THE RELATIVE RÔLES OF RADIUM AND ROENTGEN RAYS IN THE TREATMENT OF CARCINOMA OF THE UTERINE CERVIX

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In order to appreciate the relative rôles of radium and roentgen rays in the treatment of carcinoma of the cervix, the biologic reactions of tissues to the rays and also the physical properties of each type of radiation must be taken into consideration. From the standpoint of therapeutics, roentgen and radium rays in equal intensities produce the same biologic reactions and have the same physical properties. It has not yet been proved that there is any difference in biologic reactions between the two which might be dependent upon the quality of the rays (i.e., wave length) that cannot be explained on a purely physical basis. Really the only difference is that radium may be applied directly to neoplasms as a point source of radiation within the tumor or organ, while the roentgen rays must be directed from an external source and cover a larger field. Each, therefore, has its individual limitations and indications.

The biologic reactions which are produced by irradiation of neoplastic or normal tissues depend upon the intensity of the radiation with the added factor of the period of time over which irradiation takes place. The factor of time is important both from a clinical and physical standpoint; for example, small amounts of radium or roentgen rays over a long period do not have identical physical or biological effects as a large amount in a short time, and the histologic changes seen in the irradiated tissues are not the same under these two circumstances.

The normal skin has been taken as a biologic unit or standard of applied radiation intensity and as a basis for determining the biologic effects of radiation or for making comparisons of the reactions of tissues to different intensities. That intensity of radiation which will produce a redness of the skin in three weeks has been called a unit skin dose or an erythema dose. Thus when malignant tissues are irradiated, it is found by microscopic study after the period of reaction, that if less than 80 per cent of this unit skin dose has been given, there is little if any evidence of change. When as much as 150 per cent of this quantity is administered, there are changes which are manifested by endarteritis, increase of the fibrous tissue, and hyaline degeneration, but there is little direct permanent damage to the malignant cells, although some of them may eventually undergo starvation by the pressure of localized fibrous tissue. Much larger doses are required to produce marked fibrosis and degeneration of tumor cells by fragmentation of their nuclei. Hence, in order to eliminate malignant tissue by irradiation, it is necessary to administer a dose which is great enough to produce the

maximum effects on the neoplastic cells, and also cause sufficient reaction in the bed of tissue in which the neoplasm is growing. These manifestations of reactions in the neoplastic tissues are brought about by two factors: first, the direct destructive effect of the rays on the nuclei of neoplastic cells, and second and of equal importance, the reactions which are created in the tissue bed of the host. These reactions of the tissue bed are also brought about by two factors, the first being the normal physiologic response of the host to any degenerative process which may exist in the tissues and the second is the influence of the irradiation in altering the normal reaction to degenerative processes which are produced by the destructive effect of the rays.

The complex processes which make up the normal physiologic responses to neoplastic growths are not yet understood. The fact that such reactions do exist may be illustrated by a few examples of how the physiologic processes of the individual alter the course of malignant diseases. A young individual succumbs to a certain type of malignant growth while an older person with apparently exactly the same disease may survive for a long period. Then, too, a pregnant woman with carcinoma of the cervix or one with carcinoma of the lactating breast is doomed because her physiologic processes are producing a growth stimulus which also stimulates the growth of the malignant neoplasm. Also, when acute inflammation exists in or around a neoplasm, the influences which are established to resist the inflammation interfere with those restraining the growth of the neoplasm, which develops more rapidly than it would in uninflamed tissues. Therefore, in treating any malignant growth by irradiation, the physiologic processes of the patient must be considered. Treatment must be directed not only toward direct destruction of the neoplasm but also toward preserving and aiding the restraining influences which normally are present.

It has been found by experiments in vitro that there is a specific dose of radiation which completely destroys any malignant tissue but if less than this dose is given, there is a proportionately diminished effect. This observation is substantiated by the findings of changes which are produced by different intensities. For small doses, the changes are more or less transient with increasing degeneration and the production of fibrous tissue as the intensity of radiation is increased. However, these experiments with tissues in vitro do not explain the effects which are sometimes observed when malignant tissues are treated in vivo and when physiologic processes are exerting their influence on the neoplasm. According to the experimental evidences in vitro, the destruction of most carcinomatous tissue requires very large doses of radiation; however, every radiologist has had the experience of treating a carcinoma with a comparatively small dose, which he knows would be insufficient ordinarily, only to observe an astonishingly rapid disappearance of

the growth. On the other hand, the administration of very large doses which should ordinarily eradicate neoplasms may be entirely ineffective.

The clinical evidences of regression of neoplasms from obviously insufficient radiation are apparently contrary to the experimental evidence of their susceptibility, and indicates that influences may exist in the organism which have a restraining effect upon the growth of tumors.

The direct destructive effects of radiation upon neoplastic cells together with the effects produced in the tissue bed by the physiologic processes of the individual constitute what we term "radiosensitivity." Not all neoplasms have the same degree of radiosensitivity, because of the variation of their growth characteristics which are the result of the differences in the physiologic response of individuals as well as the specific influence of the origin and morphology of the neoplasm. There is no method by which radiosensitivity or the degree of malignancy of a particular growth can always be determined accurately, although systems of classification on the basis of histologic characteristics have been suggested by various workers and some progress is being made. Unfortunately, these methods must vary considerably according to personal judgment, not only as to the morphology of the neoplastic cells, their origin and their arrangement, but also as to the comparative degree of reaction in the tissue bed, the manifestations of which are the cellular infiltration and fibrosis. We have learned by experience rather than by experimental evidence that most carcinomas are quite resistant to radiation, and their elimination requires ten to fifteen times as great intensity as is necessary to cause a skin reaction. Since it is impossible to predetermine the radiosensitivity of any particular growth, it is still necessary in every case of carcinoma to administer the maximum dose that eliminates the average resistant growth and one that does not interfere with the normal physiologic response of the patient.

From the standpoint of the physics of radium, the rate of absorption in tissues of the average dose of radium which is administered to a carcinoma of the uterine cervix leaves only 13 per cent of the applied intensity at a distance of 5 centimeters. Thus if 10 erythema doses are given at the cervix, only one-half an erythema will reach outside the uterus. Therefore, although this dose of radiation may eliminate most carcinomas which are confined to the uterus, it will not be sufficient to eliminate disease in the parametria or deep pelvic lymphatics which are involved in almost every case. Also the absorption of roentgen rays in tissues is so great that little more than 40 per cent of the skin dose reaches the depth of the uterus, and even under the best of conditions, the total dose which can be administered into the pelvic cavity by cross-fire technic is seldom more than 110 per cent of the skin dose. Hence it may be seen on both a physical and a biological basis that

neither radium nor roentgen rays alone can be depended upon to eliminate malignant disease of the uterine cervix when the parametria or deep pelvic tissues are involved. Fortunately, radium and roentgen treatment may be combined so that the maximum of radiation intensity required may be applied rapidly or over a longer period according to the technic which is indicated or preferred. It is also obvious that, on the basis of knowledge of the physical effects of radiation and of the known biologic effects, a patient with carcinoma of the cervix who has been treated either by radium or roentgen rays alone and who has not had the combination of roentgen rays and radium has not had sufficient irradiation.

Before the development of the high voltage roentgen apparatus, our patients with carcinoma of the cervix were treated by radium alone. While the results were fairly satisfactory and encouraging in early cases, they were not much better than those obtained by surgical procedures. About ten years ago, the method was changed to a combination of radium and roentgen irradiation. A very intensive course of roentgen rays was administered immediately following the application of radium and in the shortest possible time. This procedure soon was abandoned because so many patients had the primary reactions of uncontrollable nausea and malaise followed by secondary reactions of anemia, cystitis, and proctitis, and it was believed that the clinical results did not warrant such drastic treatment. The next step was toward moderation and the technic now employed is to apply radium, using not less than 250 millicuries for approximately 3000 milligram hours, and three to four weeks later a course of roentgenotherapy is begun. I do not apply the roentgen rays to the cervix with the idea of administering a large dose in a short time, but of irradiating the pelvic cavity homogeneously and comparatively slowly with moderate daily doses in order to increase the fibrous tissue reaction in the parametria and in the deep pelvic lymphatics which are beyond the sphere of radium activity.

Not infrequently, patients are encountered in whom the disease has advanced so far that the possibility of applying radium is precluded. In this type of case, it is advisable to begin the roentgenotherapy first, and if the growth regresses, thus indicating its radiosensitivity, treatment with radium is administered which is followed later by another course of roentgenotherapy.

In those patients presenting clinical evidence of deep pelvic metastases and hopelessly advanced malignancy, and in those in whom previous treatment obviously has been inadequate, roentgen irradiation alone is employed as a palliative measure. In such instances the growth is retarded to some extent and pain usually is greatly relieved, especially if the treatment is given in moderate daily dosage over a period of two

to three weeks. The results in most of these cases are discouraging as far as the possibility of cure is concerned but, nevertheless, the treatment is worth while from an economic standpoint because many of these patients are thus enabled to go about their duties for some time before finally becoming bedfast.

Since the combined radium and roentgen technic in the treatment of primary carcinoma of the uterine cervix was adopted, the results secured have been more satisfactory, as indicated by the fact that from 10 to 20 per cent more patients are relieved than by the other procedures. A review of our series of 303 cases of primary carcinoma of the cervix, representing all degrees of involvement, treated between 1920 and 1931 inclusive, shows that 25 per cent of the patients are alive and free from evidence of disease for five or more years, and that 29 per cent of the group treated from three to five years ago also are entirely well.

It may be concluded that our efforts in treating malignant diseases by irradiation should be directed not only to employing radiation for its direct destructive effect upon tissues but also to encourage the physiologic processes which are established to restrain the growth of neoplasms. If radium alone is depended upon to treat carcinoma of the cervix, some patients with disease outside its range of activity will not be cured. Roentgenotherapy in the treatment of carcinoma of the uterine cervix should be employed as an adjuvant to treatment with radium in order to increase the quantity of radiation; it is also useful as a palliative measure in advanced cases. Patients with carcinoma of the cervix who have not had the benefit of combined treatment with radium and roentgen rays have been inadequately treated according to our present knowledge.