A COMPARATIVE STUDY OF NEUTRON- AND X-RADIATION UPON BIOLOGICAL TISSUES IN THE CANCER PROBLEM

ISADORE LAMPE, M. D.,
University Hospital, University of Michigan

The changes observed in irradiated biological tissues are believed today to be due basically to the ionization of tissue atoms. To the biologist and the radiation therapist, modern physics has presented many new ionizing sources in the form of artificially induced radioactivity in elements normally stable. All of these are of potential value in the field of cancer therapy.

At the present time interest is centered on the potential utility of fast neutrons in the treatment of cancer. More extensive investigations on normal and abnormal biological tissues have been carried out with fast neutrons than with any of the other products of research in the field of nuclear physics. Although the results of these studies are of interest to biologists in diverse fields, to those engaged in the treatment of cancer, there exists one primary question. Will neutron radiation be more effective than X-rays in the treatment of cancerous diseases of the human organism?

In studying the biological effects of neutrons, many investigations previously performed with X-rays have been repeated with neutrons. The results of these studies reveal the essential qualitative similarity of tissue reactions to neutrons and x-rays. Several workers have shown that neutron irradiation increases the rate of mutation formation in fruit-flies (*Drosophila melanogaster*) (1, 2); geneticists have employed x-rays for this purpose for many years. Certain phases of the process of mitosis (which determines cell division and therefore tissue growth) can be suppressed both by neutron and x-ray irradiation (3, 4).

The embryological development of Drosophila eggs is disturbed in the same fashion by x-rays and neutrons. The larvae surviving both types of irradiation demonstrate aberrations of organ development(5). Both radiations suppress the growth of wheat seedlings and inhibit cell division of the fern spore.

Experiments carried out on mammalian tissues demonstrate that identical changes are produced by both radiations. Whole body irradiation of mice with neutrons and x-rays produces death of the animals; the blood-forming tissues, the lymphoid tissues and organs, as well as the lining cells of the intestines are damaged or destroyed (6). The characteristic changes seen in the blood cell picture of animals irradiated with x-rays is found with neutron irradiation. Experiments with transplantable mouse cancers have shown that suppression of the growth of the tumor transplants is brought about by both radiations (7).

More recently with the development of collimated neutron beams, the reaction of skin to neutrons has been observed in rabbits and in man. The changes appear to duplicate those following x-ray irradiation.

Thus the effects of neutrons have been observed in a variety of biological processes: mutation production, suppression of mitosis, inhibition and impairment of embryological development, suppression of cell division and of growth of tissues; the destructive action of this radiation on mammalian tissues has been demonstrated. In each instance it seems that, in kind, the changes are of the type seen following x-ray irradiation.

Certain quantitative aspects of neutron ionization merit consideration. Early in their work Lawrence and his associates found it convenient to measure neutron ionization with the same small ionization chamber as is used currently to measure x-ray ionization (8). The work of Gray on the measurement of gamma ray energy indicates that under certain conditions the use of such chambers for measurement of neutron ionization is valid (9). When used with x-rays, the scale units represent roentgens, the international unit of ionization quantity; when used with neutrons, the same unit deflection has been arbitrarily termed the n-unit.

The relationship of the quantities of ionization in tissue that the two units represent has not been definitely determined as yet; this is a matter of considerable importance. By irradiating fern spores with alpha particles Zirkle demonstrated that the biological effectiveness of the radiation was greatly influenced by the ion concentration along the path of the ionizing particle; the biological effectiveness varied approximately as the 5/2 power of the ion concentration (10). In view of the greater concentration of ions along the tracks of protons and other recoil particles produced by neutron irradiation, a greater biological effectiveness was to be expected for neutrons than for x-rays.

A number of comparisons on various biological test objects have been carried out by Lawrence and his associates (7, 11) and also at the University of Michigan (12); it was found that in apparently every instance neutrons were more effective than x-rays in producing equivalent biological reactions. The differences in efficiency ranged from a factor of 2 in inhibiting hatching of Drosophila eggs to a factor of almost 12 in suppressing organ growth in wheat seedlings.

Although these figures cannot be accepted at face value until the relationship between the two units of ionization has been clearly established, there is indirect evidence to indicate that the greatest possible error probably does not exceed forty per cent (12).

In an interesting report, Zimmer and Timofeeff-Ressovsky have shown that neutrons are less effective than x-rays in affecting the mutation rate of Drosophila (1), and have demonstrated that, since mutation production depends on the formation of one ion pair in a gene, a decrease in effectiveness should be obtained with the type of distribution of ions created by neutron irradiation. For those biological reactions which require the formation of multiple ion pairs in the so-called "sensitive" volume, the distribution of neutron ionization should be more effective than that obtained with x-rays.

It appears then that in neutrons we possess not only a radiation which produces changes similar to those seen with x-ray irradiation but a radiation which is apparently of greater effectiveness in exciting reactions of the kind we are concerned with in the treatment of cancer.

This radiation probably will be more lethal than x-ray in its action on the cancer cell but does this mean that it will be more effective in treating cancer in the human body?

In order to be effectively employed, a radiation must act in a selective fashion: the tumor must be destroyed but the regional normal structures must be preserved. It is because of the existence of such a favorable differential action on cancerous and normal tissues that x-rays and gamma rays have attained a measure of success in the treatment of malignant neoplastic diseases. Other factors being equal, neutron radiation will be more effective in the attack on cancer in the human organism if its differential action is found to be more favorable than that of x-rays. The absolute biological effectiveness is only of secondary importance.

Because collimated neutron beams were not available until recently, it was necessary to approach the problem of the differential or relative actions of x-rays and neutrons in an indirect manner. From a broad biological viewpoint a cancer and its regional normal tissues represent related tissues in the same organism and the basic problem devolves to a consideration of the comparative action of neutrons and x-rays upon two such tissues.

In the first investigations by Lawrence and his associates, a number of different types of biological test objects were used: Drosophila eggs, fern spores, transplantable mouse tumors, mice, and wheat seedlings (7, 11). It was found that the relative effects of the two radiations upon these organisms presented decisive differences. Had these experiments indicated that the relative effects of the two radiations upon such diverse types of biological tissues were consistently the same, certainly it would have appeared highly improbable that a remarkable difference could be expected for two tissues as closely related as cancerous and normal cells in the human organism.

In order to create a situation in which the relative effects of the two radiations could be studied on tissues as closely related as a tumor and its regional normal structures, Drosophila eggs were irradiated at different stages in their development (12). Here again though dealing with two sets of tissue in the same species of organism, significant differences were found. By irradiating wheat seedlings, the relative action of the radiations upon different organs (root and shoot) in the same individual organism was investigated and despite the essential similarity of the tissues composing these organs, the relative effects of the two radiations were found to be consistently different.

On the basis of the demonstration that differences in the relative action of neutrons and x-rays exist not only for distantly related but also for closely related biological tissues, it appears highly probable that a difference in the relative action of the two radiations upon cancerous and normal tissues may exist. The selective action of neutrons probably will differ from that of x-rays. As yet no evidence exists to indicate whether the selective effect will be more favorable or less favorable than that of x-rays; it is evident that this represents an incomplete solution of the problem. At the present time, at the University of California and to a lesser extent at Michigan, several collimated neutron beams are being used in a direct attack upon the problem; a more adequate estimate of the potential usefulness of neutrons in cancer treatment may become available in the near future.

BIBLIOGRAPHY

(1) **Zimmer, K. G.,** and **N. W. Timofeeff-Ressovsky.** Dosimetrische und strahlenbiologische Versuche mit schnellen neutronen II. Strahlentherapie, 63: 528–536, 1938.

(2) **Nagai, M. A.,** and **G. L. Locher.** The production of mutations in Drosophila with neutron radiation. Genetics, 23: 179–189. 1938.

(3) **Marshak, A.** Effect of fast neutrons on chromosomes in mitoses. Proc. Soc. Exp. Biol. and Med., 41: 176–180. 1939.

(4) **Spear, F. G., L. H. Gray,** and **J. Read.** Biological effects of fast neutrons. Nature, London, 142: 1074–1075. 1938.

(5) **Enzmann, E. V.,** and **C. P. Haskins.** Note on modifications in the morphogenesis of *Drosophila melanogaster* occurring under neutron bombardment. Amer. Nat., 73: 470–472. 1939.

(6) **Lawrence, J. H.,** and **R. T. Tennant.** The comparative effect of neutrons and x-rays on the whole body. Jour. Exp. Med., 66: 667–687. 1937.

(7) **Lawrence, J. H., P. C. Aebersold,** and **E. O. Lawrence.** The comparative effects of neutrons and x-rays on normal and neoplastic tissue. Occas. Publ. Am. Ass. Adv. Sci., No. 4: 215–219. 1937.

(8) **Lawrence, J. H., P. C. Aebersold,** and **E. O. Lawrence.** Comparative effects of x-rays and neutrons on normal and tumor tissue. Proc. Nat. Acad. Sci., 22: 543–557. 1936.

(9) **Gray, L. H.** An ionization method for the absolute measurement of gamma ray energy. Proc. Roy. Soc. London, Series A, 156: 578–596. 1936.

(10) **Zirkle, R. E.** Biological effectiveness of alpha particles as a function of ion concentration produced in their paths. Am. Jour. Ca., 23: 558–567. 1935.

(11) **Zirkle, R. E., P. C. Aebersold,** and **E. R. Dempster.** The relative biological effectiveness of fast neutrons and x-rays upon different organisms. Am. Jour. Ca., 29: 556–562. 1937.

(12) **Zirkle, R. E.,** and **I. Lampe.** Differences in the relative action of neutrons and roentgen rays on closely related tissues. Am. Jour. Roent. and Rad. T., 39: 613–627. 1938.