PATHOLOGICAL CHANGES ACCOMPANYING INJECTIONS OF AN ACTIVE DEPOSIT OF RADIUM EMANATION

I. INTRAVENOUS AND SUBCUTANEOUS INJECTIONS IN THE WHITE RAT

HALSEY J. BAGG

From the Huntington Fund for Cancer Research, Memorial Hospital, New York City

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Very little is known concerning the changes that occur in living tissue following the injection of solutions of an "active deposit" of radium emanation. This investigation was undertaken to determine what changes occur in the principal organs of the animal body following such a treatment, and to afford data that might act as a guide in the treatment of certain types of cancer, in which the solution method of radium therapy appeared particularly adapted. Since the main facts of this investigation became apparent, cases of leukemia and lymphosarcoma have been treated by the methods employed in these experiments. In these diseases the lesions were so widely disseminated as to suggest treatment by the method of intravenous radium injection.

The scope of the investigation may be divided into two parts, one dealing with experiments concerning intravenous, and the other with subcutaneous injections of the "active deposit" of radium emanation.

APPARATUS AND METHODS

At the Memorial Hospital the Duane type of radium emanation apparatus is used. It was devised by Doctor William Duane, and adequately described in The Boston Medical and Surgical Journal (1).
Instead of collecting the radium emanation by compressing it in small glass tubes, this being the usual method, the emanation for these experiments was collected in the form of what is called an "active deposit" upon common salt. A small quantity of salt was placed in the upper glass bulb, attached to a larger bulb as indicated in figure 1, and the bulbs were then sealed to the end of a radium emanation purifying apparatus. Then a considerable quantity of emanation, in the form of a gas, was forced into the bulb containing the salt. This was done by first creating a vacuum, and later forcing the purified emanation ahead of a column of mercury, until all the emanation was contained in the small bulb in which the salt had been placed. After about three hours the salt had received the maximum amount of radio-active deposit. The glass bulb was then cut from the apparatus, and the salt, containing the active deposit of radium, was dissolved in sufficient distilled water to bring the solution to the strength of a physiological salt solution. The liquid was drawn into a 2 cc. Luer syringe, which was covered by a lead shield as a protection for the fingers of the experimenter, and the syringe, needle, and solution were measured in an accurate electrometer. The activated solution exhibited all the known
phomena of radium metal itself. The strength of the solution was determined in millicurie units. In this manner a considerable quantity of active radium substance was obtained in a relatively small amount of liquid. For example, the usual amount collected was about 150 mc. in 2 cc. of solution.

This method of collecting radium deposit was found to be very economical. Only a little of the main supply of the hospital's emanation was actually used, since only a small part, 2 to 3 per cent, of the emanation had actually been given off as a deposit on the salt, and after the three hours exposure the remaining emanation was removed and collected in glass tubes for routine therapeutic use.

In the solution used in these experiments the radiation consisted of alpha, beta, and gamma rays, but the greatest physiological effects produced in the tissues were probably the result of alpha ray activity. (For a further consideration of the physical properties of radium emanation see references (2), (3) and (4).)

Following the well known physical phenomenon, the radioactivity, after reaching its maximum strength in three hours, decayed at a uniform rate, and so it was necessary to dissolve the salt, measure the syringe and needle, and inject the solution into the animals with as little loss of time as possible. However, in all cases a larger amount of radium was collected than was needed at one time, so that one might take advantage of the radium decay by waiting until the solution had reached a desired dosage before the injections were made. If preparations are made in advance for quickly injecting the solution, only a relatively small amount of the radio-activity is deposited upon the walls of the syringe and the needle. After the injection is made the empty syringe and needle are at once measured in an electrometer, so that the amount of radio-activity left in the apparatus may be determined. When this is subtracted from the previous figure, obtained for the syringe plus the solution, the amount of radium that was actually contained in the solution may be calculated. After a little experience it is possible to approximate very nearly a required dose. All the doses were given in millicurie units of "active deposit" of radium
emanation as described above, and if reference is later made to
the injected solution as, radio-active substance, activated solu-
tion, etc., be it understood that these terms are used inter-
changeably with "active deposit."

Only healthy, three-quarters to full grown, rats were used in
this investigation. They varied in weight from 200 to 250
grams. The injections were made under light ether anesthesia.
Caudal vein injections were made in the intravenous series,
while in the subcutaneous groups the solutions were deposited
under the skin in the right shoulder region.

Some of the animals were killed by the experimenter for his-
tological study. These animals were put under ether anesthesia
and the organs quickly removed and placed in fixative.

EXPERIMENTAL RESULTS

Series A. Intravenous injections

In this series twelve animals were used, and caudal injections
were given in doses ranging from 2.6 mc. to as high as 135 mc.
each.

Table 1 gives in the first two columns, the serial number for
each animal, and the dose employed in millicuries. In the third
column is indicated the time when the animals died, apparently
as a result of the treatment. The last column indicates the
day on which the animals that received the smaller doses were
killed by the experimenter for histological study. We find in
table 1, that doses ranging from the smallest, 2.6 mc., to 10.6
mc., were not sufficient to cause the death of the animals within
a month's time after the injection. From this group of animals
that survived the treatment for a considerable period, one was
killed on the thirty-fifth and another on the thirty-seventh day
after treatment. Two were killed on the forty-fourth and two
on the forty-fifth day, and finally one was killed on the seventy-
eighth day after treatment. The table indicates however, that
an increase from 10.6 mc. to 11.2 mc. proved fatal in the case
of animal VIII. This animal died within two and a half days
after treatment. Likewise, all the doses above 11.2 mc. resulted
in immediate, acute effects. Animal IX, after receiving an intravenous injection of 19.8 mc., was so ill at the end of four days that it would soon have died as a result of the treatment, had it not been killed by the experimenter in order that its organs might be preserved in the most favorable condition for histological study. Animal X received a dose of 27.8 mc., and died at the end of three days. In like manner animal XI, that received 29.6 mc., after showing very severe symptoms, died at the end of the third day. Animal XII, after receiving 135 mc.,

<table>
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<th>ANIMAL NUMBER</th>
<th>NUMBER OF MILLICURIES OF RADIUM EMANATION</th>
<th>DAY ON WHICH ANIMAL DIED AS A RESULT OF THE TREATMENT</th>
<th>THE DAY FOLLOWING THE TREATMENT ON WHICH THE ANIMAL WAS KILLED FOR AUTOPSY</th>
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*Was very ill at the end of the fourth day and was then killed.
† Died a few hours after the treatment, between 5 p.m. and 9 a.m.

the largest dose of radium that was used in any one instance, died a few hours after the injection.

The experimental data that follow give the histological reports for the twelve animals that received radium treatment by the intravenous method. The organs showing the greatest pathological changes were, the liver, the lungs, the kidneys, and the spleen. The bone marrow and adrenals were considerably altered in certain cases, and changes occurring in the vascular supply of the brain were noted. No data were obtained for the changes that occurred in the blood following the treatments as...
it was decided to test this point on a larger type of animal. This is now being done, and the results will be published at a later time.

The experiments are presented according to the size of the dose employed. From the standpoint of the general physiological reactions, animals I to VII inclusive may be said to show more or less chronic effects, while animals VIII to XII, that received the larger doses, exhibited decidedly acute reactions. Animal III, for example, was treated on June 10, 1918, with an injection of 4.3 mc., and was killed by the experimenter forty-five days later. This was one of the smaller doses, for, as may be seen in table 1, animal VII was treated with as large a dose as 10.6 mc. and still lived until it was killed forty-four days later. And yet the pathological findings for animal III showed an intense congestion of the liver, with severe acute degeneration of a fatty granular nature. The kidneys were also intensely congested and hemorrhages occurred in the glomeruli, cortex, and medulla. A condition of purulent bronchitis and broncho-pneumonia was found in the lungs, while the spleen was intensely congested and hemorrhagic, with reduction in size of the follicles.

It was found, that even with a still smaller dose, such as 2.6 mc., which was given to animal I, there was produced in the kidneys an intense acute congestion, edema of the lungs, and also reduction in size of the lymph follicles in the spleen. In the last two organs, however, the small dose of radium produced no hemorrhages, and it is well to note here that with larger doses congestion associated with hemorrhages occurred in these organs almost constantly.

Animal IV was treated with 5.7 mc. of radium, and, although the liver of this animal showed some congestion, still this condition was less marked than was found for the larger doses. There was but little congestion in the kidneys, and the lungs were in a fairly good condition. In this case the spleen appeared considerably affected. It was intensely congested, and this condition was almost as pronounced as that which occurred in the spleen of animals that had received very large doses.
With a somewhat larger dose of radium, 7.1 mc., animal V presented changes in the liver similar to those of animal IV; but in the case of animal V, the kidneys and lungs showed intense congestion, while in the spleen no appreciable congestion was found. In the case of animal VI, that received a somewhat larger dose, 8.8 mc., and was killed by the experimenter thirty-seven days after the treatment, the principal conditions noted in the organs were: a cloudy swelling of the liver cells, with advanced parenchymatous hepatitis; congestion of the kidneys, adrenals, spleen, and lungs, and also in the last named organ a perivascular edema.

The largest dose of radium that was survived for a considerable length of time, occurred in animal VII. This animal received 10.6 mc. and was killed, for purposes of autopsy, on the forty-fourth day. The liver was congested, but the condition in this case was not as marked as in the animals that received the still larger doses. The kidneys were in a state of severe granular degeneration, with intense congestion, while the swelling of the tufts of the glomeruli filled the capsules completely, but there was no cell necrosis. The lung lesion was an acute bronchitis, associated with areas of bronchopneumonia. The spleen showed intense hyperplasia of the lymph follicles, and some congestion.

As we go from animal VII to animal VIII, although the increase in dose was only 0.6 mc., we find in the latter case that the animal died two and a half days after its treatment. The dose in this case was 11.2 mc. and following it we find the occurrence of more active, acute conditions. The liver contained focal areas of necrosis, usually near the blood vessels and associated with hemorrhage. The kidneys were congested and hemorrhagic, and the lungs showed intense congestion, with hemorrhagic pneumonia. There was an edematous condition about the blood vessels and the bronchi. However, the spleen and also the brain, showed but relatively little congestion. Plate 1 shows the conditions that resulted in the kidney of this animal.

Following an injection of 19.8 mc. of radium, animal IX soon became very ill. It exhibited all the signs of an acute enteritis,
and it was killed by the experimenter on the fourth day after its treatment. The liver of this animal was intensely congested, and the kidneys showed hemorrhagic nephritis, with dilatation of the large blood vessels. The lungs in this case were also congested.

Animal X received an injection of 27.8 mc., and died as a result of the treatment three days later. As in the preceding case, the animal also exhibited severe symptoms of an intestinal disturbance. The histological data showed an intensely congested liver, especially of the capillaries. There was perivascular edema of the large blood vessels of the portal canals, and in some cases there appeared to be a beginning thrombosis and fibrinous deposit in the blood vessels. In the kidneys a severe, acute degeneration had taken place, which was associated with an intense congestion, involving to a marked extent, the glomeruli and the cortical tubules. The splenic follicles were prominent. The splenic pulp, the brain, and the lungs were intensely congested. In the lungs a partial destruction of the large veins was noted.

On January 10 animal XI received 29.6 mc. of radium. On January 12 it appeared fairly normal, but on the next day it became very ill and died during the following night. The kidneys were congested, and a granular degeneration was present in the cells of the tubules. In some places this degeneration almost amounted to necrosis. In the lungs there was extreme venous and capillary congestion. This marked congestion had also extended to the spleen. The sinuses of that organ were choked with large phagocytic cells and old blood pigment, indicating a considerable red blood cell destruction. The follicles in the spleen were reduced in size. The bone marrow of the sternum was extremely congested. Few marrow cells remained, and in some places there were none at all. The marrow spaces were occupied by a deposit of diffuse blood. The fat cells were indistinct, and many appeared to be broken up into globules of various sizes.

The largest dose of radium administered at one time was given to animal XII. This animal received an intravenous injection
of 135 mc. It died during the night of the same day, between 5 p.m. and 9 a.m. Unfortunately the liver and spleen were destroyed by its cage mates, but satisfactory sections were obtained from the kidneys, adrenals, lungs, and bone marrow. The kidneys showed diffuse congestion, and there was enormous congestion in the adrenals. In the lungs the alveoli were filled with red blood cells. There was a marked perivascular and peribronchial edema, and there were also evidences of an interstitial bronchitis, with a marked desquamation of the epithelial cells of the bronchi.

A recapitulation and discussion of these results will be deferred until the following data for the second series, series B, are given.

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<th>ANIMAL NUMBER</th>
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**SERIES B. SUBCUTANEOUS INJECTIONS**

In table 2 are given the results obtained from the series of subcutaneous injections. These injections were made under the skin in the right shoulder region. The method of arranging the data is the same as in the first table. Comparing the two sets of results we find them similar in regard to the lethal effects that were produced in the animals. Here it is seen that doses up to about 10 mc. are not fatal. In this series a subcutaneous injection of 17 mc. killed an animal in five days. It is possible that
the destructive effects produced from subcutaneous injections are less severe than in the case of the intravenous injections. The data suggest this conclusion, but are not sufficient to be conclusive. This point will be discussed later in the report.

Two animals received subcutaneous injections of 3.5 mc. each, and lived until they were killed by the experimenter sixty-four days after treatment. Another animal, that received 7.0 mc., was killed in the same manner on the sixty-fourth day. Two animals, each receiving 9.1 mc., were killed on the sixth and fourth day respectively. Two animals received doses of 17.0 mc. each, and they died, apparently as a result of the treatment, one on the fifth, and the other on the fourth day following the injections. Two more animals were injected and each received 19.0 mc. One died at the end of six days, the other was in a fairly good condition when killed by the experimenter. This animal, no. VIII of series B, was apparently exceptional in its resistance to the lethal effects of radium. Its organs suffered definite lesions, however, which will be described later. The tenth, and last animal of the series, was killed in five days by a dose of 20.5 mc. It exhibited symptoms of severe intestinal disturbance.

In the data that follow for the series of subcutaneous injections, it will be noted that, as in the case of the intravenous injections, the liver and kidney suffer largely as a result of exposure to radium emanation. However, probably due to the relatively slower rate of diffusion throughout the body in the case of the subcutaneous method, the lungs in this series are very much less affected. Only three out of ten animals that received subcutaneous injections gave definite lung lesions, while the lungs of the remaining seven animals were apparently normal. This condition held even after comparatively large doses.

It was also noted that the local reaction of the subcutaneous tissues in the region of the point of injection was slight. This is probably due to the fairly rapid manner in which the solution was diffused in the tissues of the shoulder region. In none of the cases was necrosis produced. In some of the early caudal vein injections, however, a small part of the radium was depos-
INJECTION OF AN ACTIVE DEPOSIT OF RADIUM EMANATION

ited outside the blood vessel, and in such cases a small necrotic area was produced at the point of injection. This condition resulted because the diffusion was slow, and the radio-activity was deposited locally.

Animals I and II received subcutaneous injections of radium amounting to 3.5 mc. each. They were killed by the experimenter sixty-four days after the treatment. The liver in both cases showed congestion and fatty degeneration, with the presence of many giant cells, and numerous hyperchromatic nuclei. In each case the lungs were normal, while the bone marrow and spleen of animal I showed no definite lesions, yet the kidneys of this animal were much congested. The renal tubules appeared normal, but there was hyperchromatism of the cells of the glomeruli. In animal II the renal tubules were dilated and filled with coagulum, while in the cells there was a granular degeneration. The bone marrow was congested, but otherwise was little altered, while the spleen was severely congested and contained prominent follicles.

A single subject, animal III, was injected with 7.0 mc., and was killed sixty-four days later. In this animal the liver showed the greatest changes, exhibiting a very marked fatty degeneration, with the nuclei of many cells much enlarged and hyperchromatic. The kidney was normal, but for a certain amount of capillary congestion. The lungs, bone marrow, and spleen were normal, except that the spleen was small, and in the bone marrow there was some dilatation of the sinuses.

Two animals, nos. IV and V, were each given a subcutaneous injection of 9.1 mc. of radium. The former was killed on the sixth day and the latter on the fourth day following. Animal V showed but slight degeneration of the liver, but there was a multiplication of the nuclei of the cells of that organ. The liver of animal IV, however, showed fatty degeneration and was severely congested. The kidneys in both animals were congested, but showed only a slight degeneration. The lungs of animal V were normal, while in animal IV, bronchopneumonia and catarrhal bronchitis were present, and in the latter animal there was congestion of the bone marrow, and but few foci of the marrow cells remained.
Animals VI and VII were each given subcutaneous injections amounting to 17.0 mc. One died four days later, and the other five. Before death each exhibited symptoms of severe intestinal disturbances. Unfortunately the histological data are lacking, and for this reason approximately the same doses were repeated for two other animals, nos. VIII and IX. These latter each received a dose of 19.0 mc. Animal IX died on the sixth day, but animal VIII proved particularly resistant and lived until it was killed on the seventh day. Although animal VIII lived for a week after its treatment, and was apparently in a fairly good condition before it died, still its organs proved to have suffered profound pathological changes. A severe granular and fatty degeneration occurred in the liver which was associated with much congestion, and the production of cells with large nuclei. In the kidneys there was congestion and granular degeneration, while the lungs contained a slight bronchopneumonia, with perivascular edema. There was not much congestion in the spleen, but an increase in size of the malpighian bodies was noted.

The following results were obtained for animal IX. Congestion and acute degeneration were present in the liver and kidneys, while in the lungs there was a marked bronchopneumonia. In the spleen great congestion had occurred, with damage to the splenic cells. The malpighian bodies were small, and the bone marrow was largely replaced by blood.

The largest subcutaneous injection was given to animal X. The animal received 20.5 mc., and died after five days. There was found in the liver a very severe congestion and degeneration of the hepatic cells, with the formation of many giant cells, with large nuclei, which were homogenous and hyperchromatic. The renal tubules were dilated, and a granular degeneration and erosion of the cells had taken place. The lungs were normal, but the bone marrow was replaced by blood, no marrow cells being retained. The conditions occurring in the liver of this animal are shown in plate 2.
SERIES C. CONTROL GROUP

A large series of sections was used as a control to these experiments. These sections were taken from normal untreated animals, killed in the same manner as the treated individuals, and also from animals injected intravenously and subcutaneously with salt not exposed to radium. A third control group was composed of animals injected with salt that had been exposed to a very large amount of radium emanation, and was then allowed to "decay," until the active deposit had lost its radio-activity. These animals came from the same stock that was used in series A and B, and were of about the same size, weight, etc., as the animals of the experimental groups.

The animals treated with ordinary salt, and those treated with salt that had been exposed to a large amount of radium emanation and then allowed to "decay," showed absolutely no symptoms of enteritis and appeared to be perfectly normal, as regards both their physical condition and the histological study of their organs.

DISCUSSION OF RESULTS

The results of this investigation show that injections of an active deposit of radium emanation, applied by the intravenous or the subcutaneous methods, bring about very definite changes in the animal body. It has also been found that sublethal doses, although they permit the animal to live for a fairly long time, result in pathological changes in the organs of a more or less chronic nature. It is noteworthy, in this regard, to refer to the changes that occur in the liver, especially those resulting from small doses of radium injected subcutaneously. Here we find a fatty degeneration, which, in the animals of this series, was very pronounced and frequent and was found to be present a long time after treatment. This condition was associated with the appearance of many giant cells and large nuclei, probably as a result of a regenerative process. It is interesting to note at this point that Mills (5) reported in 1910, a similar condition resulting from external applications of radium. He found that
by exposing a series of mice to gamma rays, and using for thirty minutes over the region of the liver, what amounted to about 25 mgm. of radium bromide, "a transient change in the liver cells, somewhat resembling a cloudy swelling," took place. In the present investigation, as previously stated, the changes in the tissues are probably due mainly to alpha ray activity, and so it would appear that the type of degeneration referred to above may result from one or from a combination of the three types of radiation given off by the radium.

Following comparatively large doses of radium the animals died in from a few hours to six days. The accompanying lesions were severe congestion, frequently associated with diffuse hemorrhages, in the liver, kidney, lung, spleen, and bone marrow. In the case of intravenous injections the lungs were found to be severely affected. The large doses of radium produced a proliferation and desquamation of the epithelial cells of the bronchi, and there was also an apparent rupture of the blood vessels themselves, so that the air spaces were filled with red blood cells. This condition was associated with marked edema about the blood vessels and the bronchi. A similar vascular response for the blood vessels of the skin, was observed by Thies (6), for, after exposing the skin of guinea-pigs for six hours to 20 mgm. of radium bromide, he noted a dilatation of the blood vessels, and the presence of capillary hemorrhages.

This investigation shows that in the kidneys the most frequent condition following, or accompanying congestion, was a granular degeneration and erosion of the renal cells.

The changes in the bone marrow resulted in its replacement by blood. In many cases it was found that following a radium injection no marrow cells remained. This observation confirms the work of Thies, obtained by irradiating white mice in toto.

Congestion of the spleen was found to be the most constant feature resulting from radium treatment. This was also found to be associated, in some cases, with hemorrhage and a destruction of red blood cells.

In certain cases, following fairly large doses of radium, the blood vessels of the brain were found to be intensely congested.
The small vessels were dilated and gorged with blood. This observation is in line with that of Danysz (7), who reported the presence of hemorrhages in the brain and spinal cord of mice exposed to radium.

It seems fairly evident from a comparison of the results of this investigation with those already obtained by other investigators, that the changes that occur in the animal tissues following an injection of a radio-active solution, either in the blood stream directly, or indirectly by the subcutaneous method, are apparently similar to the changes that follow the external application of radiations from radium bromide itself.

There have been some data accumulated concerning the elimination of radium after its injection in the animal body, and they are mentioned at this point as they probably have some bearing on the interpretation of the results of this study. To quote from Meyer (8), 1906-1907, who obtained his results by using solutions of radium bromide, "The liver, lungs, and kidneys appear to be among the first organs to show the presence of radium after its intravenous injection. The ultimate fate of radium introduced subcutaneously, intraperitoneally, or per os is not materially different from that of radium introduced intravenously."

Berg and Welker (9) reported, 1905-1906, that "after subcutaneous injections, radium (bromid), like barium, calcium, and similar elements, is eliminated per rectum. The intestine seems to be the main channel of radium excretion."

Salant and Meyer (10), 1907-1908, found that "the elimination of radium takes place chiefly through the liver, the kidneys and the small intestine, and to a lesser extent also, through the large intestine in some of the herbivora."

From some unpublished work of the present writer, it was found that if shortly following an intravenous injection of the "active deposit" of radium emanation, prepared as described in this article, the blood vessels of the large viscera were ligated, and the organs, plus the blood they contained, were then tested for their radio-activity, the liver showed the presence of the greatest amount of this activity. The activity found in the two kidneys together was about a third the amount found in the
liver. The stomach and intestinal tract contained slightly more radium than the kidneys, and the lungs slightly less than half the amount detected in the latter, while in the spleen there was a little less radium than was detected in the lungs. This work was performed on the rabbit, and will later be reported in more detail.¹

It would appear therefore that radium injected intravenously or subcutaneously, either in the form of a bromide, or as an "active deposit" solution, will, after a short time, reach all parts of the animal body. Attention is called to the observation of Salant and Meyer, that radium after a subcutaneous injection is eliminated by way of the kidneys, the liver, and the small intestine. In such a case the lungs were not called upon to eliminate the radium, at least not to the extent recorded for the other organs. This observation would tend to explain the results regarding the lung changes noted in the animals of the present investigation.

In series B there was much less lung damage following a subcutaneous injection, than was recorded for the lungs in series A, where intravenous injections were given. It would appear from the work of Meyer and the present writer, that when radium is placed directly in the blood stream of an animal the lungs of that animal are exposed to a considerable amount of radioactivity.

From a careful histological study of the results of these experiments, no data have been obtained showing that the nucleoplasm of the cell is more severely damaged, or damaged more quickly, than the cytoplasm. To be sure, atypical nuclei have often been noted, but these were associated with severe degenerative changes in the cytoplasm as well. The cytoplasm in the degenerating cells was clumped in granules, and it appeared that water had been taken in by the cell to a considerable extent. This condition might very well have resulted from a change in the permeability of the cell membrane, due to the destructive

¹ Since the above was written the author has found that in 1914 Dr. William Duane reported a similar experiment before the American Philosophical Society. His results gave a somewhat higher proportion of deposited activity in the spleen and liver.
action of the radium rays. It seems probable that following such a condition the cell metabolism would be interfered with, and the nucleoplastic changes that subsequently occur would be but secondary in character, or at least simultaneous but not primary.

SUMMARY AND CONCLUSIONS

1. Following injections of an "active deposit" of radium emanation there is a diffusion of the radio-active substance throughout the animal body, which results in pathological changes in the various organs.

2. Pathological changes occurring in the liver, lungs, kidneys, adrenals, spleen, bone marrow, brain, and vascular system were presented in detail. The most interesting changes were those that were found in the liver, and resulted from comparatively small doses of radium injected subcutaneously. A fatty degeneration, associated with many giant cells and hyperchromatic nuclei, was found in the liver for a comparatively long time after the treatment.

3. Following large doses of radium, congestion and hemorrhages were frequently found in practically all the organs and in the severe, acute cases the animals died after showing symptoms of marked enteritis.

4. The most frequent pathological condition that occurred in the kidney was a granular degeneration and erosion of the renal cells.

5. It was found that injections of radium resulted in the destruction of the cells of the bone marrow, and replacement by blood.

6. Congestion of the spleen was the most constant feature following radium treatment, and in some cases this was associated with hemorrhages, and the destruction of red blood cells.

7. The method of injection appears to determine, to a certain extent, the severity of reaction in certain organs. For example, following subcutaneous injections there was comparatively no pathological reaction, of an appreciable extent, in the lungs, but with intravenous doses, of about the same strength,
the lung lesions were severe, and consisted of proliferation and desquamation of the epithelial cells of the bronchi, marked edema, congestion, and hemorrhage.

8. It appears that doses of radium less than 10 mc. are sub-lethal for the animals of this investigation. Doses above this amount may kill within a few hours to a few days after treatment, the reaction being somewhat less severe if the subcutaneous rather than the intravenous method of injection is used.

9. A similarity was noted in tissue reaction between radium injected intravenously or subcutaneously, and radium applied externally.

10. The fate of radium, after its injection in the animal organism and its subsequent elimination, was discussed in some detail. The results of this investigation tend to show that the liver, gastrointestinal tract, kidneys, lungs, and spleen receive the greatest amount of radio-activity.

11. Degenerative changes in the cell, and their possible interpretation were also discussed. The histological study tends to show that cytoplasmic changes occurring in the cell are profound, and as severe as the changes in the nucleoplasm.

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REFERENCES

(7) Danysz: Compt. rend. Soc. de biol., 1903, cxxxvi, 461; ibid., 1903, cxxxvii, 1296.
Kidney of animal VIII, series A. Death occurred two and a half days after the intravenous injection of 11.2 mc. of radium. Note the congestion and hemorrhage. (For further reference see text.)
INJECTION OF AN ACTIVE DEPOSIT OF RADIIUM EMANATION

HALSEY J. BAGG

PLATE 1

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Liver of animal X, series B. The animal died five days after a subcutaneous injection of 20.5 mc. of radium. The central area shows a region of fairly normal liver cells, on either side there is severe congestion and degeneration with the presence of giant cells. (For further reference see text.)