Despite war needs, commercial aviation should not be neglected. The committee believes, it says, "that commercial aviation will prove of ever-increasing importance to the United States in promoting international trade and good will, especially in the Western Hemisphere. When the present wars have ended, aviation will have an opportunity to prove its real value to civilization in shortening the distances between nations and in facilitating international trade and commerce. When that day comes, the extension of world trade routes of the air will bring some compensation for the awful destruction wrought and to be wrought by military aviation before peace again prevails."

SPECIAL ARTICLES

LOCALIZATION OF LITHIUM IN TUMOR TISSUE AS A BASIS FOR SLOW NEUTRON THERAPY[1]

THE destructive action of x-rays and fast neutrons on living tissue is known to be due to the action of energetic electrons resulting from the absorption of the x-rays, and of recoil nuclei, especially hydrogen nuclei, which have been projected by neutron impact. The biological action in either case is a result of energy absorption by the tissue from the high-energy, charged particles. With either x-rays or fast neutrons, however, the destructive action occurs throughout the irradiated tissue, and no satisfactory method has been found for localizing the damage, in the case of cancer therapy, to the tumor zone. Very often skin damage sets an upper limit to the dose which can be delivered through the skin to underlying tissue.

Since the passage of slow neutrons through body tissue is not accompanied by the production of energetic recoil protons, there should be little or no resulting damage from this cause. However, if these slow neutrons be introduced into a zone which has been perfused with certain chemical elements such as boron or lithium, or their compounds, nuclear capture reactions will occur which release very energetic particles, and result in the local destruction of tissue.

The foregoing considerations suggest an investigation of the applicability of neutron-boron or neutron-lithium techniques to the localized treatment of tumors. The method would be based on the introduction of boron or lithium compounds into the tumor region and the subsequent irradiation of this region with slow neutrons. The neutron capture reactions would then result in localized damage to the tumor.

Zahl, Cooper and Dunning[2] injected growing mouse sarcomas with various forms of slow neutron-capturing materials. When the whole animal whose tumor was so injected was irradiated with slow neutrons, a significant increase in tumor regression was observed which presumably resulted from the nuclear disintegration products of the capture process.

In connection with this work, however, it was pointed out that the method of direct hypodermic injection of slow neutron-capturing materials into the tumorous area does not seem clinically feasible. The authors suggested that for any future employment of the boron-slow neutron process in tumor therapy, some device other than simple hypodermic injection should be developed for localizing either boron or lithium, or related materials, in malignant tissue.

The possibility of selective localization in malignant tissue of slow neutron-capturing materials through the medium of intravenous injection was suggested by the work of Ludford,[3] Duran-Reynals[4] and others who observed that certain acid dyes, when introduced into the blood stream, would accumulate in greater concentration in tumor tissue than in normal tissue. Since most of such localizing dyes are sodium salts of the azo-sulfonic acid complex, it was hoped that by substituting lithium atoms for the sodium atoms which are normally present in the dye-salt molecule, the dye molecule would act as a vehicle for localizing lithium in the malignant tissue.

Lithium salts[5] of Pontamine Sky Blue 6B, Trypan Blue and carminic acid were prepared and injected intravenously both into mice bearing spontaneous mammary tumors and mice bearing implanted tumors of the Sarcoma 180 strain. After suitable periods following intravenous injection of the dyes, animals were sacrificed and tumor and other tissues removed and analyzed spectroscopically for lithium content.

Since the purpose in capturing the slow neutrons is to make available the nuclear reaction energy for cellular destruction, it is of interest to compare the amounts of energy made available by the addition of boron and lithium to the tissue in various concen-

[1] We wish to express our appreciation to Dr. C. P. Rhoads and Dr. G. Failla for courtesies extended us at Memorial Hospital, and to Professor J. R. Dunning, of Columbia University. Grateful acknowledgment is made to Lucius N. Littauer, who generously supported certain portions of this work.

[2] Paul A. Zahl, Franklin S. Cooper and J. R. Dunning, *Proc. Nat. Acad. Sci.*, 26: 589–598, 1940. Similar *in vitro* work has been reported by P. G. Kruger, *Proc. Nat. Acad. Sci.*, 26: 181–192, 1940.

[3] R. J. Ludford, *Proc. Roy. Soc.* (London). Series B., 104: 493–511, 1929.

[4] F. Duran-Reynals, *Amer. Jour. Cancer*, 35: 98–107, 1939.

[5] Grateful acknowledgment is made to the Dyestuffs Division of the E. I. du Pont de Nemours and Company and to the National Aniline and Chemical Company for the preparation of the lithium salts of their dyes.

trations. Fig. 1 shows the energy absorbed by the tissue as a function of the concentrations of boron, lithium and their active isotopes.[6] The energy, however, does not become zero at zero concentration because there are neutron reactions with some of the elements in normal tissue, especially hydrogen, nitrogen, chlorine and phosphorus. These reactions liberate a considerable amount of energy but much of it is in the form of penetrating gamma-radiation, and only a small fraction of this is absorbed locally. However, the reaction with nitrogen and the radioactive decay of chlorine and phosphorus yield ionizing particles whose energy is completely absorbed at the site of the reaction. The total energy absorbed by the tissue and due to capture of all the slow neutrons by normal tissue constituents is shown by the horizontal line in Fig. 1. The addition of boron or lithium results in a net increase of absorbed energy, only because more energy is made available when a neutron is captured by boron or lithium than when the neutron is captured by one of the elements of the tissue.

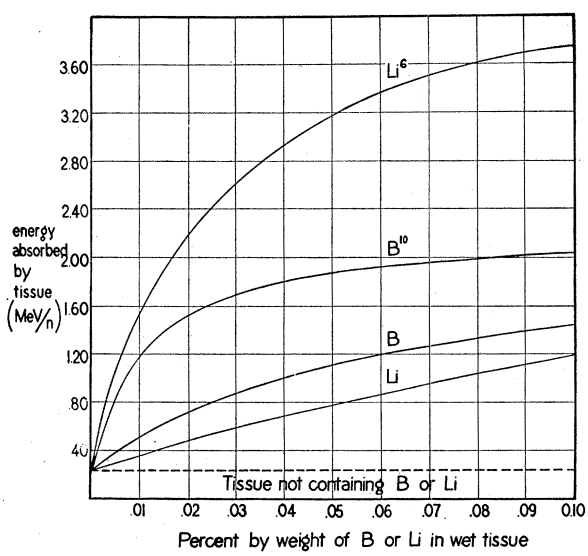

FIG. 1. Energy absorbed by tissue containing varying amounts of boron or lithium or their isotopes. The energy is supplied by slow neutron capture reactions with these elements and with constituents of the tissue.

It is evident from Fig. 1, that increasing the amount of boron or lithium in tissue will continuously increase the total energy absorbed. However, it is not the total energy absorbed but rather the difference in energy between tumor and healthy tissue which determines the optimum treatment condition. This differential dose should be made as large as possible; the absolute amount of the dose can then be adjusted by varying the quantity of slow neutrons administered. In any practical case it would hardly be possible to restrict the added materials entirely to the desired region, *i.e.*, the tumor mass. Rather there will always be boron or lithium in some concentration throughout the region exposed to the slow neutrons. The difference in the radiation dosage supplied to the tumor mass and that to the surrounding tissue, *i.e.*, the dose differential, will therefore depend considerably on the difference in concentration of boron or lithium in the tumor region and in the adjacent tissues. The ratio of these concentrations, which we have called the localization factor, is not, however, the only consideration. The dose differential depends also on the absolute quantity of added material and, in fact, the dose differential passes through a maximum as the quantity of boron or lithium is increased.

In the experimental work done thus far we have attained a localization factor of approximately 2.0 and a maximum concentration of approximately 0.01 per cent. to 0.03 per cent. lithium in the tumor mass. This corresponds to a maximum gain of about 43 per cent. in the radiation dosage of the tumor over that of other tissues in the same mouse. If the isotopes of lithium or boron were available in pure form this advantage could be considerably increased.

The physical and biological considerations here presented apply directly to techniques which might be developed for the treatment of tumors that lie near the surface, thereby permitting the ready penetration of slow neutrons throughout the tumor zone. These considerations also apply to the treatment of deep-seated tumors by a beam of fast neutrons, since they form the basis for an auxiliary technique to utilize the slow neutrons resulting from the slowing down of fast neutrons of the beam. The possibility, not existent with x-rays, of thus securing an increment of ionization localized at a tumor containing boron or lithium provides one of the important reasons for considering the potentialities of fast neutron therapy in conjunction with slow neutron effects.

A detailed study of this problem and an elaboration of the experimental results is being published elsewhere.[7]

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[6] Only the boron isotope of mass 10, *i.e.*, B^{10}, is implicated in the capture of slow neutrons by boron. Since B^{10} atoms comprise only 18.4 per cent. of atoms making up the chemical element boron per unit weight, the "undiluted" B^{10} atoms are 5.5 times as effective as boron in capturing neutrons. Similarly, Li^6 is 12.7 times as effective as lithium. These isotopes are not at the moment available in the quantities necessary for the use indicated, but this condition will not necessarily continue to hold.

[7] Paul A. Zahl and F. S. Cooper, "The Use of Neutrons in Cancer Therapy." *Radiology* (in press), 1941.