THE TREATMENT OF TUMORS BY X-RAYS AND RADIUM.*

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IN making this brief communication upon the treatment of tumors with x-rays and radium, I would first express to you my thanks for the privilege accorded me of presenting a report before this eminent society of surgeons.

While the subject is one of the greatest interest to the surgical world, it is one to which few surgeons of wide operative experience have given much of their personal attention, and the therapeutic use of radium and x-rays has been carried out chiefly by physicians and institutions devoted primarily to radio-therapy. My own experience has had to do more particularly with radium than with x-rays, and dates only from 1912, when we first obtained radium in Boston in quantity sufficient to engage in a serious investigation of its effects upon tumor growth.

The institution which I represent—the Cancer Commission of Harvard University—was so fortunate as to secure at that time the services of Professor William Duane, a physicist who had worked for some years under M. and Mme. Curie in Paris, where he had made himself familiar with the subject of radio-activity and had contributed by his investigations to the knowledge of that subject. Under Professor Duane's guidance, and with the coöperation of Dr. W. T. Bovie, who has been working for our Commission in the field of research between Biology and Physics, the attempt was made to apply to the actual treatment of patients the physical principles of radio-activity, which had been established, and to carry on further investigations both in the laboratory and in the clinic, with a view to determining the most effective methods of employment of these powerful and beneficent agents.

Our knowledge of the physics and chemistry of radium far exceeds in accuracy our knowledge of its biological effects, for the reason that our knowledge of biology, so far as the ultimate composition and physiology of cell protoplasm is concerned, is chiefly theoretical. Whatever theory of protoplasmic structure we accept, however, it can be said that as a result of the exposure to radiations of x-rays, or radium, changes occur in living tissues which are at first invisible and unappreciated by our coarse

methods of observation, but which later manifest themselves by certain phenomena varying from a modification of growth, either in rapidity or form, to the death and destruction of the cells or tissues involved.

The term *reaction*, or *radium reaction*, has been widely used to express the phenomena following radiation. The comparison is aptly made to the exposure of the sensitive photographic plate, whereby changes occur in the silver salts as a result of radiation. These changes in the silver emulsion, however, are not to be detected by our ordinary methods of observation, until a further chemical reaction, the process of development, brings the latent image into view. Whether the changes occurring in the photographic plate and those occurring in living cells by exposure to radiation are of one and the same nature is a matter of further investigation. It has been held that a process similar to, if not identical with, the ionization of gases may be the means by which these changes in the finer physico-chemical composition of the sensitive film or of the tissue cells are brought about, but much further investigation is needed upon this subject.

Again, the conditions controlling the process of development of the latent effects of radiation on the living cell are quite unknown. Some experiments of Dr. Bovie¹ would indicate that slight variations of temperature suffice to make these changes manifest, and doubtless other agents, such as the chemical changes of anabolism and katabolism perhaps might serve as accelerators or retarders of development in the living tissue. The subject is one of great complexity, because we realize that we are forced to use rays of several different characters when dealing with x-rays and radium. The alpha, beta and gamma rays of radium, the hard and soft x-rays, and the secondary radiations produced by the absorption of x-rays and gamma rays in objects of different composition in their path differ in their powers of penetration, and also in their quantity and in their physical qualities as well. The effects upon living tissues of the different types of rays have been the subject of much investigation, but, as yet, we are only upon the threshold of our knowledge of this subject. It may, however, be accepted as a fact that rays which are not absorbed produce little if any effect upon the tissues through which they pass, and that the penetration of the different rays through

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tissues of uniform density follows a definite physical law.

As regards the tissues themselves we recognize that differences in susceptibility to radiation exist, such that cells of one kind, as the germ cells of the testicle, are apparently affected far more seriously by a given length and quality of exposure than are the cells of another character, such as those of the external skin. In fact, it is not unreasonable to suppose that the external skin, by adaptation, has acquired or developed a degree of susceptibility to the effects of radiation in the long process of adaptation of men and animals to their environment.

There is good reason to believe, also, that there are certain periods in the life cycle of a single cell when it is more susceptible than at other periods, and it is held that cells undergoing nuclear division are especially vulnerable to the effects of radiation.² The law of Bergonié and Tribondeau³ states that immature cells and cells in an active state of division are more sensitive to radiation (x-rays) than are cells which have already acquired their fixed adult morphological or physiological characters. This law is based upon studies made with x-rays upon the testicle of the rat. It must be remembered, however, that our methods of investigation enable us to detect alterations in cells which are in an active state of division more readily than in cells which have acquired their fixed adult morphological and physiological characters. Redfield,⁴ however, obtained very pronounced changes in the fertilization membrane of the Nereis egg by exposures far below that required to produce changes in subsequent processes of mitosis.

In the treatment of tumors by radiation the specific sensitiveness of certain tissues has assumed a very important place. It has been stated, for instance,⁵ that "certain types of cancer-cell will be affected four to seven times more readily than healthy cells." An accurate comparison of this sort is extremely difficult to make, as we have no satisfactory standards for measurement, and it would seem to be safer, in our present state of knowledge, to confine our estimates of the comparative degrees of sensitiveness of cells to phenomena which can be measured in the laboratory.

By many experiments it has been established that exposure to radiation is capable of causing the death *en masse* of tissues of varying cellu-

lar composition. This may be called the "massive destructive" effect of radium, and it can be demonstrated on plants or animals. Animal tissues are composed of cells of many different varieties, and when a *mass* of tissue is destroyed the cells of all of those varieties die; the dead tissue is separated from the living cells about it (demarcation) and is discharged as a slough or sequestrum. Thus in a severe radium or x-ray burn of the skin the epithelial cells of the epidermis and of the hair follicles and sweat glands, the cells of the corium, the blood vessels, nerves and lymphatics, and those of the subcutaneous fat and fibrous tissue all die, and are cast off, leaving an ulcer lined with granulation tissue, and notoriously slow to heal.

It is well within the bounds of possibility that certain more sensitive types of cells may be destroyed by direct radiation over an area wider than that in which massive destruction occurs of all of the affected cells which compose the tissue radiated. In this wider area, the more resistant cells, such as those of the connective tissues, are not destroyed but are excited to a more vigorous growth. This possibility is borne out by clinical observation for it is well recognized that a radium, or x-ray burn is slower to heal than a burn produced by an ordinary cautery, and the pronounced scar tissue growth surrounding the area of massive destruction and slough is the most pronounced characteristic of the radium or x-ray burn.

There is usually a "latent" period of longer or shorter duration before the results of radiation are manifest. Changes in the electrical conductivity of tissues occur more promptly than do the gross changes of cytolysis or degeneration, but in any case the tissues exposed die, and according to the importance of those tissues to the individual, the individual dies, or sets about the normal processes for the demarcation and extrusion of the damaged tissue and the repair of the defect.

When the exposure to radiation is insufficient to cause the massive destruction of tissues other effects are observed. Protozoa exposed to mild doses of radiation display an inhibition of the phenomenon of cell division lasting for variable periods of time.⁶ After this period of inhibition has elapsed, recovery may take place and the cells begin to divide again, and in some cases at a more rapid rate than before radiation, so that ultimately the total growth from the radiated cells may exceed in number the growth derived

from the unirradiated controls. Here we see what can be described only as phenomena of inhibition and of stimulation.

In other experiments, cells of embryonic character (tadpoles)⁷ exposed to radiation showed temporary arrest of growth with subsequent development into abnormal forms (monsters). This is an example of a modification of growth differing somewhat from either of the first two described effects, though possibly dependent on a combination of inhibition and stimulation.

While admitting that our methods of observation are far too crude to permit any but the broadest generalization, we may say that, as a result of radiation (1) living tissue may be destroyed *en masse*; (2) growth may be temporarily inhibited; (3) rapidity of growth may be stimulated, and (4) the manner of growth may be modified. In the terms of these four phenomena we must consider the action of radiation in the treatment of disease.

While the massive destruction of a complex tissue demands a dose of radiation sufficient to kill the cells of all of the different types of the area involved, it must be borne in mind that the effects of stimulation, inhibition and modification of growth may be exerted upon individual types of cells in the tissue area exposed to radiation, depending upon the dosage, the susceptibility of the cells to radiation, and doubtless upon many other factors of which we have at present insufficient knowledge. We must remember, too, that for the treatment of non-malignant diseases, and for the palliative (non-curative) treatment of cancer, all of the cells exposed to radiation need not be destroyed. Satisfactory results may well be produced if only fifty or seventy-five per cent. of the growing cells are affected by the exposure. If we are to cure cancer, however, by radiation, the exposure must be shown to be one hundred per cent. efficient in destroying the disease, or recurrence is to be expected.

In the practical application of radiotherapy to the treatment of tumors, the mass destructive effect of a lethal dose of radiation is frequently employed. Superficial non-metastasizing carcinomata of the skin of both the squamous and the basal-cell variety are often completely destroyed by this use of radium. The destructive effects of radium are employed also in the treatment of some of the metastasizing forms of cancer, in situations where the operative removal of the tumor is for one or another rea-

son impracticable or impossible. Here the insertion method by the use of bare tubes of emanation, or the needles holding radium salts or emanation at their tips, has proved effective in producing the death *en masse* of the tumor tissue. These measures can be employed with safety, however, only in situations where the location of the tumor tissue on the surface of the body permits the normal suppurative processes for the separation of the necrotic tissues and their discharge to take place without the risk of deep and dangerous infection. While many attempts have been made to bury tubes of emanation in the substance of deeply situated tumors, such as brain tumors or sarcomata of different varieties, in our experience either the dosage has been so small as to be ineffective, or a degenerative process has resulted with secondary infection such that an opening to the surface for drainage was made necessary. For the treatment of certain malignant tumors on the surface of the body when operative removal of the tumor is impossible, or in combination with operation when operative removal alone is insufficient, the use of the massive destructive action of radium, by the method of the insertion of tubes of emanation, finds a field of the greatest usefulness.

Since it is the absorbed rays rather than the penetrating rays which produce the greatest effects on living tissues, it is probable that the beta rays are the ones which are most concerned in producing massive destruction by the use of radium. For this same reason massive destruction is produced only in close proximity to the source of radiation, and the filtration of the tumor tissue itself protects the more distant portions of the growth from deleterious effects. In our own experience with a dosage of fifteen millicuries of radium emanation inserted in a tumor mass in a bare glass tube, and allowed to remain in place for an indefinite period of time until the emanation has decayed, a massive destructive effect has rarely been obtained at a distance of more than one centimeter from the source of radiation.

Inhibition of growth: The phenomenon of temporary inhibition of growth is observed alike in the laboratory and in the clinic. Without gross changes in the appearance of the tissue, cells exposed to radiation may remain quiescent for a considerable period of time, only to wake to active and continued growth after the radium effects have passed away. In the clinic this

phenomenon appears as the recurrence of a tumor apparently destroyed by radium treatment.

While we cannot establish any definite limit to the duration of this phenomenon of inhibition of growth we must believe, from our observations of recurrence of cancer after radium treatment and after operation, that a very long time may elapse—in some cases several years—before cancer cells of certain types resume their activity and attain a sufficient growth to permit clinical recognition as a recurrence of the disease. It must be accepted as a positive fact, however, that radiation can retard or inhibit growth for a considerable period of time.

It is now generally conceded that small doses of radiation produce a stimulant effect on growth. This is in accord with the general physiological principle that a small dose of a destructive or paralyzing drug or agent has a stimulating effect, and it has been demonstrated in the laboratories both in relation to plants and to animal tissues.

The exact nature of the change which takes place in the tissue cell as a result of radiation and which results in a subsequently increased rapidity of growth, is quite unknown to us. We must admit, however, that it is most improbable that one dose of radiation should contribute a constituent of growth which was previously lacking, as would be the case if a plant or animal were supplied with a greater quantity of light, heat or moisture. On the contrary, the primary inhibition of growth followed by the later increased rapidity of cell division would appear to justify the assumption that damage was done to some part of the cell mechanism by the radiation, and that as a result of this damage the normal (protective) processes in response to injury were excited and repair begun. It is well known that nature's efforts at repair often exceed in their amount the actual defect.

Certain observers⁸ go so far as to maintain that the effect of stimulation by radiation is sufficient in actual experiment to lead to the production of cancer, and cite the development of cancer in x-ray lesions in support of this assertion. While we have not a sufficient knowledge as yet of the reasons for, and of the stages of the development of x-ray cancer, many observers believe that x-ray cancer is a result of the long-continued and slowly healing x-ray burn, and of nature's efforts to repair this de-

fect, rather than a specific late effect of the radiation of the epithelial cells themselves.

There is another aspect of the effects of radium when used in the treatment of tumors which is of some importance, and that is the effect exerted on the normal tissues surrounding the area of disease. A sufficient number of observations have been recorded to make it certain that changes in the blood vessels and in the connective tissues in the way of a new growth of cell elements are the earliest observable histological changes after radiation. How much of this change is primarily the result of the radiation of the connective tissue cells themselves, and how much due to the natural process of inflammation and repair excited by the presence of the damaged tumor tissue, it is impossible to state. It is of note, however, that a marked new growth of connective tissue elements occurs before any recognizable change in the epithelial cells makes its appearance. In the clinic we have an example of this effect upon connective tissue growth, in the diffuse fibrous tissue formation found at operation in the exposed area after prolonged x-ray or radium treatment. It is to this cause that surgeons attribute the well-known tendency to diffuse capillary hemorrhage and the lowered resistance against infection which is shown in cases of this character when subjected to secondary operation.

It has been well said that the ideal use of radium for the treatment of a tumor would be obtained if we could thrust into the middle of the tumor an amount of radium sufficient to destroy the tumor tissue completely, and at the same time to stimulate the surrounding connective tissues of the host to active proliferation such that the area became walled off by a dense fibrous tissue barrier. While admittedly a matter largely of theory, there are competent observers who attribute much of the so-called retarding effect of radiation upon deep tumors to the stimulating effects upon the surrounding connective tissue rather than to the destructive or inhibiting effects of radiation upon the tumor cells themselves.

The modifications of growth which result from the radiation of living cells depend to a great extent upon the nature of the tissue investigated. Thus normal tissues may be made abnormal, and developing embryonic cells may be made to develop in an abnormal way even to the extent of the production of monsters. In

the clinic, the ability of radiation to modify the growth of cells is shown in the application of radiotherapy to the relief of benign lesions of the skin, such as papillomas and keratoses. In these cases the destructive effects of radiation are not needed or desired. After a mild reaction the deeper cells of the epidermis which have previously been growing in an abnormal manner, begin to grow in a more normal manner; the abnormal cells are cast off and the lesion is cured without a scar. It is this peculiar and but little understood action of radiation that has led to some of the misunderstanding of the limitations of radiotherapy, for this action, while of the greatest value in the treatment of non-malignant lesions, can be counted upon but little in the attempt to eradicate malignant disease. No modification of growth of cancer cells short of death and destruction of every cell is sufficient to cure the patient of cancer. In cancer we find epithelial cells infiltrating the tissues at a distance from their normal situation. It is by this criterion rather than by the cell morphology that we recognize the disease, and no matter how extensively their growth is modified, so long as cancer cells are living and capable of subsequent further cell-division and growth in their abnormal situation, the patient is not cured of his disease. There is thus a very definite limitation to the possible employment of the modifying or alterative effect of radiation in the cure of cancer, and however valuable the effects of radiation may be in inhibiting or retarding the growth of cancer cells in palliative treatment, it is the destructive effect which must be obtained if we seek to cure the disease.

We must now consider the so-called "selective action" of radium upon tumor tissue. It is true that some of the benign lesions, like papillomas and keratoses, which yield to the "modifying" effect of radium, without a destructive effect, are of the class of so-called pre-cancerous lesions, but this does not give us reason to presuppose a similar reaction when dealing with cancer tissue. It is also true that variation in the sensitiveness of different tissues to radiation is a well-established fact. It is generally recognized that the lymph adenoid tissues and those of the ovary and testicle are especially sensitive to radiation. With these considerations in mind let us judge whether the actual experience in the clinic bears out the supposition that cancer tissue has a specific sensitiveness to radiation.

Certain tumors of lymph-adenoid tissue, such as malignant lymphoma (Hodgkin's disease) and lympho-sarcoma appear to exhibit a definite and positive sensitiveness to radiation in that when they are for the first time subjected to deep radiation profound changes in their structure take place—the tumor masses shrink and occasionally disappear, without undue damage to the normal tissues overlying the disease. In our experiences these changes are temporary rather than permanent, and although a recurrence of the tumor masses in the same or in other lymph-nodes may again react favorably to radiation, sooner or later the sensitiveness is lost, and the patient ultimately succumbs to the disease. In myeloid leukaemia, also, profound changes in the blood picture, in the size of the spleen, and in the patient's comfort result from deep radiation of the spleen; but, again, the improvement is temporary and is followed by recurrence of symptoms and ultimately death. These two diseases, although of a fatal character, are not really comparable to carcinoma but they are often invoked as evidence of a selective action of radium. This action, however, is one of modification of growth or even possibly of stimulation of certain types of tissue, rather than of a destructive effect, and the beneficial effects of treatment in both of these conditions are, as a rule, temporary—the disease is not cured.

The cells of the ovary and of the testicle are, again, notoriously susceptible to radiation. This subject has been studied more in relation to the x-ray than in relation to radium, but it is well known that ovarian function and menstruation can be brought to an end by intrauterine applications of radium, and with all the symptoms of the menopause. The condition of azoöspemia has also frequently been found in male x-ray workers, although there is reason to believe that recovery from this condition may subsequently occur when exposure ceases.

When cancer is superficial and accessible to direct radiation of any desired dosage either by surface applicators or by insertions, it can often be permanently destroyed. In no case of actual cancer, however, have we succeeded in this purpose without the production of a destructive lesion, and in many cases we fail to destroy the disease entirely, and at some subsequent time the disease recurs. In some cases, indeed, as when a basal-cell carcinoma involves the bones of the face, or a carcinoma of the

tongue extends into the tissues of the floor of the mouth, the cancer tissue appears to be more resistant to radiation than the normal tissues in its vicinity. In these cases, at least, no specific sensitiveness is manifest.

Advanced cases of cancer of squamous-celled or glandular origin which have extended to the regional lymph-nodes are frequently subjected to treatment with radium. The extension of carcinoma to the regional lymph-nodes is a familiar occurrence, and the enlargement of these nodes is commonly accepted as evidence of this extension having taken place. We must not forget, however, that other causes for enlargement of lymph-nodes exist, and it is not at all uncommon to see an inflammatory process in the regional lymph-nodes due to the ulceration of a primary carcinoma. Even in the presence of a certain amount of infiltration with cancer cells, inflammatory changes may occur and lead to fluctuations in the size of lymph-nodes far too rapid to be interpreted as due to cancer growth alone. In almost every fatal case of carcinoma of squamous-celled or glandular origin, extension of the disease to the regional lymph-nodes ultimately takes place. We have given radium treatment in a very large number of these cases, but in no case have we succeeded in destroying, permanently, the disease. It is true that shrinkage in size of an enlarged node is occasionally observed, but we are inclined to attribute this, when it occurs, to a change in the accompanying inflammatory process rather than to a destruction of cancer tissue. As a result of prolonged radium or x-ray treatment, areas of glandular involvement may further show a diffuse thickening of the surrounding connective tissues, and we have thought that a retardation of the progress of the disease may have occurred, but we have yet to see the permanent cure of any such case, and such improvement as is manifest may well be due in part, at least, to the stimulating effects of radiation on connective tissue growth rather than to any specific destructive effect on cancer tissue.

We have seen that cells engaged in mitotic cell division are generally believed to be more sensitive to radiation than resting cells. One of the characteristics of cancer tissue is the large number of mitotic figures present, as well as the fact that many of these mitoses are of an irregular or atypical character. The number of mitotic figures is indeed accepted as a

rough indication of the rapidity of growth of a given tumor, and thus an index of its degree of malignancy. Unfortunately, we have little accurate knowledge of the amount of time consumed in a mitotic cell-division in cancer tissue in the body, but it is not unreasonable to suppose that a part, if not the greatest part, of the supposed sensitiveness of cancer tissue to radiation is dependent upon the number of cells actually undergoing mitosis during the period of exposure. If this is so, a fractional destruction of the tumor only can be expected as a result of repeated deep radiation, for during each exposure only those cells in mitosis would be affected, and a diminishing but constant residue of unaffected cells would always remain to wake into activity and grow at some subsequent time, and produce recurrence. We must also recognize that there is abundant evidence that repeated exposures to radiation produce a gradual loss of sensitiveness on the part of the tissues exposed, so that the attempt to accomplish a fractional destruction of tumor tissue by deep radiation is by this fact, also, made more difficult. The clinical observations of the results of deep radiation on cancer tissue are in accord with this theory, for although inhibition or retardation of growth may be observed, the destruction of the tumor and the cure of the disease are not accomplished.

In general, we may say that experience in the clinic and in the laboratory has shown that the massive destruction effect of radiation (by direct application) is necessary for the cure of malignant disease.

While certain tissues show a sensitiveness to deep radiation, which is of value in the treatment of non-malignant diseases, and in the palliative (non-curative) treatment of malignant disease as well, the cure of cancer (estimated in surgical terms on a three- or five-year basis) is not accomplished without massive and total destruction of the tumor by direct application of the source of radio-activity.

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