THE BIOLOGICAL ACTION OF NEUTRON RAYS[1]

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NEUTRON rays have the remarkable property of being more readily absorbed in light substances rich in hydrogen such as biological tissues than in denser substances like iron or lead. If you should use a fluoroscope and look through the body with neutron rays, you would find that the bones would appear relatively transparent and the flesh would look darker. Neutron rays also are unique in the manner in which they produce ionization. X-rays produce ionization by liberating high speed electrons from atoms, while neutrons, being tiny dense particles of neutral matter, pass right through the electron clouds of atoms and ionize only by making intimate collisions with the correspondingly dense atomic nuclei.

The great difference in the mode of ionization by neutrons and x-rays can actually be photographed, thanks to the ingenious cloud chamber method of C. T. R. Wilson, which makes use of the fact that fog droplets form on ions in an atmosphere of supersaturated water vapor. Ionization in the Wilson cloud chamber thus can be seen in detail in the sense that each ion can be made to manifest itself as a visible fog droplet. Figure 1 is a cloud chamber photograph of the ionization in a chamber filled with a mixture of hydrogen, oxygen, nitrogen, and water vapor produced by a mixture of gamma rays and neutron rays from the cyclotron. You see some very thin lines of fog droplets. Indeed, you can see some of the individual droplets of these tenuous ionization tracks. These were produced by the high speed electrons liberated by the gamma rays which in passing through the chamber produced only a few ions per centimeter of path. This is the sort of ionization produced by x-rays.

The much thicker and much more dense ionization tracks were produced by neutrons. At one end of a dense track, a

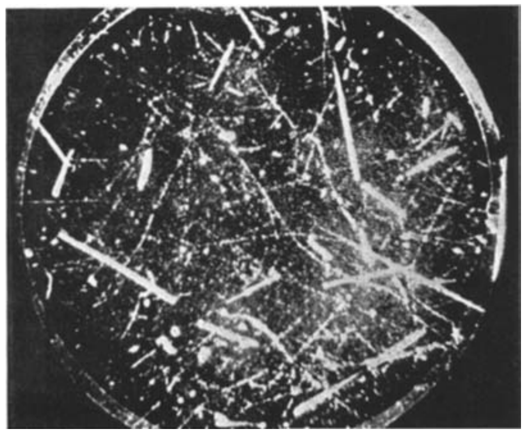


Fig. 1. Wilson cloud chamber photograph of ionization in a mixture of air, hydrogen, and water vapor produced by neutron rays and gamma rays from the cyclotron. The thin tracks of ions were produced by secondary electrons liberated by the gamma rays while the thick and very dense tracks were produced by the recoil protons resulting from collisions of neutrons with the hydrogen atomic nuclei. This picture gives a general impression of the great difference in the distribution of ionization in tissues produced by neutron rays and x-rays. In comparison to x-ray ionization, neutron ionization is very much more localized and intense.

neutron struck a hydrogen atomic nucleus, a proton, and the proton recoiled with tremendous energy. The recoil proton, being a heavy charged particle, rapidly dissipated its energy by producing very intense ionization over a short distance—before coming to rest and picking up an electron, thus becoming an ordinary hydrogen atom again. The heavy fog tracks in the cloud chamber several inches long were produced by recoil protons having energies of more than a million volts. Electrons of such energies would make ionizing tracks a hundred times longer. The ionization produced by a recoil proton is something like one hundred times more dense than that produced by an x-ray secondary electron, and so we see that neutron ionization, in comparison

[1] Read before the Radiological Society of North America at the Twenty-second Annual Meeting, in Cincinnati, Nov. 30–Dec. 4, 1936.

with x-ray ionization is very much more localized and very much more intense where it occurs.

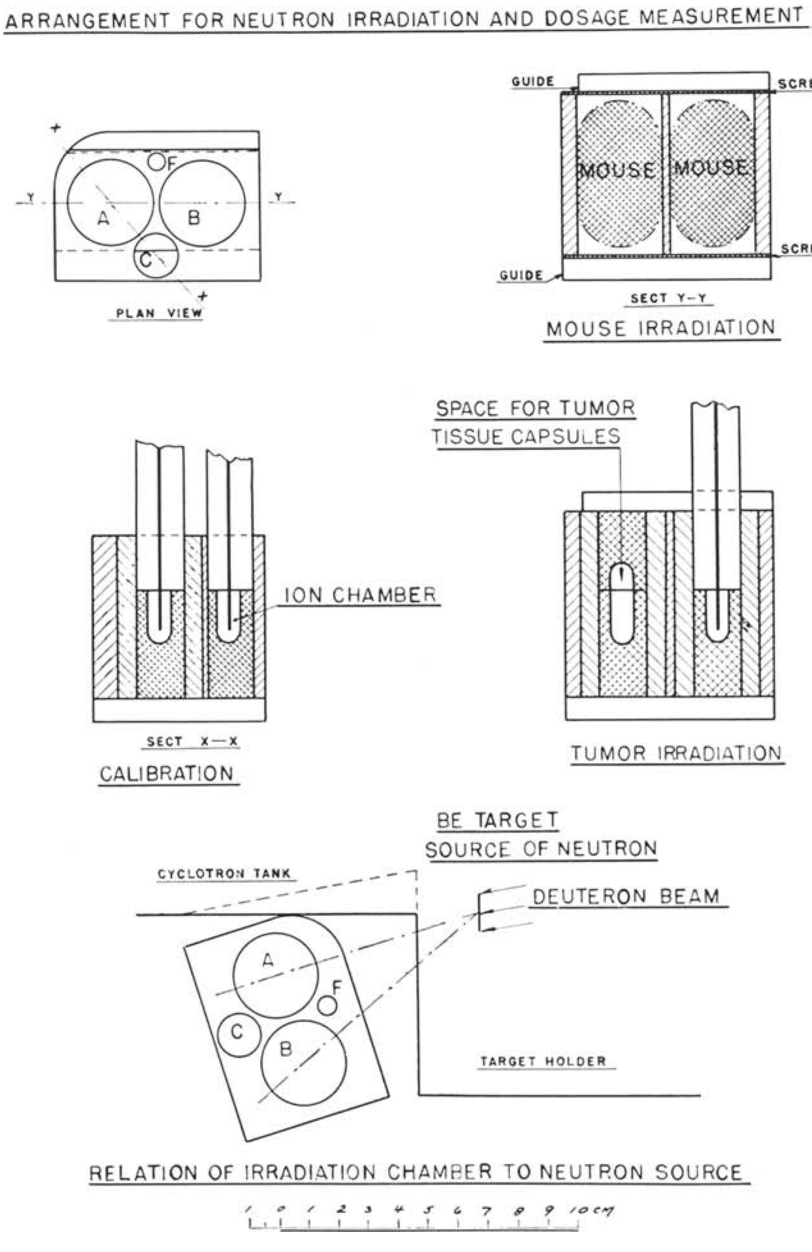
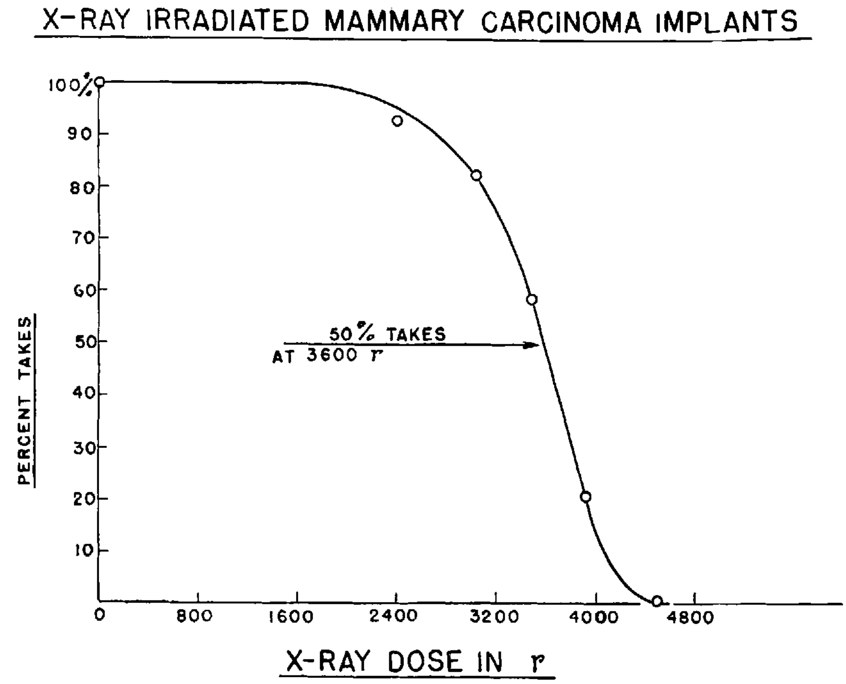


Fig. 2.

In view of this great difference in the physical behavior of neutrons and x-rays, one is led to wonder whether the two forms of radiation are also very different in their biological action.

The questions here involved are of both theoretical and practical interest. According to some theories of the biological processes induced by ionization it is the total amount of ionization and not the distribution in a biological system that is of importance, a point of view which would indicate that neutron rays would parallel x-rays completely in their biological action. Observations of differences in biological effects produced by the two radiations would therefore contribute significantly to our understanding of biological effects due to ionization. With this in mind as well as the possibility that neutron rays might have valuable practical applications, some experiments in our laboratory on the comparative biological effects of neutrons and x-rays have recently been carried out. Perhaps I should remark here that these experiments were originally undertaken for the immediate practical purpose of obtaining information for the protection of workers in our labo-



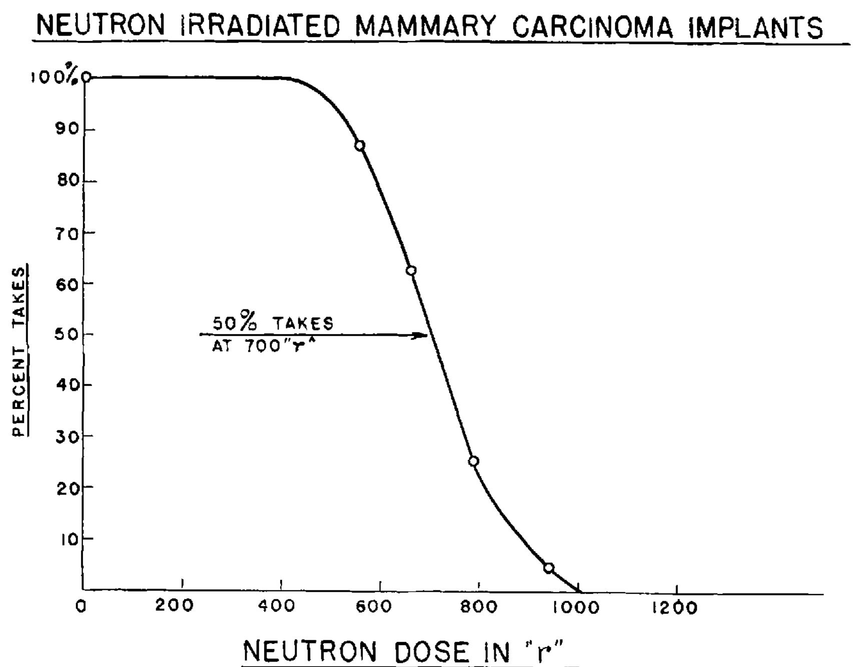


Fig. 3 (*upper*). Fig. 4 (*lower*).

ratory. We did not want to repeat the unfortunate experiences of many of the early roentgenologists. It was fortunate that my brother, Dr. John H. Lawrence of the Yale University School of Medicine, was visiting me the summer before last and took the occasion to look into this vital question.

First of all he placed some rats near the source of neutrons and found immediately that the neutron rays are indeed very lethal and that they kill a rat by a few minutes' exposure. When I say kill, I mean that the rats died in about two or three days' time after exposure. In these first experiments, studies of the effects of both x-rays and neutrons on the blood counts of rats were made, which also indicated that for the same total amount of ionization in tissue of the animals, the neutrons were more effective than x-rays. That summer Dr. R. E. Zirkle, of the Johnson Foundation of Medical Physics of the University of Pennsylvania, also spent a period of time in our laboratory and studied the comparative effects of neutron rays and x-rays on the growth of wheat seedlings, with results likewise indicating a greater biological effect per unit of ionization for the neutron rays.

COMPARISON OF LETHAL POWER OF NEUTRONS AND X-RAYS
WHOLE BODY IRRADIATION OF NORMAL MICE

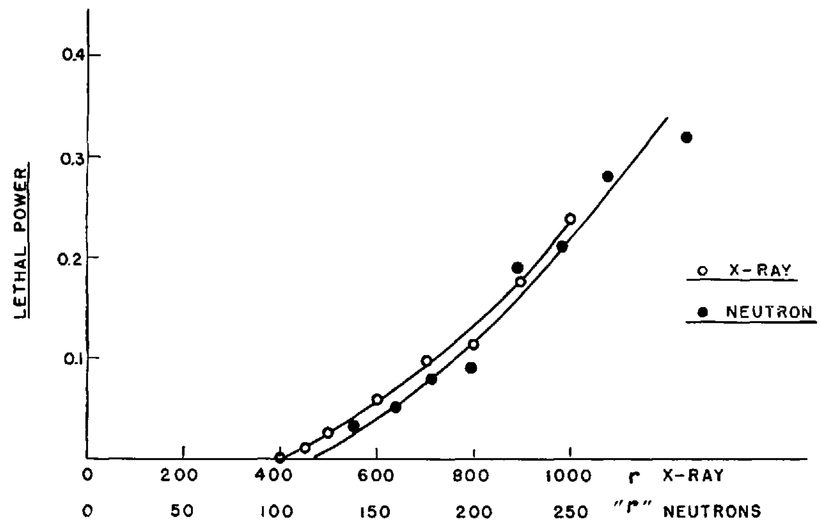


Fig. 5.

These early experiments have been published[2] and I have not time to go into them here, excepting to say that they more than gave us information as a basis for providing protection for us in the laboratory, for they gave indications that neutron rays have different selective actions on biological substances when compared with x-rays. In comparison with the action of x-rays, the neutrons seemed to be relatively more effective on the wheat seedlings than on the blood counts of the rats. Because, as I have already indicated, this possibility of a different selective action by neutrons is of much theoretical interest, and also because it has its immediate practical implications—for, as you all know, an important factor in radiation therapy is the selective action of radiation on tissues—my colleagues have

[2] Zirkle, R. E., and Aebersold, P. C.: Relative Effectiveness of X-rays and Fast Neutrons in Retarding Growth. Nat. Acad. Sci., February, 1936, **22,** 1934–1938.

Lawrence, J. H., and Lawrence, E. O.: The Biological Action of Neutron Rays. Proc. Nat. Acad. Sci., February, 1936, **22,** 124–133.

been impelled to continue with the experimental investigations. I should like now to give you a brief account of some of the

NEUTRONS & X-RAYS ON 5 OBJECTS

		RATIO	
MAMMARY CARCINOMA	X-RAY 3600 r / NEUTRON 700 r	5.1	
NORMAL MICE [LETHAL POWER]		3.8	
DROSOPHILA EGGS	X-RAY 180 r / NEUTRON 87 r	2.1	[ZIRKLE & AEBERSOLD]
WHEAT SEEDLINGS	X-RAY 600 r / NEUTRON 120 r	5.	"
FERN SPORES	X-RAY 52,000 r / NEUTRON 21,000 r	2.5	"

Fig. 6. Summary of comparative effects of x-rays and neutron rays on five biological objects, showing that the ratio of the doses of the two forms of radiation required to produce the same biological action in the several instances varies from 2.1 to 5.1. These results show that neutrons have a selective action on biological substances which in general is different from that of x-rays.

recent results. My associates will doubtless publish a more detailed report of their work elsewhere.

It was, first of all, of interest to determine as definitely as possible whether or not neutrons do have a different selective action on biological substances when compared with x-rays, and for this purpose Dr. R. E. Zirkle, Mr. P. C. Aebersold, and Mr. E. R. Dempster chose to study three biological effects, namely, the killing effects of the radiations on *Drosophila* eggs, the growth inhibiting effect on wheat seedlings, and the inhibiting effects on the fern spore, *Pteris longifolia.* These biological objects, being small, were admirably suited for the work, because it was possible to irradiate large numbers of individuals in a comparatively small volume so that statistical fluctuations could be made small and the objects could be placed rather close to the neutron source without producing serious errors due to the inverse square law, *i.e.*, the variation of intensity of radiation over the biological objects.

The several biological materials were placed in small capsules in a hole in a wooden block, the hole having a diameter about one centimeter, at a distance of about seven centimeters from the beryllium target of the cyclotron, which is the source of the neutrons. The dosage of neutrons was measured by a Victoreen condenser r meter (which may be called the dosage indicator) inserted in an adjacent hole in the wooden block. The dosage indicator of course was readily calibrated in terms of the radiation intensity in the hole containing the biological specimens. Time does not permit going into a discussion of neutron dosage measurement here, although we have carried out some experiments which indicate that the neutron dosage measurements obtained with the Victoreen meter are approximate indications of the ionization in ordinary biological tissues. The question of absolute ionization in tissue in relation to the dosage measurements is here not essential, as we are interested at this time only in dosage ratios and can regard the dosage measurements as in arbitrary units.

Dr. Zirkle, Mr. Dempster, and Mr. Aebersold found that about 87 r of neutrons kills about one half of the flies' eggs, while for x-rays they found that it takes about 190 r to produce the same effect—in line with the well established values of Packard and many others. In other words, it was found that, in terms of the Victoreen measurements, the neutrons are about twice as effective as x-rays. In the case of the fern spore, Dr. Zirkle and Mr. Aebersold found that the neutrons are about 2.5 times as effective as x-rays. Thirdly, they found that, in inhibiting the growth of wheat seedlings, the neutrons are about five times as effective as the x-rays.

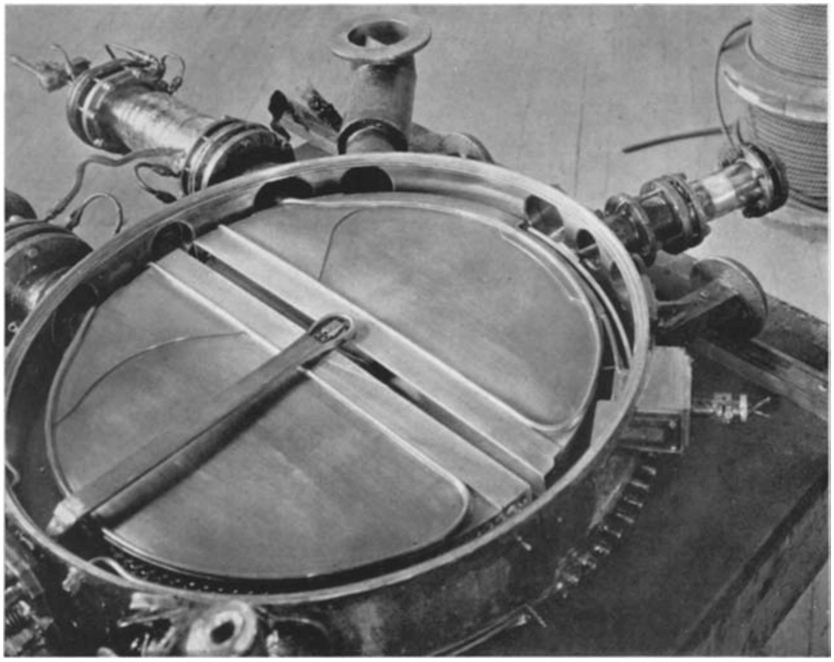


Fig. 7. View of cyclotron vacuum chamber with cover plate removed.

I think we can say that these experiments established quite definitely that neutron rays and x-rays do not parallel each other in their biological action. The selective action of neutron rays on tissue is in general different from that of x-rays.

This result immediately raises the very important question of the action of neutron rays on tumor tissue—whether the neutrons have a greater selective action than x-rays. The first experiments on this question were carried out by Dr. John Lawrence on the experimental mouse tumor, Sarcoma 180, which was very kindly supplied by Dr. Francis Carter Wood. An account of these experiments has been published,[3] and I need only mention here that they did give indications that neutron rays do have on this tumor a greater selective action than x-rays in the ratio of about 4 to 3.

Recently Dr. Lawrence and Mr. Aebersold have studied[4] the comparative effect of the two radiations on another mouse tumor, a mammary carcinoma, obtained from Dr. Strong, of Yale. This mammary carcinoma, like the Sarcoma 180, is an easily transplantable tumor so that it could be dissected from one animal, cut up into small tumor particles, exposed to the radiations *in vitro*, and then injected into many animals, following which the ultimate growth of the tumors in the animals could be observed at various times up to several months. The tumor particles were wrapped in filter papers, moistened with suitable physiological solu-

[3] Lawrence, John H., Aebersold, P. C., and Lawrence, E. O.: Comparative Effects of X-rays and Neutrons on Normal and Tumor Tissue. Proc. Nat. Acad. Sci., September, 1936, **22**, 543–557.

[4] These biological investigations were aided by a grant from the Josiah Macy, Jr., Foundation.

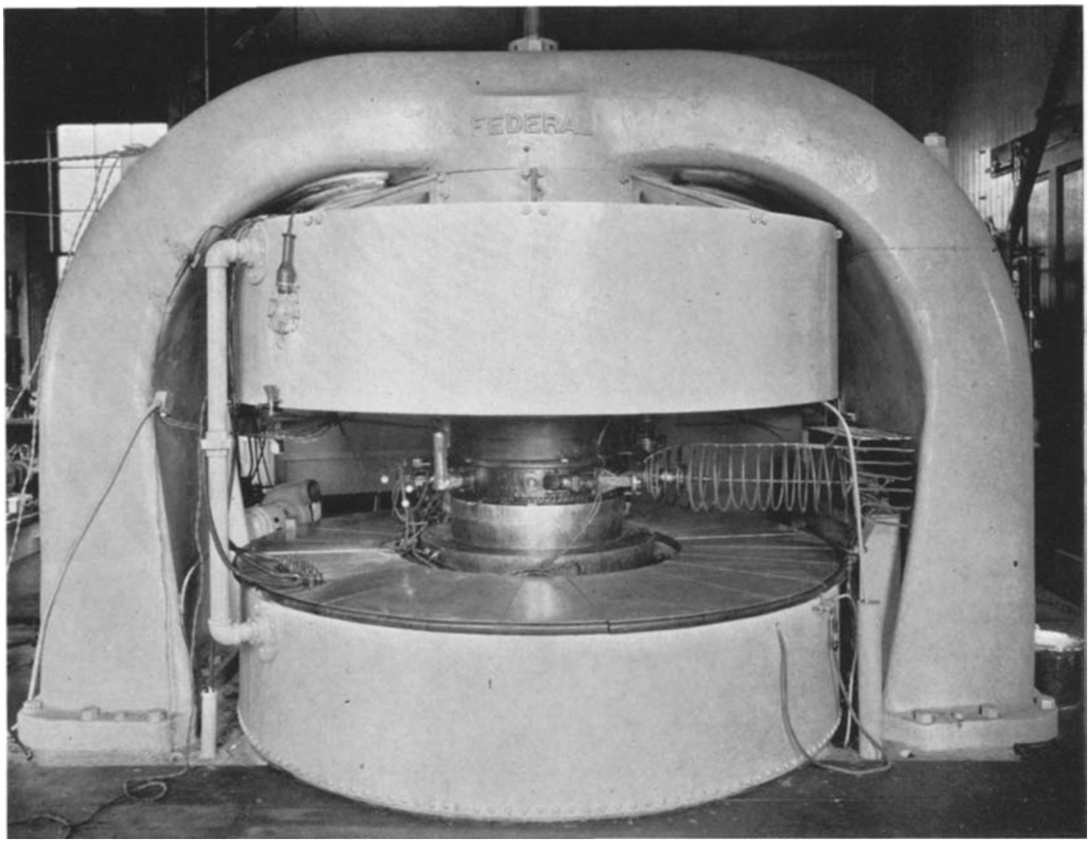


Fig. 8. General view of the cyclotron.

tions, and then placed in a capsule in a hole in a wooden plug block which had dimensions about equal to those of a mouse. The reason for placing the capsule in the plug of wood was to insure that the tumor particles were exposed to about the same quality of radiation as would be produced on the interior of a mouse exposed to the radiation at the place occupied by the wooden plug. As I shall bring out more clearly later, mice were also exposed to the neutrons, for it was the purpose of the experiment to compare the effect on the tumors and on the mouse as a whole. The plug of wood, as shown in Figure 2, fitted into a suitable hole in a larger wooden block. This abundance of wood surrounding the biological objects tended to produce a homogeneity of radiation over the irradiated substances.

Figures 3 and 4 show the results of the observations both with neutrons and with x-rays. More than a thousand tumor particles were exposed to the radiations so that statistical fluctuations were small and the results quite definite. We see that an x-ray dose of about 4,500 r was required to kill all of the tumors, while 50 per cent were prevented from growing in the mice by an exposure to 3,600 r. Now turning to the neutron experiments, we see that similar curves are obtained, shown in Figure 4. Here we see that about 1,000 r kills them all and that the 50 per cent point comes at 700 r, so dividing 3,600 by 700, we see that the neutrons are about 5.1 times more lethal.

Now, of course, from the standpoint of the possibility of radiation therapy the fact that neutrons are five times more lethal on tumors than x-rays in itself is not of particular significance, for it is the selective effect, the relative effect on the tumor in relation to the surrounding healthy

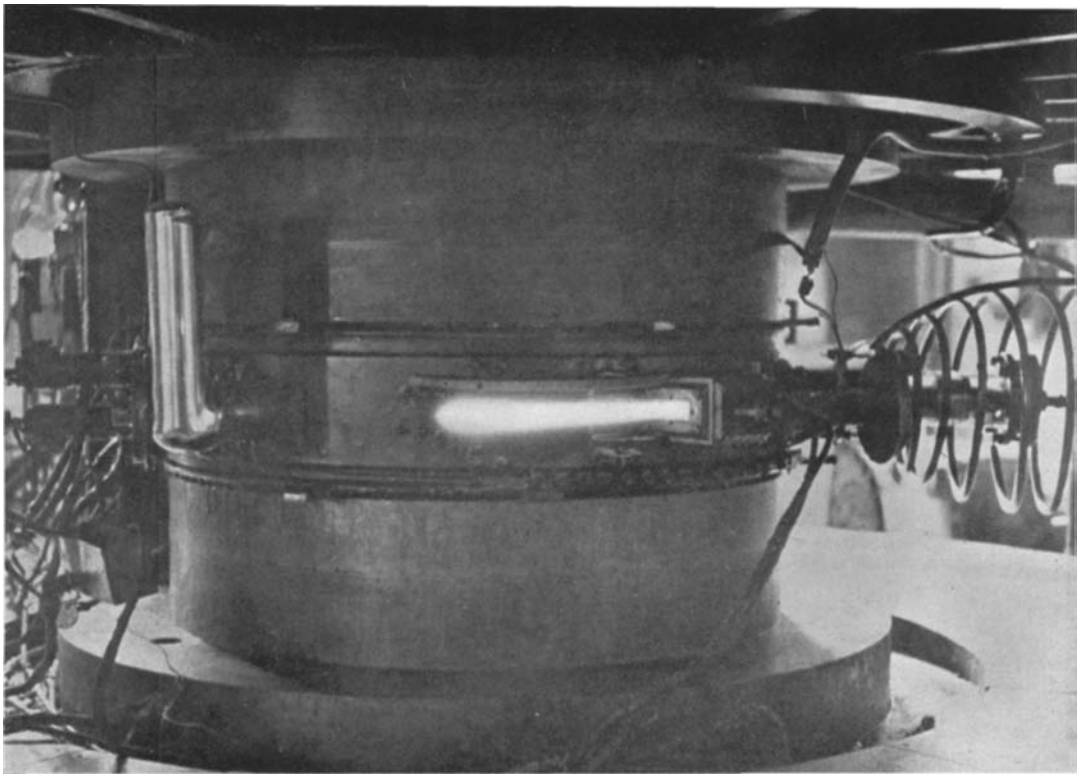


Fig. 9. Photograph of beam of 5.8 million volt deuterons emerging into the air through a platinum window in the wall of the cyclotron chamber.

tissue, that is of importance. In order to get one measure of the comparative effect of neutrons on healthy tissue, mice as a whole were exposed to both neutrons and x-rays and the lethal effects observed. Hundreds of mice were exposed to various doses of both forms of radiation and the effects on the subsequent lives of the animals were observed for several months. As a convenient indication of the lethal effect on the healthy mice we adopted as a measure what might be called the "lethal power" of the radiation, which is the reciprocal of the number of days the animal lives after exposure to radiation. Thus, if the animal lives a very long time, the reciprocal of the number of days is a very small number, and accordingly the lethal power is very small. If the animal lives a short time, for example, two days, the lethal power is one-half, which is on this scale a large lethal power. The average lethal powers for the large number of animals exposed at various doses is shown in Figure 5. Here we see that nice smooth curves are obtained and the curves are nearly superposable with the abscissa of the dosage scale for the x-rays four times larger than that for the neutrons. The 120 r of neutrons just produced a perceptible killing effect on the healthy mice, while it takes about 400 r of x-rays to do the same thing. In other words, for a detectable lethal effect, the neutrons are about 3.3 times as effective as the x-rays, while for larger lethal powers the ratio approaches 4 and we may take 3.8 as an average ratio.

Results of all these experiments are summarized in Figure 6. For the small biological objects that have been recently studied, for which the dosage measurements are of greatest precision, it is found that the ratio of the biological effectiveness of x-rays and neutrons varies all the way from 2.1 for the flies' eggs to 5.1 for the mammary carcinoma. We could express these ratios the other way around.

For example, in therapy one is interested in the effect on the tumor relative to the effect on the host, the mouse in these experiments. The ratio of the 50 per cent tumor dose to the perceptible killing mouse dosage for x-rays is 3,600 divided by 400, a ratio which is 9. In other words, the mouse can tolerate over its whole body only one-ninth the dose of x-rays required to kill 50 per cent of the tumor particles *in vitro*. With neutrons the ratio is 700 divided by 120, that is, 5.8. Instead of only one-ninth the tumor dose, the mouse can stand about one-sixth of the 50 per cent tumor killing dose and so we see that the experiments indicate that a more effective dose on the tumor using neutrons can be given without killing the mouse.

If these indications of a greater selective action of the neutron rays on tumor tissue prove to be true for carcinomas *in vivo*, it is a very important matter. My colleagues, Dr. John Lawrence and Mr. Aebersold, as well as myself, regard these observed ratios as preliminary and we are still looking for possible systematic errors in the experiments. We have, however, all along looked very carefully, and as far as I can see, these results are approximately right.

Now in the remaining time I should like to show slides of the apparatus that has been used in these experiments, with a few comments, because you will possibly be interested in whether or not the practical clinical implications of the results here presented are really of more than laboratory and scientific interest; whether it is really a practical matter to use neutron rays in medical therapy as you use your x-ray machines.

Instead of bombarding a target of a heavy metal with high speed electrons, as is done in the production of x-rays, neutron rays are produced by bombarding a target of a light metal, notably beryllium, with very energetic deuterons, the nuclei or ions of heavy hydrogen. In order to produce sufficient intensity of the neutron radiation from the beryllium target for the purposes of biological work, it is necessary to bombard the target with deuterons of several million volts of energy, because the production of neutron rays increases rapidly with voltage. In our laboratory the deuterons are accelerated to these high speeds by causing them to spiral around between the poles of a large electro-magnet under the combined action of the magnetic field of the magnet and a high frequency oscillating electric field. I need not go into the details of the apparatus called the cyclotron, which does this, excepting to say that the ions are accelerated in a drumlike vacuum chamber spiralling around inside the semicircular hollow electrodes and finally emerging at the periphery of the chamber, where they are caused to strike the beryllium target. A general view of this vacuum chamber is shown in Figure 7 and the chamber between the poles of the large electro-magnet is shown in Figure 8.

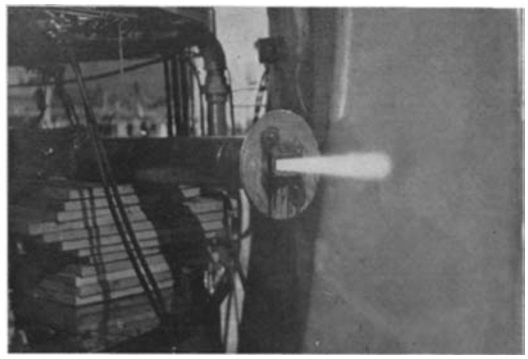


Fig. 10. Here the energetic beam of atomic projectiles (5.8 million volt deuterons) emerges 6 feet from the chamber wall at the end of an attached vacuum tube.

In the present experiments, bombarding currents of about 20 micro-amperes of 5.5 million volt deuterons were used. The biological objects were placed in the wooden receptacle adjacent to the wall of the vacuum chamber (which, however, cannot be seen in this photograph).

I should like to insert here another slide (Fig. 9) showing the beam of energetic deuterons emerging from the vacuum chamber through a thin platinum window into the air. The atomic ions pass through the air for a distance of about ten inches before losing their energy; and in addition to producing nuclear effects, including neutron rays, they produce x-rays and gamma rays and visible radiation. The beam has a lavender color to the eye and is photographed in a few seconds.

For some purposes it is desirable to direct the beam of deuterons at a target considerably away from the main vacuum chamber and this can be done by attaching a suitable vacuum tube. Figure 10 shows the beam emerging into the air through the platinum window at the end of a brass tube extending six feet out from the cyclotron chamber. Of course, the beryllium target could be placed at the end of this tube, an arrangement that would be obviously convenient for medical purposes.

The magnet shown in the previous slide is much larger than needed for the acceleration of the ions to speeds thus far used. We intend to draw more fully on the power of the magnet soon now and will produce much larger currents of deuterons at high voltages. At the present time the neutron intensities are a bit weak for extensive medical experiments, but with the enlarged apparatus it is probable that the neutron emission from the beryllium target will be effectively equal in biological action to the usual yield of x-rays from a deep therapy x-ray machine.

We have done some experiments on collimating neutron rays, and find that there are no great difficulties in the way of producing a beam of neutrons suitable for purposes of medical therapy. Instead of using port holes in lead it is necessary to use channels through tanks of water or paraffin or any absorbing substance rich in hydrogen.

The view of the cyclotron which I have shown in the illustrations perhaps gives you the impression that the apparatus is extremely large and costly but it is not so bad as it seems at first sight. At the present time I am of the opinion that a cyclotron can be engineered and developed in a way that will make it entirely practical for the purposes of medicine.

Finally, may I say that these experiments encourage us in the view that the recent discoveries of nuclear physics, notably the neutron rays and the artificial radio-active substances have extremely important bearing on the medical sciences, and so I am glad that through the active interest and generous support of the Chemical Foundation we are now building a new cyclotron designed primarily for medical research and therapy. In another year or so it will be in operation and I do hope that some day I may have the pleasure of coming back here and reporting to you further progress in this new field of radiology.