td>4,600,000</td>
<td>6 hours</td>
<td>5,800,000</td>
</tr>
<tr>
<td>X</td>
<td>4,500,000</td>
<td>½ hour</td>
<td>5,100,000</td>
</tr>
</tbody>
</table>

Charts 15a and 15b. Charts Showing Changes in Red Blood Count Specimen Charts

I. Blood-pressure

Blood-pressure estimations were carried out simultaneously with the blood-counts in five instances (cases VI, VII, VIII, IX, and X) with the idea of trying to determine whether any
evidence could be found for the formation of any substance having a lowering effect on the blood-pressure. Cholin has been shown to be one of the products of radium action and has been supposed by some authors to be responsible for the beneficial effect of radium on tumors (10). This substance exerts a depressor effect when introduced into the animal organism. The following table will show the results noted:

<table>
<thead>
<tr>
<th>TIME OF READING</th>
<th>CASE VI</th>
<th>CASE VII</th>
<th>CASE IX</th>
<th>CASE XI</th>
<th>CASE XA</th>
<th>CASE VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>148-82</td>
<td>148-84</td>
<td>152-88</td>
<td>112-80</td>
<td>122-86</td>
<td>114-68</td>
</tr>
<tr>
<td>½ hour after application</td>
<td>136-68</td>
<td>150-86</td>
<td>142-82</td>
<td>110-82</td>
<td>120-88</td>
<td>112-68</td>
</tr>
<tr>
<td>1 hour after application</td>
<td>130-60</td>
<td>138-80</td>
<td>120-78</td>
<td>114-86</td>
<td>126-90</td>
<td>110-66</td>
</tr>
<tr>
<td>2 hours after application</td>
<td>142-80</td>
<td>142-78</td>
<td>136-80</td>
<td>110-80</td>
<td>114-86</td>
<td>116-66</td>
</tr>
<tr>
<td>4 hours after application</td>
<td>130-66</td>
<td>140-76</td>
<td>144-78</td>
<td>116-86</td>
<td>122-90</td>
<td>116-68</td>
</tr>
<tr>
<td>6 hours after application</td>
<td>134-66</td>
<td>136-76</td>
<td>112-80</td>
<td>120-82</td>
<td>114-66</td>
<td></td>
</tr>
<tr>
<td>9 hours after application</td>
<td>128-66</td>
<td>140-84</td>
<td>120-100</td>
<td>126-86</td>
<td>120-70</td>
<td></td>
</tr>
<tr>
<td>12 hours after application</td>
<td>128-66</td>
<td>138-84</td>
<td>116-90</td>
<td>112-80</td>
<td>122-78</td>
<td></td>
</tr>
<tr>
<td>18 to 25 hours after application</td>
<td>122-64</td>
<td>130-78</td>
<td>130-82</td>
<td></td>
<td>120-68</td>
<td></td>
</tr>
<tr>
<td>26 to 36 hours after application</td>
<td>132-68</td>
<td>138-80</td>
<td>132-78</td>
<td></td>
<td>126-86</td>
<td>106-66</td>
</tr>
</tbody>
</table>

From this table it will be seen that in cases VI and IX, and to a less extent in case VII, there is a tendency towards a fall in blood-pressure. The others, however, show no such tendency. It seems fair to assume that the small drop noted in the three first cases may be explained as the result of complete rest in bed, especially as the three patients in question were ambulatory at the time of treatment while cases VIII and X were bedridden.

CONTROL CASE

In order to control these observations, we selected an eleventh patient who also had an inoperable carcinoma of the cervix uteri, and counted her blood under exactly the same conditions as prevailed with the treated cases. While there was considerable fluctuation in the counts during the day, the features noted above were not reproduced. Thus, for instance, we find no initial drop in the total white count during the con-
A. Before any treatment  
(Check period)  

CHARTS 16A AND 16B. CHANGES IN TOTAL WHITE COUNT

A. During control period  

CHARTS 17A AND 17B. CHANGES IN LYMPHOCYTE PERCENTAGE  

Note: V.L. = Vacuolated lymphocyte; Pyk.L. = Pyknotic lymphocytes
trol period, while during the radium treatment the usual curve is noted.

In a similar way, the percentage counts of lymphoid cells

and polymorphonuclears show no characteristic reaction during the untreated period, while during the radium treatment the typical curves are reproduced.
Most striking of all is the number of myelocytes and metamyelocytes found during radium treatment, as contrasted with their absence during the control period (see chart 19).

It is further noteworthy that pyknotic lymphocytes were abundant during the radium treatment, indicating destruction of the lymphoid elements, and completely absent during the control period (see chart 17B).

From a study of this case, therefore, it would seem fair to assume that the changes noted are indisputably dependent on the action of the radium, and not mere variations within physiological limits.

The remote effects of radium treatment as shown by the counts made on these nine patients may now be analysed. For the purpose of avoiding false deductions, the cases will be divided into those which were treated with radium alone (group 1) and those which had x-ray treatments in addition (group 2). In the former class there were three patients in the group studied: two of these were followed for only twenty-four and forty-six days respectively, but the third was followed up till the time of death.

In the latter class there were six cases: of these one was followed for thirty-four days, one for fifty-four days, one for fifty-seven days, and the remaining three until the time of death.

All intervals will be reckoned from the date of the first radium treatment, irrespective of whether that particular treatment was used for the purpose of studying the immediate blood changes.

In the following tables the blood changes are summarised by charting the various counts at arbitrary intervals. Unless otherwise stated the figures given are the average figures calculated from two to five counts on successive or almost successive days. This procedure was adopted to avoid the possibility of recording some single atypical count as representing the average count of the period. In some instances, only one count was made at a given period, so that sometimes it has been impossible to take the average of several counts. These instances are noted.
Tables Showing Remoter Blood-Changes Following Radium Treatment³

<table>
<thead>
<tr>
<th>CASE III</th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>11,000</td>
<td>7,600</td>
<td>2,100</td>
<td>69</td>
<td>19</td>
</tr>
<tr>
<td>3 weeks after</td>
<td>10,600¹</td>
<td>8,400¹</td>
<td>1,200¹</td>
<td>84¹</td>
<td>12¹</td>
</tr>
<tr>
<td>4 weeks after</td>
<td>12,000</td>
<td>9,850</td>
<td>1,500</td>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>5 weeks after</td>
<td>8,500</td>
<td>4,500</td>
<td>2,400</td>
<td>53</td>
<td>28</td>
</tr>
</tbody>
</table>

In this group of cases the blood-changes may be summarised as follows:

**Case III.** (1) A slight decrease in the total white count, most marked at the end of six weeks.

(2) A sharp change in the relative polymorphonuclear and lymphocyte count from four to five weeks after treatment, due chiefly to a marked decrease in the absolute lymphocyte count.

(3) A reversal of this process at the end of six weeks, with marked decrease of the absolute and relative polymorphonuclear count and increase of the absolute and relative lymphocyte counts to a point slightly above normal. Comparison of these figures with those of three weeks previous shows the change to be primarily due to a depression of the polymorphonuclear count rather than to a lymphocytic increase.

To summarise the findings briefly, it appears that there was in this case first a depression of the lymphocytic series lasting from four to five weeks after treatment, and later a depression of the polymorphonuclears, appearing first after six weeks and accompanied by a recovery of the lymphocytic series.

**Case IV.** (1) A moderate decrease in the total white count, the lowest point being reached in four weeks, after which time the count begins to rise again.

¹ Blood-counts marked with the figure 1 throughout these tables are single counts. All others represent an average drawn from two or more counts on successive or almost successive days.
(2) A steady decrease in the total lymphocyte count, the percentage count increasing slightly for four weeks and then beginning to drop. In this case the fall in total lymphocytes during the first four weeks is not nearly so marked as the fall in the polymorphonuclear count and is roughly proportional to the fall in the total white count. Furthermore, during the fourth to sixth week the decrease in the total and relative lymphocyte counts is subordinated in importance to the rise in the polymorphonuclear count.

To summarise, this chart shows a primary depression of the polymorphonuclear count lasting four weeks, followed by a compensatory stimulation. Accompanying this effect there is a slight but progressive depression of the lymphocytic series, reaching the lowest point at the end of six weeks. These findings are a contrast to those noted in case III.

Case VI. (1) A fall in the total white count and the total polymorphonuclears during the first one and one-half months
after a brief preliminary rise, followed by an irregular slight rise until three months and a sharp terminal rise from three and one-half to four months.

(2) A steady drop in the total lymphocyte count and a more gradual drop in the percentage count. The steady fall is interrupted at two months by a temporary rise in the total count, but at this period the rise in the total white count is proportionally almost as high.

(3) While at two and one-half months there is a temporary decrease in the total polymorphonuclear count, the rise in the polymorphonuclear percentage begins at that time and presages the later rise in the total polymorphonuclear count.

To summarise, then, we have in this case a drop in all white blood cells in about the same proportion during the first one and one-half months. The lymphocytic drop, however, starts at two weeks, the polymorphonuclear drop at one month. After the first one and one-half months there is a further decrease in the lymphocytes and a disproportionately large increase in the total white count and polymorphonuclears, ending in an enormous leucocytosis during the two weeks preceding death.

DISCUSSION OF RESULTS

Group 1

The remoter changes in blood-findings may be divided into the early and late changes.

Early changes. (1) All three charts show early depression of both lymphocytic and polymorphonuclear counts. In two of the three cases the lymphocytes show the drop earlier than the polymorphonuclears; in the third case the drop in both is simultaneous. The time when these phenomena appear is not constant, the lymphocytes showing a drop at two weeks in two cases and at four weeks in the third case. In the third case, however, it is not possible to say that the drop did not appear earlier, inasmuch as no count was taken until three weeks after the first treatment.
In the same way, the polymorphonuclears show the drop at two, four, and six weeks respectively in the three charts.

(2) One case (III) shows a recovery of the lymphocytes at the sixth week, another (VI) at two months. The third case (IV) shows no such reaction up till the last count (at six weeks). It is interesting to note in this connection that case III lived nine months after treatment was begun.

In case VI the lymphocytic recovery is accompanied by a sharp reaction in the polymorphonuclear series, for, although the absolute lymphocyte count rises to a point above normal, the total white count also rises and the relative lymphocyte count remains about as before. This patient died four months after treatment was begun. Case IV shows at six weeks a beginning leucocytosis and a further depression of the lymphocytes, changes which point to impending death. The patient died four months after treatment was begun.

_Late changes._ (1) The most noteworthy late change is the terminal leucocytosis. In case VI this is found to be very marked and is characterised by enormous increase in the absolute polymorphonuclear count together with moderate decrease in the absolute lymphocyte count, factors which combine to give a very low relative lymphocyte count and correspondingly high relative polymorphonuclear count.

(2) Before the leucocytosis sets in another change may be noted. This is the change in relative counts from two and one-half to three months after the institution of treatment, the lymphocytes decreasing, the polymorphonuclears increasing. This apparently is the signal for the collapse of the patient's resistance and presages the terminal stage.

It may now be asked with reason: How big a part does the radium play in causing these changes, and how far are they due to the disease process? In answer it would seem fair to claim that the radium is responsible for the early changes, that is, the fall in lymphocytes and polymorphonuclears; but that the later changes, i.e., the marked change in relative counts and the terminal leucocytosis, represent the breakdown of the body's resistance and its final effort to combat the flood of
toxic products circulating in the blood stream. In this sense, the lymphocyte may be said perhaps to act as a rough indicator of the bodily resistance toward the later stages of the disease before the terminal leucocytosis has set in. Its practical value in this connection, however, is small, because it does not show any characteristic change until the break-down of the patient is clinically all too obvious.

Tables Showing Remoter Blood-Changes Following Combined x-ray and Radium Treatments

<table>
<thead>
<tr>
<th>CASE I</th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months after</td>
<td>9,5001</td>
<td>5,9001</td>
<td>2,4501</td>
<td>621</td>
<td>261</td>
</tr>
<tr>
<td>5 months after</td>
<td>7,500</td>
<td>4,850</td>
<td>1,350</td>
<td>65</td>
<td>18</td>
</tr>
<tr>
<td>6 months after</td>
<td>7,400</td>
<td>3,750</td>
<td>2,200</td>
<td>51</td>
<td>30</td>
</tr>
</tbody>
</table>

Several short treatments: Heavy treatment begun just before next count

<table>
<thead>
<tr>
<th></th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 months after</td>
<td>6,2001</td>
<td>4,8501</td>
<td>8751</td>
<td>781</td>
<td>141</td>
</tr>
<tr>
<td>12 months after</td>
<td>13,500</td>
<td>11,350</td>
<td>1,200</td>
<td>84</td>
<td>9</td>
</tr>
<tr>
<td>12½ months after</td>
<td>14,500</td>
<td>12,200</td>
<td>1,450</td>
<td>84</td>
<td>10</td>
</tr>
</tbody>
</table>

Case I. (1) The total white count shows a steady drop, lasting until the eleventh month, followed by a marked rise from the twelfth to thirteenth months.

(2) The lymphocytes show a sharp drop between two and one-half and five months, followed by a compensatory rise at the sixth month, while the polymorphonuclears show only an absolute decrease after the first five months, the relative decrease appearing first at six months, at which period it is overshadowed by the lymphocytic increase.

(3) The lymphocytes show a marked drop at the eleventh month which accounts for the greater part of the drop in total white count. The percentage of polymorphonuclears correspondingly makes a great jump, although the absolute number shows only a slight increase.
(4) At the twelfth month there is a sharp increase in total white count and polymorphonuclear count, which explains the increase in polymorphonuclear percentage and the decrease in lymphocyte percentage.

To summarise, this chart shows at five months a primary decrease in lymphocytes, followed by a temporary compensatory rise (at six months) and, finally by a gradual relative decline. The corresponding fluctuation in the total white count is determined largely by the lymphocytic changes until the twelfth month, when there appears a polymorphonuclear leucocytosis. This final change is presaged as in case VI at eleven months by a change in relative counts without any increase in total white count.

<table>
<thead>
<tr>
<th>CASE II</th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>16,500</td>
<td>13,350</td>
<td>1,650</td>
<td>81</td>
<td>10</td>
</tr>
<tr>
<td>5 months after</td>
<td>19,000</td>
<td>15,600</td>
<td>2,300</td>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>6 months after</td>
<td>18,000</td>
<td>15,500</td>
<td>1,800</td>
<td>86</td>
<td>10</td>
</tr>
<tr>
<td>7 months after</td>
<td>21,000</td>
<td>18,500</td>
<td>1,700</td>
<td>88</td>
<td>8</td>
</tr>
<tr>
<td>8 months after</td>
<td>44,000</td>
<td>41,350</td>
<td>1,750</td>
<td>94</td>
<td>4</td>
</tr>
</tbody>
</table>

Case II. This chart shows: (1) A steady increase in total white count.

(2) A gradual increase in percentage of polymorphonuclears.

(3) A gradual decrease in percentage of lymphocytes except for one period (six months) when there is a slight temporary rise, accompanied by a rise in actual numbers. This represents a transitory stimulation following the first trial of a thirty-hour treatment. In this chart, again, the terminal leucocytosis is foreshadowed by the changing percentage counts. This change is due to a steady increase in the absolute polymorphonuclear count, the absolute lymphocyte count remaining practically stationary throughout.
Case V. The chart of this case shows: (1) A fall in total white count continuing until fifteen weeks after treatment was instituted, after which time the terminal rise begins.

(2) The lymphocytes show a primary drop after four weeks which is proportionally greater than the rise of polymorphonuclears. At fifteen weeks the polymorphonuclears show a more distinct drop than the lymphocytes.

(3) At nineteen weeks both groups of white cells show an approximately proportional rise, while at twenty-two weeks the polymorphonuclears show a rise, though this is not so marked as the drop in lymphocytes. This is a beginning terminal leucocytosis. If later counts had been made the polymorphonuclears would probably have shown a large relative increase.

Summary. This chart shows a primary lymphocytic drop followed by a drop in polymorphonuclears, the former starting at four weeks, the latter at eighteen weeks. The relative counts show an almost steady increase of polymorphonuclear cells and an almost steady decrease of lymphocytes. The terminal leucocytosis is preceded as usual by a definite though gradual change in the relative proportion of polymorphonuclears and lymphocytes.

Case VIII. This chart shows: (1) Irregular fluctuation of total white count and of total polymorphonuclear count.

(2) Depression of lymphocytic series from the second to the third week, as evidenced by a primary drop in total lymphocyte count despite an increase in total white count, and by the decrease in relative count at the third week in spite of the drop in total white count at that time.
### CASE VIII*<sup> </sup>

<table>
<thead>
<tr>
<th></th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>8,600&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6,500&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1,550&lt;sup&gt;1&lt;/sup&gt;</td>
<td>76&lt;sup&gt;1&lt;/sup&gt;</td>
<td>18&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 weeks after</td>
<td>12,100&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10,400&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1,330&lt;sup&gt;1&lt;/sup&gt;</td>
<td>86&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>3 weeks after</td>
<td>7,200</td>
<td>6,400</td>
<td>575</td>
<td>89</td>
<td>8</td>
</tr>
<tr>
<td>4 weeks after</td>
<td>11,000</td>
<td>9,450</td>
<td>1,320</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td>5½ weeks after</td>
<td>9,100</td>
<td>7,450</td>
<td>1,080</td>
<td>82</td>
<td>12</td>
</tr>
<tr>
<td>6½ weeks after</td>
<td>11,000&lt;sup&gt;1&lt;/sup&gt;</td>
<td>8,250&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2,100&lt;sup&gt;1&lt;/sup&gt;</td>
<td>75&lt;sup&gt;1&lt;/sup&gt;</td>
<td>19&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>7 weeks after</td>
<td>8,500</td>
<td>7,500</td>
<td>510</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>9½ weeks after</td>
<td>Dead</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This patient was given radium treatments at an earlier date [August 1915] in a different institution. Dosage and filtration at that time were not recorded.

3. A readjustment of relative counts from the fourth to sixth weeks.

4. A sharp drop in absolute and relative lymphocyte count at the seventh week without any leucocytosis, presaging the death of the patient two and one-half weeks later.

Summary. This case shows an initial depression of the lymphocytes followed by temporary recovery, and a final sharp drop shortly before death. The polymorphonuclears show no definite changes.

### CASE IX

<table>
<thead>
<tr>
<th></th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>8,400</td>
<td>5,600</td>
<td>1,850</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>1 month after</td>
<td>6,500</td>
<td>5,000</td>
<td>1,000</td>
<td>77</td>
<td>16</td>
</tr>
<tr>
<td>2 months after</td>
<td>13,000</td>
<td>10,300</td>
<td>1,700</td>
<td>79</td>
<td>13</td>
</tr>
<tr>
<td>3 months after</td>
<td>14,000&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11,350&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2,100&lt;sup&gt;1&lt;/sup&gt;</td>
<td>81&lt;sup&gt;1&lt;/sup&gt;</td>
<td>15&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>4 months after</td>
<td>15,500</td>
<td>14,700</td>
<td>450</td>
<td>95</td>
<td>3</td>
</tr>
<tr>
<td>Last count, 4 months, 9 days</td>
<td>19,300</td>
<td>17,500</td>
<td>1,150</td>
<td>91</td>
<td>6</td>
</tr>
<tr>
<td>4 months, 10 days</td>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Case IX.* This chart shows the following:

1. A preliminary drop in total white count, followed by a steady slight rise and slight terminal leucocytosis.

2. A sharp drop in lymphocytes, absolute and relative, accounting for most of the preliminary drop in total white count.

3. A steady increase in polymorphonuclear count, absolute
and relative, with corresponding decrease in lymphocytes, most marked in the relative counts.

Summary. This chart shows a marked fall in lymphocytes one month after treatment was begun, accompanied by a slight decrease in polymorphonuclear count. This is followed by a steady increase in polymorphonuclear count and an irregular lymphocytic curve. The lymphocytes do not show a further marked drop until a short time before death. The last count, taken the day before death, shows a final effort to rally on the part of the lymphocytes. The usual terminal leucocytosis is seen.

<table>
<thead>
<tr>
<th>CASE X</th>
<th>TOTAL WHITE BLOOD CELLS</th>
<th>TOTAL POLYMORPHONUCLEARS</th>
<th>TOTAL LYMPHOCYTES</th>
<th>PER CENT POLYMORPHONUCLEARS</th>
<th>PER CENT LYMPHOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>14,000</td>
<td>10,800</td>
<td>2,250</td>
<td>77</td>
<td>16</td>
</tr>
<tr>
<td>2 weeks after</td>
<td>9,000</td>
<td>7,000</td>
<td>1,500</td>
<td>78</td>
<td>17</td>
</tr>
<tr>
<td>3 weeks after</td>
<td>9,500</td>
<td>6,650</td>
<td>2,350</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>4 weeks after</td>
<td>8,000</td>
<td>5,600</td>
<td>2,000</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>5 weeks after</td>
<td>6,500</td>
<td>4,200</td>
<td>1,800</td>
<td>65</td>
<td>28</td>
</tr>
<tr>
<td>6 weeks after</td>
<td>7,500</td>
<td>4,850</td>
<td>2,300</td>
<td>65</td>
<td>31</td>
</tr>
<tr>
<td>Last count 6½ weeks, 3 days before death</td>
<td>13,000¹</td>
<td>9,100¹</td>
<td>3,250¹</td>
<td>70¹</td>
<td>25¹</td>
</tr>
</tbody>
</table>

Case X. This chart shows a decrease in total white count from the initiation of treatment until a week before death, followed by a terminal rise. The lymphocytes show a primary drop in absolute count after the first two weeks but a steady rise in percentage count, reaching its maximum a week before death. Even after the terminal leuco'cytosis appears the lymphocytes maintain a high percentage, although most of the increase is in the polymorphonuclears.

Group 2

From such a mass of detailed observations it is hard to deduce any broad principle. For the sake of simplicity the remote results will again be divided into the early and late blood-changes. Early changes. These can be studied in cases V, VIII, IX, and X.
(1) There is first to be noted, as in group 1, a primary lymphocytic drop in all cases. This is usually both absolute and relative, although in one case (X) the relative figure shows almost no change. This case is atypical in other ways, as will be seen later.

(2) Three out of the four cases (V, IX, and X) also show a fall in the absolute polymorphonuclear count, though in only one case is the fall relatively as great as the fall of lymphocytes (case X). In one case (VIII) there is no fall in the absolute polymorphonuclear count. In other words the action on the lymphocytic system is more constant and profound than the action on the polymorphonuclears.

(3) All cases show some tendency on the part of the lymphocytes to attempt a recovery; case V at nineteen weeks, case VIII at four and six and one-half weeks, case IX at three months, and case X from three to six weeks.

(4) The time at which these changes take place is not constant. The lymphocytic fall occurs at from two to four weeks and may be maintained in some degree until the end of the second month. The attempt at recovery, however, may occur at any period thereafter, from three weeks to nineteen weeks.

Late changes. (1) Terminal leucocytosis. This was found to be present in five out of six cases. The sixth case (VIII) died while no longer under observation and no autopsy was performed. It did not seem probable at the time when she left the hospital that she would die for some months, whereas she actually died two and one-half weeks later. The possibility of some intercurrent condition must be considered here, and it must also be borne in mind that she may have developed a leucocytosis after leaving the hospital.

(2) The terminal leucocytosis is due primarily to an increase in polymorphonuclears, although there is often an absolute as well as relative decrease in lymphocytes at the same time.

(3) Almost all the cases showed a tendency towards relative increase of polymorphonuclears and relative decrease of lymphocytes before the terminal leucocytosis appeared.

(4) The one case which showed no leucocytosis upon dis-
charge (case VIII), that is to say two and one-half weeks before death, did show a great decrease in absolute and relative lymphocyte counts just prior to this date, a condition which has been shown to precede this terminal leucocytosis.

(5) One case (X) showed a steady relative increase in lymphocytes from two weeks until six and one-half weeks, three days before she died. This, however, was not accompanied by an absolute increase until the terminal leucocytosis appeared. In other words, the relative increase was really due to a decrease in polymorphonuclears, in which connection it is interesting to note that the smears showed myelocytes and nucleated red cells, in spite of falling white count, indicating an exhausted bone-marrow which was endeavoring to its utmost to compensate for its loss of normal function.

From a glance at these findings it will readily be seen that the essential effects of radium treatment are the same, whether it be given in conjunction with x-ray or not. Thus in both groups of cases the early depressing effect on the lymphocytes, and to a less marked degree on the polymorphonuclears, is found; in both groups, also, there is a tendency to lymphocytic regeneration after varying periods in those cases whose resistance has not altogether broken down. In both groups we find a change in relative counts toward the end, the polymorphonuclears increasing, the lymphocytes decreasing; and, finally, in both groups there is almost invariably a terminal leucocytosis, due primarily to absolute increase in polymorphonuclears, but usually accompanied by some decrease in absolute lymphocyte count. It seems reasonable, therefore, to disregard the scattered x-ray treatments as factors in determining the blood-changes here noted.

GENERAL SUMMARY AND CONCLUSIONS

1. The blood of ten cases of squamous-cell carcinoma of the cervix uteri and vagina has been studied, in order to ascertain the immediate and remote effects of radium and x-ray treatments upon the formed elements of the blood.

2. The immediate effects of radium on the blood are not
altered qualitatively by previous x-ray or radium treatments, although the quantitative action may be somewhat diminished during a second treatment.

3. The remote effects of radium on the blood are essentially similar to the effects of combined x-ray and radium treatment.

4. Individual slight differences in response to radium applications are often noted to occur again on a second application in the same individual.

5. The immediate effects of radium on the blood are the following:
   a. An immediate drop in total white count reaching its maximum from one-half to six hours after the application.
   b. A return of the total white count to its former level within twenty-four hours after the application, usually within the first twelve hours.
   c. An occasional secondary rise of the total white count to a point well above its original level from twelve hours to three days after the application.
   d. A close adherence of the total polymorphonuclear count to the curve of the total white count.
   e. An absence of characteristic changes in the total lymphocyte and total large mononuclear counts.
   f. A tendency of the total lymphocyte count to follow in some degree the fluctuations of the total white count, especially when these are marked. This effect is not constant.
   g. A tendency of the relative lymphocyte count to drop, and of the polymorphonuclears to rise during the course of treatment. This tendency is reversed during the period immediately following the removal of the radium.

6. Remote effects of radium treatment on the blood are as follows:
   a. Early.
      (1) Fall in lymphocyte count from two to four weeks after treatment, sometimes lasting till the end of the second month.
      (2) Fall in polymorphonuclears after treatment, sometimes simultaneous with the fall in lymphocytes but usually coming later and being less striking.
(3) An attempt of the lymphocytes to recuperate, as shown by a rise in most cases at some later date, varying from three to nineteen weeks after treatment, to the approximate level seen before treatment.

b. Late.

(1) Change in the relative counts as the patient’s resistance weakens, with increase in polymorphonuclears and decrease of lymphocytes, but without leucocytosis.

(2) Terminal leucocytosis, due in the main to increase of the absolute polymorphonuclear count, although usually accompanied by an absolute decrease in lymphocytes.

THEORETICAL CONSIDERATIONS

In conclusion, it may not be amiss to speculate briefly upon some points brought out in the above study.

1. In the first place, what do these figures show us to prove or disprove the theory that the lymphocyte is the essential factor in immunity or resistance to tumors? It seems fairly clear from the above that in the terminal stages of death from cancer there is a relative and often an absolute lymphopenia. It is, however, also true that this lymphopenia may not appear until a few days before death (case X); in fact, there may be a slight excess of lymphocytes as late as this. It would hardly seem reasonable, therefore, to assume that the lymphocyte is an infallible index of the patient’s state of resistance at any given period, seeing that the patient in question (case X) was just as surely moribund one week before death, when she had 31 per cent lymphocytes and a total lymphocyte count of 2300, as she was four days later when the percentage had dropped to 25. It would then be useless to attempt to estimate a patient’s resistance at any given time by referring to the absolute and relative lymphocyte count. On the other hand, if the blood has been systematically followed over a long period, it is possible to predict a fatal ending by the changing relative counts of lymphocytes and polymorphonuclears, the former decreasing, the latter increasing, though the practical value of this fact is very small, inasmuch
as the same conclusion may be reached at an earlier date by clinical observation.

2. Can these changes in the blood be used as a guide to the proper intervals and dosage of radium? This question can not be answered on the basis of the above figures, inasmuch as all the patients were so far advanced in the disease as to be beyond the hope of cure, at least with the small amount of radium which we had at our command.

Seeing, however, that the first sign of the final collapse is given by a fall in relative lymphocyte count, it does not seem unreasonable to suggest that no second radium treatment should be given until the lymphocyte count has recovered from the preliminary depression consequent to the first application. It would be interesting to know the behavior of the blood in patients treated under more favorable circumstances, that is to say, with larger doses and few applications.

3. Do these figures indicate anything of importance in regard to the mode of action of radium? It is certainly striking that the response of the hematopoietic organs to the application of so small an amount should be so immediate and yet so lasting. If we are to accept the theory that the beneficial effects of radium are dependent solely upon its local action, it must first be proved that these profound blood-changes are not incompatible with complete and lasting cure. In one instance we have known of a case which had been treated with heavy dosage of radium coming to autopsy without showing any demonstrable remains of carcinoma or any morbid process that could explain death. No studies of the blood or blood-forming organs were made. Is it not conceivable that in this case, although the carcinoma was locally cured, the patient was killed by the radium? The authors have been particularly interested in the close analogy between the immediate blood changes following radium treatment, as noted above, and those mentioned by Jobling (11) and Scully (12) as occurring after the intravenous injection of foreign protein in the treatment of arthritis and other conditions. Similar observations have been made by our colleague, Dr. B. F. Schreiner (13), following injections of
phylacogen. It is not impossible that the early blood-changes following radium application are due to the sudden introduction of protein substances, the products of cell destruction, into the blood stream, with the same effects on the blood-forming organs as are brought about by the intravenous injection of foreign protein. Even if this be the case, however, we are not justified in assuming that the therapeutic effect of radium is dependent on the formation of these products of abnormal cell destruction. It should be emphasized, in closing, that, while we have abundant evidence, both clinical and histological, that radium has a definite local action on malignant growths and that this action is detrimental to their development, there is also evidence of a more general effect whose nature we do not by any means understand. It is to be hoped that further blood-studies from the physicochemical as well as from the morphological standpoint will clear up this obscurity, and will enable us to explain some of the miraculous cures and unexpected disappointments which we encounter when employing radium as a therapeutic agent.

Finally, we wish to express our indebtedness to Dr. H. R. Gaylord, Director of the Institute, for valuable suggestions at the outset of the work, and to Miss Alice Thornton for her careful attention to the details of the routine counts and charts.

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PROTOCOLS OF PATIENTS WITH CHARTS ILLUSTRATING IMMEDIATE AND REMOTE EFFECTS OF RADIUM APPLICATIONS


Case VI. M. W. Widow. Age 56. Hemorrhages, June, 1916 and


lymph nodes, lungs, and liver; meningitis. Local lesion almost destroyed. (See chart 29.)

Days on which more than one count was made are designated by cross-lines with arrow-points at either end. The heavy vertical lines at either end of the cross-lines represent the beginning and end of the day in question. Except where marked by these cross-lines only one count was made on any given day. Days chosen for studying the immediate blood changes are marked thus: x.

1. Primary drop in lymphocytes, followed by temporary recovery, and final relative decline.
3. Terminal leucyptosis.
Chart 21

For explanation of vertical and cross-lines see under case 1.

1. Steady decline in total lymphocyte count.
2. Terminal leucocytosis, preceded by decrease in relative lymphocyte count and increase in relative polymorphonuclear count.
3. Typical immediate blood-changes following radium application, somewhat modified on second application.
For explanation of vertical and cross-lines see under case 1.
1. Typical early reaction, with immediate drop of white count, followed by secondary rise.
2. Primary drop in lymphocytes reaching lowest point at end of fifth week, followed by recovery.
3. Slight depression of polymorphonuclear series at end of sixth week.
1. Typical immediate drop in white cells after two successive radium applications, followed in both instances by a secondary rise. The reaction is slightly less pronounced on the second of the two applications.

2. Steady drop in total polymorphonuclear count until the beginning of the terminal leucocytosis.

3. Beginning terminal leucocytosis, preceded by drop in relative lymphocyte count and corresponding rise in relative polymorphonuclear count. (The chart was not continued long enough to show the full development of the terminal leucocytosis.)

4. Steady gradual drop in total lymphocytes, except for temporary stimulation at the time of the second
1. Atypical early change in white count: repeated on later application.
2. Decrease of all white cells, but especially of the lymphocytes, with rise of polymorphonuclear percentage.
3. Terminal leucocytosis and lymphopenia.
For explanation of vertical and cross-lines see under case 1.

1. Characteristic reaction in white cells immediately after radium application, less pronounced the second time than the first.

2. Tendency of total lymphocytes to fall from the time of the first application.

3. Irregular curve of total polymorphonuclears, with tendency to fall.

4. Marked terminal polymorphonuclear leucocytosis, with consequent drop in relative lymphocyte value.

5. Immediate drop in platelet and red cell counts, followed in the case of the red cells by a compensatory rise and later, by a second drop. The red cells show a terminal rise, corresponding to the rise in
For explanation of vertical and cross-lines see under case 1.
1. Characteristic primary drop in white count.
2. Change in percentage values of lymphocytes and polymorphonuclear cells during treatment.
3. Drop in red cell count, followed by marked rise.
1. Characteristic immediate drop in white count.
3. Preliminary slight drop in lymphocytes, followed by recovery.
4. Fall in lymphocytes just before discharge, both in total numbers and percentage value, indicating near approach of terminal leucocytosis. The patient left the hospital before any leucocytosis developed, but died less than three weeks later.

Chart 27

For explanation of vertical and cross-lines see under case I.
For explanation of vertical and cross-lines see under case 1.

1. Absence of secondary rise of white count after radium application. The usual primary drop is seen.
2. Tendency for slight decrease in total and percentage counts of lymphocytes.
3. Tendency to slight drop in total polymorphonuclear count, followed by terminal leucocytosis.
4. Immediate drop in platelets during radium application.
5. Drop in red count during early part of radium treatments, followed by an early secondary rise, and later by a second drop.
6. The red cells show a terminal rise, synchronous with the terminal leucocytosis.
1. Atypical immediate changes in white count: the same preliminary rise noted in subsequent treatment.

2. Steady drop in polymorphonuclears until just before the terminal leucocytosis appears.

3. Preliminary slight drop in total lymphocytes, corresponding to the drop in polymorphonuclears; this is followed by a steady rise until a few days before death. The rise in lymphocytes accounts for part of the slight terminal leucocytosis.

4. Rise of red count during each application, followed by return to a point below the former level.
For explanation of vertical and cross-lines see under case 1.

1. Absence of preliminary drop in white count during control period; marked drop during treatment.

2. Absence of secondary rise in white count during control period; marked rise on second day after radium application.