Radioactive Isotopes and Nuclear Radiations in the Treatment of Cancer*

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It is now 20 years since we began to use artificially produced radioactive isotopes in cancer research and in medical research. Actually, our first therapeutic trials were in 1936. In the early days the hope was that at the end of 20 years one could report outstanding examples of selective localization of radioactive compounds in neoplastic tissue, making it possible to give the tumor tissue many times more irradiation than the surrounding, normal tissues.

Up to the present moment, investigations with only two radioactive isotopes have given us important therapeutic applications in hyperplastic and neoplastic diseases through selective localization. These are radiophosphorus in the treatment of polycythemia vera and radioidine in the treatment of the thyroid hyperplasia of Grave’s disease and in the palliative treatment of certain thyroid cancers. However, one who has worked in the field from the beginning and who is asked to sum up his experiences can’t help saying that the therapeutic achievements have been disappointing; but even in the early days we believed that the greatest contribution of radioactive isotopes in the field of medical and cancer research would lie in tracer applications, and we have devoted most of our energies to the latter.

Even though the achievements in prolongation of life and cures in cancer have not been great so far, one should not dismiss too lightly the contributions of artificial radioactivity and nuclear radiations in cancer therapy. The clinician should not underestimate the importance of relief from pain and extension of comfortable life, and here their value is well established.

The importance of the products of nuclear physics in cancer therapy is pointed up by the fact that demands for radioactive isotopes in medical and biological research have risen rapidly in the past 10 years. The shipments of radioactive isotopes from Oak Ridge National Laboratory have risen from less than 500 in 1946 to almost 12,000 in 1954. Seventy per cent of the total dollar value of all shipments is for medical use, and one-third of these shipments are for cancer therapy. For instance, there are 30 medical groups in the United States using radioactive colloidal gold and radioactive colloidal chronic phosphate for interstitial infiltration in various types of cancer, such as prostatic, uterine, and bronchogenic. Two hundred fifty groups are using radioactive iodine, chronic phosphate, and yttrium colloids in the treatment of cancer metastasized to the pleural and peritoneal cavities. There are 400 groups using iodine-131 in the diagnosis and treatment of hyperplastic and neoplastic thyroid disease and 389 groups using P32 for the treatment of polycythemia vera and chronic leukemia. During 1954 there were over 5,000 shipments of radioactive iodine from Oak Ridge to individual users, over 2,500 shipments of radioactive phosphorus, and 622 shipments of radioactive gold. At the present time there are 80 cobalt teletherapy units in the United States in use for external irradiation therapy of cancer with high energy gamma rays, and 50 more are being planned (1).

Most of the isotopes which have been used in the therapy of hyperplastic or neoplastic diseases in the form of internal, intracavitary, interstitial, contact, tele, or fission radiation are listed in Chart 1 in the order of increasing atomic number.

Early work by Kruger in this laboratory 15 years ago (25) and by Zahl et al. (59), followed by the uranium fission experiments by Tobias et al. (55), more recently has led to the trial of boron-10 in the treatment of brain tumors, particularly glioblastomas, the radiation being derived from the fission of the boron nuclei after slow neutron capture (7). Kruger bathed tumor slices in boric acid solution in vitro and then irradiated them with slow neutrons, causing fission of the boron nuclei into lithium and alpha particles. The ionization obtained is relatively densely localized, the particles traveling about one cell diameter (55). After borax containing boron-10 was injected intravenously into patients with brain tumors who were then exposed to soft neutrons from the atomic pile, Farr, Sweet et al. (7, 18) have been able to deliver a few


1 At the International Conference on the Peaceful Uses of Atomic Energy held in Geneva in August, 1955, the author learned from Professors Modestov and Fateyeva that there are 150 such units now in operation in the Soviet Union.
hundred roentgens to the tumor tissue by such fission energy, but this is probably insufficient to give real therapeutic effect. Pathological studies of eight of the first ten patients treated at Brookhaven showed changes suggestive of irradiation effects in three patients; however, large areas of viable tumor were found in all cases (13). More recent investigations by Kruger have shown that the concentration of boron in the boundary between normal and tumor tissue in glioblastoma multiforme tumors in mice can be increased by injection of

The first example of a successful application of a radioactive isotope in therapy was the treatment of polycythemia vera with $^{32}$P. Enough experience has been gained over the past 20 years to allow one to say that the condition can be satisfactorily controlled by $^{32}$P (29). The survival of patients with polycythemia treated by $^{32}$P is about equal to that in cases of pernicious anemia treated by liver or vitamin B$_{12}$ and diabetes mellitus treated by insulin (Chart 2), and is superior to any increased survival rate yet achieved in such cancers as breast or prostatic cancer with newer methods of therapy (Chart 3). The median survival in patients with polycythemia vera is 14 years, compared with a survival of approximately 20 years for an age-matched group of the general population. Since 1936, when $^{32}$P was first used in the treatment of chronic leukemia (30), thousands of patients have been treated. As shown in Chart 3, approximately 50 per cent of the patients with

Evans Blue dye containing boron-10 in the molecule (26). Although the localization of the radioisotope achieved by use of the dye is 30 times that obtained after injection of boron-10 as borax solution, the localization is greatest at the brain-tumor interface and is not uniformly distributed throughout the tumor tissue. Consequently, there is still insufficient localization in tumor cells to provide the needed radiation. However, the use of such boron-containing dyes should be explored. If fissionable material can be synthesized into compounds that will give great selective localization in neoplastic tissue, there is little doubt that great therapeutic benefit can result.

Sodium-24 and bromine-82 have been used in the form of fluid instillation into the bladder for palliative treatment of advanced cancer of the bladder, but the survival time is not available for a large series of patients (58). The beta- and gamma-emitting isotope Na$^{24}$ has also been tried in the treatment of chronic leukemia, but the method has not found wide usage, since there is no selective localization of sodium.

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chronic lymphatic leukemia treated by P\textsuperscript{32} will survive over 5 years (28). This is somewhat better than the survival in 1,600 cases treated by conventional methods reported in the literature review by Osgood (81).

Between 1935 and 1940, in the early days of the radioisotope work, we attempted to treat a group of patients with breast cancer and prostate cancer metastatic to bone by means of intravenous or oral administration of P\textsuperscript{32} or Sr\textsuperscript{90} (27, 30, 40). It had been demonstrated that strontium, like calcium, localized to a high degree in bony tissue with less uptake than P\textsuperscript{32} in soft tissue. However, the results were not exciting, and this work was abandoned when it became evident that it would be impossible to deliver sufficient beta radiation to the bony lesions without causing severe marrow depression. Recently, Friedell (11) and others have re-introduced P\textsuperscript{32} in this form of therapy and found again that there is some relief of pain and occasional evidence of healing. This type of therapy may have a small place in the palliation of cancer metastatic to bone.

Friedell and associates have also made Sr\textsuperscript{90} applicators for use in the treatment of superficial tumors of the eyelids, conjunctiva, and corneal ulcers (12). The treatment of skin cancer and hyperkeratoses by P\textsuperscript{32} contact therapy (31) has added another successful method for the treatment of such lesions. Since 1943 Low-Beer has treated 350 hyperkeratoses by this method with a 5-year eradication rate of 98.3 per cent. Of the 190 basal-cell carcinomas treated, 97.6 per cent have been eradicated for longer than 5 years. Also, 47 hemangio mas have been successfully treated by this method. A small plaque of blotting paper is cut to fit the size of the lesion, the desired amount of Na\textsubscript{3}HP\textsuperscript{32}O\textsubscript{4} is pipetted onto it, and the plaque is then applied directly to the lesion. In the case of basal-cell carcinoma, a dose of 34,000–36,000 rep is delivered to the surface, and 20,000–22,500 rep delivered to the first millimeter depth in a period of 48 hours. This method is producing results equal to those of any other of the more conventional methods now in use for the treatment of superficial skin cancer.

Radiophosphorus as colloidal chromic phosphate (21), first used by Jones et al. (32), as well as colloidal radiogold (2, 14, 24) and radioyttrium, is being currently given to patients suffering from pleural and ascitic effusions in metastatic carcinoma. This application of radioisotopes constitutes an important addition to palliative cancer therapy. Although there is no evidence that such therapy prolongs life, there is little question that it relieves pain in many instances and slows down the accumulation of ascitic and pleural fluids, so that paracentesis is often unnecessary or need be done at less frequent intervals.

Colloidal chromic radiophosphate and radiogold are also being used interstitially for the treatment of carcinoma of the prostate before distant metastases develop (8, 9, 46). The beta radiation from these colloids allows a large tumor dose of radiation to be given without damage to surrounding tissues, as might occur with conventional x-ray
therapy. Some workers point out the fact that chromic radiophosphate has an advantage over radiogold in that the former emits only beta rays, and less elaborate radiation protection measures are needed. However, other workers believe that radiogold gives a somewhat better therapeutic effect because the greater penetration of the gamma radiation will, with the beta radiation, in effect give a more uniform dose. Radioactive Y\(^{90}\) (29) and chromic phosphate (45) beads and radon implants (10) have been used for destruction of the pituitary in certain types of cancer. The techniques for distributing radioactive materials in tissue may be improved in the future in some cases by the intra-arterial injection of the radioactive materials.

In 1948 we used colloidal chromic radiophosphate in the treatment of a group of patients with chronic leukemia, polycythemia vera, and also a group with marked splenomegaly or hepatomegaly from miscellaneous causes (6, 22). We found these results no better than those following \(P^{38}\), as \(Na_2HP_4O_4\), and, because of the chances of getting the radiocollod outside the vein with resultant radionecrosis, we have more or less abandoned the use of the various radiocollod for the treatment of this group of diseases. Gofman and associates used many other radiocollod in the same group of diseases and arrived at the same conclusion (6).

Cobalt-60 is being used in intracavitary and interstitial therapy of nasopharyngeal and maxillary tumors and uterine, prostatic, bladder, and bronchogenic carcinomas. In general, it is too early to evaluate the results in comparison with those achieved by conventional means of therapy. Hinman and co-workers (18, 47) treated 35 patients with bladder tumors by intracavitary irradiation using cobalt-60. They report that in four of nine patients with tumor confined to the mucosa the lesions were destroyed, but most infiltrating lesions were only temporarily arrested.

The cobalt bomb teletherapeutic units are of wide interest now and are being used as substitutes for 200 kv. x-ray equipment in the treatment of deep-seated tumors. Radiocobalt provides the gamma ray source in these units, but other gamma ray emitters such as cesium are also being used, especially in Great Britain. These teletherapeutic units have certain advantages over x-ray equipment, such as cost and mobility, but one cannot expect much improvement in end results over conventional methods which use x-ray or other gamma ray sources.

Since the first therapeutic use of radioactive iodine (15, 16, 17, 30), it has been widely applied in the treatment of hyperplastic thyroid disease or Grave’s disease; indeed in many hospitals it is entirely replacing surgery, and remarkably good end results are reported (5, 34). In the case of thyroid cancer, however, it is rare that radioiodine will localize sufficiently in a metastatic lesion to give a good therapeutic result or cure, even after complete thyroidectomy or after a long course of propylthiouracil or thyroid-stimulating hormone (43). The cases in which there is a good uptake of radioiodine, however, give one increasing confidence that if selectively localizing compounds can be found, lasting benefits might be obtained in advanced cancer of other types also.

Figure 1 is a gamma ray picture of the localization of \(\Gamma^{131}\) in the body of a patient with thyroid metastases obtained in the first whole-body scanner now so widely used. This whole-body scintillation scanner, developed by Anger and Tobias (8) for photographing gamma ray-emitting isotopes in the body, is shown in Chart 4. It consists of a series of scintillation counters within lead cylinders. The gamma ray energy from the isotope within the body is converted to light energy and photographed with a polaroid camera as the body is scanned. New methods for visualizing the distribution of radioisotopes in vivo, such as the one described here or the gamma ray pinhole camera (35), are expected to be of indirect use to therapy through more accurate localization of tumors. The patient illustrated in Figure 1 was a 68-year-old male with thyroid metastases in the left upper arm, the chin, the sternum, the hip, the thigh, and the ribs. Interestingly enough, two of these lesions were not discernible by x-ray examination, yet they could be picked up by the scanner. This method of locating tumors would of course have important diagnostic applications if localizing compounds emitting gamma rays could be found for other types of cancer. This particular patient had the largest uptake of radioactive iodine in metastatic lesions that has come to our attention. Comparative counting rates over the tumor and an equal volume of normal tissue showed that the tumor concentration of \(\Gamma^{131}\) was as much as 200 times that in an equal volume of normal tissue. During therapy with an oral dose of 100 mc. of \(\Gamma^{131}\), as much as 100,000 rep in radiation was delivered to the neoplastic lesions. Prior to surgical thyroidectomy there was no uptake in these metastases. Now, 6 years later, this man is symptom-free, and, at the age of 74, he is an example of the good result that can be obtained with isotope therapy when there is a high selective uptake by neoplastic tissue. Uptake in metastases can be stimulated by surgical thyroidectomy, and administration of propylthiouracil and thyroid-stimulating hormone are also sometimes helpful in increasing iodine uptake in metastases (48). Another difficulty encountered in the treatment of metastatic...
thyroid cancer with radioiodine is that the radiation dose may not be uniformly distributed in the tumor tissue. Surgery and x-ray continue to be the primary tools for treating thyroid cancer.

The high selective localization of iodine in thyroid tissue and also the selective uptake of radiophosphorus by the bone marrow and blood-forming tissues allow us to deliver relatively high doses of radiation to specific tissues. Perhaps in our present state of relative ignorance regarding the metabolic differences between the cancer cell and normal cell, it is too much to expect that a radioactive compound can be found which will localize in cancer cells selectively enough to give 25, 50, or more times the radiation than normal cells will receive. If such is to be found, the ideal isotopes to be built into the localizing compound would seem to be hydrogen-3 or carbon-14. The latter provide relatively soft beta rays traveling only a few cell diameters in tissue.

Many workers have attempted to synthesize compounds containing radioactive carbon and other radionuclides for selective localization. Reid and Jones (44) made C14-labeled tyrosine and injected some of it into animals carrying a transplanted melanosarcoma. There was some localization in the melanosarcomatous tissue, but there was an appreciable uptake by the adrenal and thyroid glands, since tyrosine is a precursor of the hormones produced by these tissues.

The metabolism of stilbamidine containing C14 was studied in multiple myeloma, and, while it did localize in the myelomatous tissue, there was an even greater uptake by the liver. These examples are typical of the many compounds...
Some of the most interesting current investigations on selective localization are typified by the studies of Pressman and associates (41). After immunizing animals to various normal tissues and neoplastic tissues and then adsorbing radioactive iodine to the antibodies, they have been able to demonstrate some localization of these antibodies in the various normal and neoplastic tissues. More recently Bale has achieved tumor localization of such antibodies 15 times greater than that of any normal tissue, indicating that this approach may be a very hopeful one (4, 50).

The therapy of cancer continues to be based primarily on early diagnosis, surgery, and postoperative x-ray therapy. Radioactive isotopes and nuclear energy have not yet added importantly to the armamentarium of cancer therapy, but the relatively poor survival in cases of deep-seated cancer impels investigators to make heroic attempts to relieve these people and extend their lives. As can be seen in Chart 5, the 50 per cent survival in the case of breast cancer, the most common type of cancer in women between the ages of 40 and 60, lung cancer, and stomach cancer is approximately 3-5 years.

One of the real advances in cancer therapy has been the revelation of the relation of hormones to certain types of cancer, including the effects of oophorectomy, adrenalectomy, and hypophysectomy on advanced breast cancer (42). Two examples in particular are the work of Huggins in the field of prostate cancer treated by orchietomy and diethylstilbesterol (19), and the treatment of metastatic breast cancer by adrenalectomy (20). Olivecrona and associates were the first to report a remission in metastatic breast cancer following hypophysectomy and have recently reported the results of this form of therapy in a series of 30 patients (33). Other workers in this field have estimated that approximately 50 per cent of patients with advanced breast cancer have tumors which are hormone-dependent, and approximately 50 per cent of the patients of this type undergoing successful hypophysectomy will show some evidence of healing (38, 39). Apparently, the response is independent of the cellular type of mammary tumor, and whether the effect is always mediated through the ovaries and adrenals or whether there is a primary pituitary factor is not yet known.

With the hope that hypophysectomy could be achieved by irradiation, for 15 months we have been making such attempts using a somewhat unique form of irradiation from the 184-inch cyclotron. This work is a projection of the animal studies of Tobias et al. (51, 54), who achieved hypophysectomy in the rat, dog, and monkey with beams of high energy deuterons or protons. One unusual feature of the beam is its pencil-like nature with very little scatter, unlike a similar beam of x-rays or gamma rays. Another unusual feature of these beams is that there is a relatively greater depth dose compared with surface dose. The comparative doses at the surface and depth for 200 kv. x-rays, 16 mev electrons, and 190 mev deuterons are given in Chart 6. The 200 kv. x-rays fall off markedly at 10-cm. depth, and the electrons from the betatron or synchrotron also fall off considerably, but the deuteron irradiation rises to a peak at 14 cm., so that the depth dose is approximately 4 times that entering at the surface.

Two animals with mammary cancer are shown in Figure 2. The one on the left is the control, and the one on the right has been irradiated by passing the beam through the chest of the animal from the opposite side, localizing it on the tumor. In other words, it is possible to deliver energy in the depths of tissues with relatively little skin effect using this form of radiation. Tobias et al. have applied this beam to the pituitaries of rats, monkeys, and dogs and have been able to remove the pituitary by this selective form of external irradiation, producing atrophy of all the target organs, effects paralleling those of surgical hypophysectomy. Four littermates are shown in Figure 3. The second from the left has had surgical hypophysectomy, and the third from the left irradiation hypophysectomy. The animal on the left has been subjected to hypothalamic irradiation which produced obesity, and the animal on the right is the control.

During the past year this beam has been applied to the pituitaries of patients with advanced breast cancer and to two patients with leukemia, one having an associated diabetes. This work has been the subject of two previous reports which give much more detail (52, 53). The patients with cancer have previously had every form of conventional therapy, including radical mastectomy, postoperative x-ray, hormone therapy, as well as oophorectomy and adrenalectomy, and they were no longer responding to these forms of therapy. The aim in this work has been to find out how successfully one can inhibit or destroy the pituitary by this selective form of radiation as compared with surgical hypophysectomy. Figure 4 shows a lateral view of the sella turcica in one of the patients with the beam centered on the crosshair. It is possible to cover most of the area occupied by the pituitary within the sella with very little radiation being delivered to the surrounding tissues, such as the hypothalamus and optic chiasm. Up to the present time, use has not been made of the Bragg curve, and the relatively great pituitary dose is accomplished by continuous head rotation, the beam being centered on the pituitary. There are real problems encountered in avoiding irradiation of the vital structures surrounding the hypophysis, such as the optic tracts, the hypothalamus, and the various cranial nerves. It has not been possible to give as much radiation to this area as one would like at the present time because of the danger of cranial nerve damage. However, already in the first fourteen patients treated there is evidence of marked pituitary suppression (Chart 7). Figure 5 shows the patient in position for treatment. Prior to irradiation the sella is very carefully brought into position by taking x-ray photographs, and with the aid of crosshairs the beam is made to fall on the exact center of the sella. During treatment the head is held tightly in a plastic mask and continuously rotated through a 60°–70° angle, 30°–
85° to the right and 30°–85° to the left. The first patient treated (Chart 7) was given 18,850 rads, one preliminary impressions regarding clinical benefits fractionated doses. As far as we know, the findings in this case are the first clear-cut evidence that target organ effects can be brought about by pituitary irradiation (note decrease of pituitary gonadotrophins and marked decrease in thyroid function as shown by fall in I[131] thyroid uptake, Chart 7).

Whether or not there will be a real application of irradiation hypophysectomy, or even surgical hypophysectomy, in cancer therapy is not yet known. Another 2 or 3 years must elapse before preliminary impressions regarding clinical benefits in this series can be gained. Also, it will require another 5 years before it is known whether hypophysectomy will appreciably lengthen life in advanced cancer of this or other types.

While I do not intend to belittle the achievements of workers with artificial radioactivity and nuclear energy in cancer therapy, the results reflected in extension of life so far are not impressive. However, when one must deal with the problem of intractable pain, he learns to appreciate any palliative procedure which will make the patient more comfortable even if significant extension of life is not demonstrated. Radioisotopes and the new accelerators and external sources of radiation have given us tremendously important new tools and, from the humane standpoint, have been a real boon to cancer therapy. If a selectively localizing compound or compounds can be found which would emit a soft form of radiation, the really important advances that could be realized are obvious. Much more basic research including that with tracers is needed to learn more of the physiology of cancer. In the search for therapeutic benefits, our relative ignorance of the nature of neoplastic growth is emphasized, and the solution to the problem will probably not be found without greater understanding of the cancer process at the cellular level.

ADDITION

At the International Conference on Peaceful Uses of Atomic Energy held at Geneva in August, 1955, the author talked at length to numerous Russian investigators and learned that during the past 3–5 years they have been very active in applying the products of nuclear physics, especially isotopes, to therapy, particularly in the use of I[131] in Grave’s disease, I[131] in the treatment of polycythemia vera and leukemia, and the cobalt teletherapeutic units for external irradiation treatment of cancer.

REFERENCES


![Fig. 1.—A scintogram of a patient with thyroid metastases at various times after injection of a tracer dose of I[131]. The scintillation scanner passes back and forth over the body, translating the gamma ray energy from the I[131] within the body into light energy, which is then photographed with a Polaroid camera.](image-url)
Fig. 2.—A: Control animal with untreated mammary tumor; B: Healing tumor after bombardment with 190 mev deuterons. The beam of deuterons was directed to the tumor through the opposite side of the animal's body.

Fig. 3.—Four littermates (left to right): hypothalamic irradiation, producing obesity; surgical hypophysectomy; irradiation hypophysectomy; control.

Fig. 4.—Diagnostic x-ray of a patient's head in position for treatment. The crosshairs mark the center of the beam. The outlines of the sella turcica are clearly shown. The black spot on the film on the left shows the shape of the beam, which can be adjusted to fit each patient. The radioautograph is made by briefly turning on the proton beam prior to developing the film. The beam spot is actual size, while the x-ray picture of the sella is enlarged by 20 per cent owing to the finite focal distance of the x-ray machine.

Fig. 5.—Patient in position for irradiation with the proton beam.


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