RADIUM IN CANCER THERAPY.*

BY

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THE decade just passed, during which radium has come into a prominent position, has been an extremely active and interesting one in the cancer field. This has been due, in part at least, to the fact that radium and its allied physical agent, the x ray, produce rapidly and readily demonstrable effects on neoplastic tissue. Cancer investigators have not previously had such a stimulus. In spite of the amount of investigation carried on for generations, improvement in cancer therapy was dependent almost entirely on technical surgical advances. Flurries of excitement have continued to centre transiently about alleged curative agents, usually of the constitutional type, but always with the same final result. The experience with radium and x rays, on the other hand, has been one of increasing confidence over a period of years. New tissue changes have been produced, the study of which continues to throw light on the intricate and complicated reactions, both histological and biological, within that maze of allied diseases covered by the term "cancer." Since most of the material for investigation has come through the treatment of patients, scientific investigators have been brought out from the dark recesses of the laboratory, and nearer, both figuratively and literally, to the practical clinical problems of cancer therapy. Even though the period of radium usage has been short, a great deal has been accomplished in very orderly sequence. The beginnings were made with small supplies of radium salt (frequently more of mesothorium than radium), meagre physical data, and no single treatment factor standardized. An empirical technique was established largely by application of the law of trial and error. Filtered applicators for surface use and for introduction within body cavities were developed. The need for guidance by the physicist was recognized in this formative period, and that assistance has been most generously given. Fortunately for the general problem the physicist's contributions, although becoming increasingly complicated, have nevertheless remained extremely practical. A serious effort has been made to meet the clinical necessities.

As standards of filter and dosage became established for surface contact applications it was evident from both clinical and histological observations that greater quantitative effect at depth was essential. For superficial lesions this was obtained by increasing the distance between the source of energy and the treated part, and by increasing correspondingly the quantity of energy delivered, according to the rule of the inverse square law. The quantities of radium available for use in most clinics at that time, however, were not sufficient to produce any marked effects at depth in bulky tumours of adult type or fully differentiated growth histologically.

In 1911 Stevenson of Dublin introduced an entirely different principle of radium therapy—one which has contributed largely toward the control of cancer as a local process since that time. By introducing a Dominici tube containing radium salt through a surgical incision as nearly as possible at the central point of the tumour, he initiated the principle of interstitial irradiation. The method was sound both physically and economically. Technical improvement in the method, designed to accomplish interstitial irradiation with a minimum of surgical trauma, found expressions in various ways. For the many small radium supplies the radium element needle of varying strength, size, and filter was the most practical solution. In some clinics, particularly on the Continent and notably at the Curie Institute in Paris, a larger type of needle with heavier filter and low radium salt content to permit of prolonged irradiation was preferred.

In America the clinics with sufficient radium supply to permit of a radium emanation collecting plant followed the suggestion made by Duane and initiated by Janeway at the Memorial Hospital in 1916—namely, the interstitial

implantation of glass capillary seeds containing radon. The practical collection and preparation of these seeds was made possible by the work of Failla,¹ who in 1924 replaced the unfiltered radon seeds by substituting a gold capillary tube. The filtered radon seed thus produced (0.3 mm. wall thickness of gold) had all the advantages claimed for the filtered radium element needles in addition to the extremely practical advantage of a wider range of applicability. It is the opinion of those who have had experience in the use of filtered radon seeds that they offer several advantages over element needles. The radon content of the individual seed may be varied to meet the peculiar requirements of the individual case. It can be inserted in many locations where element needles could not be retained with sufficient accuracy to permit of the desired prolonged irradiation. The accuracy of distribution in irregular tumour-bearing areas is greater than with the larger needles. The trauma of introduction is less on account of their smaller size. Since they are left *in situ* the trauma of withdrawal is eliminated. Their reaction as a foreign body is negligible. The period of active irradiation—approximately a fortnight—is sufficiently prolonged on the basis of our present conception of the efficiency of continuous irradiation. The advantages in conjunction with operative surgery and primary wound closure are obvious, since the seeds do not have to be removed.

With means available for more uniform and more intensive irradiation, the earlier influence of x -ray experience began to wane. The skin erythema, which had come to be regarded as an evidence of maximum irradiation intensity consistent with preservation of the normal tissues, has gradually assumed the status of a unit of radiation. Over a period of years there has been a gradual trend away from the skin erythema as a dosage limitation. It has come to be a measure of quantity provided only that the factors of the exposure are known.

The steady increase in the relative quantities of irradiation employed has been accompanied and encouraged by the improved clinical results. These advances must, of course, be shared with improvements in the quality of radiation used as well as the factors of time (period of exposure) and distance between the source of radiant energy and the part treated.

In more recent years the intensive histological study of tumour tissue before and after irradiation has contributed largely towards the advancement of radiation therapy. From the beginning, very definite changes were noted, but these centred mainly about effects on blood supply and the supporting structure of the neoplasm. The observations were sufficient to give some conception of the growth restraint produced. They explained the variation in response between widely differing types of tumours. They did not, however, explain the variations in response to comparable quantities of radiation in tumours of the same histological types. It remained for further studies in cellular pathology to clarify this.

Broder's work on the relative degrees of cellular differentiation in tumours of the same clinical and histological group not only explained the reason for many surgical failures, but incidentally many unusual reactions to radiation as well. While the histological grading of tumours on the basis of relative degrees of cellular differentiation must vary in different clinics, it is nevertheless of considerable practical assistance. Each group of workers must have its own conception of what is meant by a certain grade: one shades into the other. It is a piece of work which is scarcely capable of translation exactly from one clinic to another. Nevertheless, the principle is the same, and the differences in relative appraisal are not great. Information of this kind guides the clinician in determining the general character of the treatment to be given. Surgery is more apt to be resorted to in the fully differentiated tumour and avoided in the undifferentiated. The relative intensity of irradiation required varies inversely. The possibility or probability of metastases to be anticipated, and the ultimate prognosis, are judged to a considerable degree on the same basis.

The intensive histological study stimulated by radiation changes has made other contributions in the field of tumour pathology. New types, definite clinical entities,

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have been recognized. The transitional cell carcinoma which Ewing² has described (and the lympho-epithelioma of Schmincke³ and Regaud⁴) was formerly grouped with epidermoid carcinoma in general, or occasionally classed as a reticulum cell sarcoma until its peculiar radio-sensitivity resulted in its recognition as a type of epithelial tumour distinct both histologically and clinically. Endothelial myeloma of bone—Ewing's tumour—was recognized in the same way after the study of a bone tumour which showed a peculiarly rapid regression, followed by regeneration of bone after moderate external radiation. The large and varied group of soft part tumours of connective tissue origin formally passed over as fibrosarcomas, or spindle-cell sarcomas, is much better understood, owing to careful histological study in conjunction with irradiation. They present a wide variation in cellular structure, and a corresponding variation in radio-sensitivity. All gradations in relative radio-sensitivity and radio-resistance are recognized, and must be used as a guide in selection of type and intensity of treatment. The origin of the majority of this group of tumours from the nerve sheath has been one of the notable contributions of the study.

With the accumulation of reasonably accurate and suggestive information about radio-sensitivity from histological study and clinical observations it was natural to inquire further into the factors of quality and intensity of radiation necessary to produce the desired changes.

It is true that some of the most spectacular early results in radiation therapy were obtained by irradiation of low intensity with radium or α rays, and in such unstable tumours as lymphosarcoma and teratomas of the testis or ovary. The most impressive histological changes, however, were in the more adult types of growth, and in order to produce these changes interstitial irradiation with radium or radon was the agent used. When external radiation effects were studied, there appeared to be some difference in the reaction to comparable quantities of radium and α -radiation. The fragments of evidence available suggested the possibility of more desirable effects from external irradiation if radium in sufficient quantity was employed.

Observations at clinics, such as Kelly and Burnam's in Baltimore, and the Memorial Hospital, where radon packs have been employed for several years, lent support to this view. Regaud's⁴ method of prolonged distance radiation of low intensity also favoured radium as superior on account of the shorter wave-length of gamma radiation. Economic factors have, unfortunately, made it impossible to provide a sufficient number of large radium element packs, in order that adequate external distance radiation may be carried on without regard for the expenditure of energy or funds in large numbers of patients.

In those instances where adequate quantitative external radium radiation of maximum intensity has been possible, there is no doubt in the minds of the clinical observers of the superiority of radium over the most efficient α -radiation available to date. This has been the experience of the Memorial Hospital staff during fifteen years' use of a large radon pack, an experience decidedly strengthened during the past three and a half years with a 4-gram radium element pack. The total time of exposure undoubtedly contributed something toward this balance in favour of radium, but beyond this the main factor lies in the difference in *quality* of the radiation employed. When the economic difficulties have been overcome, or when shorter wave-lengths of α rays equalling the gamma rays of radium in quality are produced for practical use, a tremendous improvement in practical radiation therapy will result. The possibilities attendant upon total quantity per individual case, optimum period of total exposure, distance from source of energy to treated surface, and daily ratio of delivery of the radiation have not as yet been touched.

It is only in this one field of external distance radiation that there has been any appreciable overlapping of radium and α rays. Unfortunately, the number of cancer sufferers who have had the advantage of a superior quality of radiation, made possible by the extravagant use of large quantities of radium, represents only a negligible per-

centage of cancer patients in general. In large measure the immediate advantages of this form of radium usage are academic rather than real. The experience, however, points the way to more efficient radiation for the future. It is hoped that means will be found to provide large quantities of radium for more general use. It is hoped, also, that the experience already accumulated in favour of shorter wave-length gamma radiation will stimulate the engineers engaged in α -ray research and manufacture to provide equipment for α -radiation which will approach in quality the gamma rays of radium. All of the available radium is needed for the type of application to which it is physically best adapted—namely, for interstitial implantation, and for use in various applicators within body cavities. α -radiation should be the agent for external long-distance application—as it now is—but it ought to be of greater efficiency.

Viewed in this light it is apparent that there is very little practical overstepping or duplication in the fields of radium and α rays; the two forms of radiant energy are very similar physically except for a difference in quality. The character of the source of that energy in each instance governs the adaptability. Radium is an agent for use over or within localized tumour-bearing areas; α rays are for use over large surfaces. The two agents are complementary and not competitive. Further, there is evidence in favour of the combined use of these two agents beyond that of simple physical adaptability. Clinical and histological observations have been made on the difference in reaction with comparable quantities of the two types of radiation. Clinical observations have been made on the improved therapeutic reactions where the two have been combined. The experimental work of Quimby and Pack⁵ has shown that when the two types of radiation are employed together and in equal quantitative ratio, the skin tolerance, as judged by threshold erythema, is increased by 20 per cent. or more.

It is only recently that serious consideration has been given to the accurate study of the quantities of radiation delivered within the tumour-bearing area necessary to produce complete regression of tumour tissue. Accuracy and standardization at every turn is essential if we are to develop a technique and dosage which may be depended upon to control a given type of growth and with a minimum of damage to adjacent normal structures. Preliminary dosage was of necessity empiric. Many factors enter into every dosage computation: the character and quantity of energy in the applicator employed; the time of exposure; the filter; the distance from source to area treated; the relative distance of points on the periphery of the tumour from the radiation source; the character of the tumour bed; the type of tumour and its degree of relative cellular differentiation.

With variations in each of the factors it was evident that any efforts toward greater accuracy and standardization must begin with one only. At the Memorial Hospital, Martin and Quimby⁶ undertook a study of the quantity of radiation necessary to produce complete regression of various types of epidermoid carcinoma. A series of cases of intra-oral epidermoid carcinoma, in which complete regression of growth had been produced, was selected. The histology of the growths was carefully re-checked for type and relative degree of radio-sensitivity; the size of primary growth and metastatic nodes, if any, and the relative relationship of one to the other were noted. The component parts of the radiation dose— α -radiation, external radium, and interstitial radon—were calculated physically in terms of threshold skin erythema doses within the tumour-bearing area. In order to do this, for irregular-shaped growths particularly, it was necessary to translate the volumes into spheres or a series of smaller spheres, depending upon the shape of the growth, to get the dosage intensity at the most remote point of the tumour. The intensity recorded was the minimum intensity at this most remote point. Obviously a considerable portion of the growth received a good deal more than the recorded dose. From a study of this series of cases it was found that an intensity of seven to ten skin erythema doses at all points within the tumour-bearing area was necessary to produce complete regression

of adult epidermoid carcinoma. Growths showing a lesser degree of differentiation, such as transitional cell carcinoma and lympho-epithelioma, required a much lesser intensity—three to five skin erythemas.

The tendency in these doses, selected empirically and on an experience basis only, was to overdose the smaller growth and to underdose the larger. When a series of failures were measured in the same way, the reason for failure, in most instances, was only too apparent. The failure to provide dosage of sufficient intensity in the more bulky growths or in outlying areas accounted for most of the losses. The next step was the application of the data thus obtained to the treatment of cases. A series of cases of varied histological type were treated by calculating the dosage to begin with in terms of a certain number of skin erythema doses. This intensity was determined on the basis of the histology and the experience gained from the studied series. The method of delivery of this dosage was directed by the physicist on the most economic basis— x rays, radium externally, or by interstitial implantation. The results in this series corresponded with the findings in the cases studied in retrospect. It was found possible to depend on the result of treating a given area by this means of dosage calculation, providing the measurements and clinical evaluation were correct and the technique of treatment, especially radon implantation, was accurate. It might well be added that control of local infection on ulcerating surfaces is essential if this or any other type of irradiation therapy is to be counted upon. Doses for these cases in the last series, determined empirically and on an experience basis, did not vary more than 10 per cent. from the doses found necessary on the basis of measurement and physical and mathematical calculation.

The work has demonstrated very conclusively that adult type epidermoid carcinoma requires seven to ten erythema doses throughout the tumour in order to ensure its complete control, and that the undifferentiated types require at least one-half of this intensity. This is of the utmost practical importance. It not only explains the failures in bulky growths of this type where interstitial radiation was used, but too sparingly, but it indicates the futility of expecting complete control of epidermoid carcinoma by external irradiation alone in all except the most anaplastic growths at least, with the present facilities and methods for external irradiation.

The maximum dosage that can be delivered by external radiation within the oral cavity during a two- or three-week interval with our present equipment, either x -ray or radium, and consistent with the tolerance of the patient, is, at most, three skin erythemas of the intensities to which reference has been made. Very few of the epidermoid carcinomas fall in the group sufficiently radio-sensitive as to be completely cleared up by three erythemas. Consequently, interstitial implantation in some form is imperative if clinical cure is to be accomplished by irradiation.

With such data available it is unfortunate to see so many radiologists continuing to treat epidermoid carcinoma of the mucous membranes—the most common type of epithelial tumour—with x rays alone or, worse, with x rays and small plaques of radium on the surface.

The most effective treatment of cancer by radiation methods is too complicated a problem for the radiologist to shoulder alone. The same is true of the relationship of the clinician to the general management of the cancer patient. The assistance of the pathologist and physicist is necessary in determining the treatment rather than when the therapeutic procedure, whatever it may be, has been carried out. The problem is one for group study throughout. The best interests of the patient are served where the surgeon, working in co-operation with the pathologist and physicist, is thoroughly familiar with radiation, and thus combines the necessary operative surgery with the radiation therapy. A more orderly and conservative co-ordination is thus attained than by transferring the patient from one department to another. If this is not possible, there should at least be the maximum of contact and co-operation between surgeon and radiologist. The majority of cancer cases require in their total round of treatment, surgery, radium, and x -radiation. The more closely this is correlated the better.

With the information—clinical, physical, and histological—accumulated to date to guide us, it seems proper to inquire into its practical application in radium therapy. At least, the limitations of radium application are better understood. From a physical standpoint the intensity of irradiation is limited by tissue necrosis; as a cauterizing agent radium is not justifiable. Technically, the anatomical and physiological problems which limit operative surgery apply also in large measure to radium. Damage to large blood vessels and nerves must be avoided. In the upper abdomen, physiological problems attendant upon intensive local irradiation require study before anything may be hoped for through the combination of operative surgery and direct radium radiation. In spite of the benefits to be derived from radium therapy, it must not be forgotten that it is a local agent. The constitutional character of the later stages of cancer limits its use. For the most part, palliation in such cases is a medical and an x -ray problem.

In the major groups of neoplastic diseases the specific value of radium varies widely, and its usefulness is dependent upon many factors. Distinction must be made between efforts at cure and palliative relief only. If a reasonable hope for clinical cure can be entertained, the maximum of intensity, even though painful for a period, is justifiable and desirable. If palliation only is the object, the patient's comfort from day to day demands first consideration, and the type and intensity of irradiation should be governed accordingly. Radium may represent the sole therapeutic agent in certain instances, or it may be only an associated aid in others. Even within the individual groups the adaptability varies with the degree of growth advancement and the accumulated experience of radio-sensitivity or radio-resistance.

The distinction between relative radio-sensitivity and curability should be clearly understood. The most radio-sensitive tumours are those showing the minimum of cellular differentiation: they melt away rapidly under heavy or even moderate external irradiation. They also are of the type which disseminate early, widely, and usually through both lymphatics and blood stream. While the local process may be readily controlled, the tendency to generalization is such that the percentage of ultimate curability is very low. It is also of interest that subsequent and repeated metastases show a progressive lessening in the degree of response to irradiation. The patient's general physical resistance is of course deteriorated, but, added to this, the later metastatic processes show a tendency toward differentiation and are hence more radio-resistant. While the primary, fully differentiated epidermoid carcinoma is most difficult of all epidermoids to control, the result, once attained, is assured of a far greater permanence than in the more radio-sensitive undifferentiated types. Real curability is greater in the more radio-resistant types.

Rules for guidance in making the finer distinctions in choice of therapeutic procedures cannot be laid down. Appraisal of the many factors entering into the decision is, in the final analysis, a matter of experience, preferably co-operative group experience. Whether that group represents a special clinic or simply a cancer service within a larger organization depends upon the local and individual circumstances.

Skin cancer, unless extremely advanced or altered in its tumour bed by repeated recurrences, is by choice a radium problem. In all except the most superficial lesions, heavily filtered radium at distances of one to three centimetres gives best results. The wider zone of tissue radiated prevents recurrences at the border. The penetration at depth is greater; the scar is much better because of the lesser amount of fibrosis. It is more adaptable to localized application than x rays, and superior to thermic or electro-cauterization because of the wider zone of tumour bed affected.

With carcinoma involving the mucous membrane of the mouth, nose, and throat, the problem is much more complicated. The growths are predominantly epidermoid carcinoma—a metastasizing tumour involving chiefly cervical nodes. A variety of anatomical structures may become involved. Infection may play a major part by

discounting the normal reaction to irradiation, and by contributing to secondary necrosis of tissue. Problems of surgical drainage arise. Invasion of bone or cartilage by tumour tissue or infection, or both, may add to the complications. Interference with the taking of food or with breathing may arise. Procedures for treating cancer under such varying circumstances differ, of course, in the various clinics. These variations in procedure may depend upon the basic premisses accepted in the individual clinic, or be governed by the treatment facilities available.

At the Memorial Hospital external radiation—radium or α rays, or both—is employed over both primary growth and cervical lymph nodes in all cases. Radium, in the form of filtered radon by interstitial implantation, is depended upon for control of the primary growth. Infection and tumour invasion of bone within the mouth or sinuses is a surgical problem. The cervical nodes are left to external radiation unless palpably involved. The palpably involved node of adult type epidermoid carcinoma, unilateral and with intact capsule, is treated by complete unilateral neck dissection, plus radon implantation within the wound in such fashion as to irradiate heavily any suspicious areas. Bilateral involvements or nodes with perforation of the capsule by growth are treated by a combination of operative surgery with radium—surgical exposure under local anaesthesia and filtered radon implantation. The metastatic nodes of undifferentiated growths are treated by irradiation entirely, even though technically operable. Direct radon implantation is usually indicated, and to facilitate this surgical exposure is resorted to. The treatment of intra-oral cancer affords the best and most varied example of the value of combining operative surgery and radiation in meeting the needs of the individual case.

In some clinics with a limited radium supply, the practice of removing the primary growth surgically, usually by one of the cautery methods, and following this by radium needle applications, is prevalent. From experience with radon implantation plus surgical removal in certain instances to overcome deep-seated infection, it would seem desirable to reverse the order of that procedure. The condemned area might well be utilized as a radium needle holder, the growth devitalized before operation, and the adjacent tissues substantially irradiated preliminary to surgical traumatization.

With extrinsic laryngeal cancer, treatment by irradiation, external and interstitial, is the only resource, except for the few highly radio-sensitive growths where α rays alone in maximum dosage may be sufficient to produce complete regression. If broad surgical principles are adhered to, all of these growths are inoperable. Intrinsic laryngeal cancer presents a different picture. A certain percentage of these growths are surgically operable. The anatomy of the parts facilitates removal by total extirpation of the larynx. Metastasis rarely occurs until late in the course of the disease. Under such circumstances the selection of treatment procedure becomes a matter of preference. In our clinic radium is employed through choice. In the majority of cases direct radon implantation, following heavy external irradiation, is carried out through the exposure by laryngotomy—again an example of combining a conservative operative procedure with irradiation for the purpose of greater technical accuracy.

Continuing, the mucous-membrane-lined tract downward into the bronchial tree, oesophagus, and upper gastro-intestinal tract, leaves much to be desired from all forms of treatment, especially radium. Few growths lend themselves to interstitial implantation anatomically, and the hazards of infection are great. A considerable degree of palliative relief has been produced in these areas through the growth restraint induced by external radium or α -radiation. Further benefit lies probably in technical improvement of the methods of external radiation, except possibly in cancer of the upper gastro-intestinal tract. This field ought to claim the sympathies and ingenuity of a master gastro-intestinal surgeon, willing to forgo some of his preconceived ideas, inform himself of the fundamentals of irradiation therapy, and thus combine forces in a new approach.

In the rectum and lower bowel much has already been accomplished both curatively and palliatively by intensive irradiation with and without surgical co-operation, and as indicated by the special features of the individual case.

Cancer of the female pelvic organs is extremely interesting radiologically. In the treatment of cancer of the cervix uteri radium has achieved its most notable success. It is the agent of choice. The involved part is extremely tolerant of heavy irradiation; it is relatively insensitive to pain; it is accessible. Histologically, more than half of the growths are of the plexiform epidermoid type, showing a relative lack of cellular differentiation and hence radio-sensitive. Historically, it is interesting to note that the gynaecological field was one of the first to employ radium, and this vision and courage on the part of a few pioneer gynaecologists did much to advance radium therapy to the position which it now occupies.

Carcinoma of the corpus uteri differs from the cervix growth in histological type, in anatomical relationships, in accessibility, and in its mode of extension and dissemination. Radium undoubtedly fills a useful place in early questionably malignant lesions and in advanced questionably operable cases. In the intermediate, well-established group, however, hysterectomy is the method of choice.

These two types of growth in the same organ afford a clear-cut and nice distinction in the choice of a treatment method.

Growths of the external genitals, male or female, are for the most part epidermoid carcinomas, and hence are subject to the same general principles of treatment as epidermoid carcinoma elsewhere. The same is true of bladder cancer, except for its inaccessibility. The papillary type of epidermoid carcinoma predominating in the bladder is relatively radio-resistant, so that heavy irradiation dosage is necessary for its control. In spite of this, direct exposure by suprapubic cystotomy and direct filtered radon implantation is preferable in most cases to the various operative procedures advanced.

Cancer of the prostate may yield completely to interstitial irradiation; in any event a variable degree of growth restraint may be brought about. Radium is, in general, the agent of choice, not because of the brilliance of the results, but because it accomplishes at least as much and affords greater palliation with less hazard than operative measures.

Cancer of the breast represents one of the largest groups of malignant disease. The histological types and variations are numerous. Fat predominance in the tumour bed is not duplicated elsewhere. Metastasis, whether by direct permeation of lymphatics or by showers of vascular tumour emboli, is early. The tendency toward generalization of metastatic involvement is much greater than is ordinarily thought to be the case. Metastatic extension beyond the axilla is not only surgically inoperable, but is so deep seated, as well as generalized, that it is radiologically inaccessible. Breast growths, as a group, are relatively radio-resistant, not only on account of their histological structure, but because they tend to infiltrate adjacent fat tissue. An active radiation reaction is difficult to produce in fat tissue, probably because of the limited blood supply and the tendency toward fat necrosis under the influence of heavy irradiation. In spite of these discouraging factors, radiation has contributed much to the treatment of the breast group. For widespread irradiation, α rays are obviously the agent of choice. For localized applications externally or for implantation, radium has its place.

Pre-operative and post-operative irradiation is accepted as of distinct value; the former is preferred. Questionably operable cases and breast cancer in the aged are better treated by irradiation than by operative measures. The strictly operable group is thus sharply limited. The palliative benefits of irradiation in breast cancer are probably greater than in most other groups. The benefits of radiation are not limited, however, to palliation only. The group of clinically cured cases, treated by irradiation only, is steadily increasing. In certain instances this has been accomplished by heavy, prolonged external treatment. For the most part, however, it has been in conjunction with some form of interstitial irradiation. The measure-

ment of dosage intensities by Lee and Pack, following the plan employed by Martin and Quimby in their dosage intensity calculations for intra-oral cancer, suggests the need for greater relative intensities in breast cancer than in mouth cancer. They have demonstrated at the same time that these required doses of intensities, well beyond ten erythemas, can be carried through practically. Their minimum standards of intensity have not yet been determined, and it may be found that a very considerable percentage of the cases respond to a much lower relative quantity of irradiation.

In the lymphatic, glandular, neoplastic, and pseudo-malignant diseases—lymphosarcoma, Hodgkin's disease, and leukaemia—radium may be useful, and is occasionally of real value for some specific reason. In general, however, the widespread character of the involvement lends itself best to treatment by α -radiation. The treatment is palliative only.

The bone tumour problem is as discouraging as it is fascinating. Radiation has made but two distinct contributions, attributable alike to either α rays or radium, or both. Giant-cell tumours of bone are curable by external irradiation. The peculiar response of endothelial myeloma of bone to radiation led originally to its recognition as a definite clinical entity, and irradiation has remained the treatment of choice. The tendency to early and widespread dissemination of this growth, however, renders cure extremely doubtful. The true osteogenic tumours of bone are extremely radio-resistant, and radium has done nothing more than afford a moderate degree of palliative relief and growth restraint.

"DECEREBRATE RIGIDITY" IN MAN.

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At the outset we wish to point out that, although the title of "Decerebrate Rigidity" in Man has been given to this short paper, we have made the publication rather to encourage interest and observation in this subject and to relate a very interesting clinical case than to record a detailed clinico-pathological study; for, from this latter point of view, our records are incomplete.

As Walshe⁶ points out, the variety of clinical features already included under this designation indicates that there has been no clear guiding conception of what a very definite condition true decerebrate rigidity is, and the term bids fair to become a vague label including all obscure forms of tonic spasm in a category which has a thoroughly false air of scientific precision.

Experimental Decerebrate Rigidity.

Since Sherrington⁷ detailed his experimental results of transection of the brain stem of animals and described the resulting picture of "decerebrate rigidity" or "reflex standing," there has been considerable difference of opinion as to what clinical picture constitutes its counterpart in man.

Experimental decerebrate rigidity occurs when the greater part of the anterior portion of the brain is removed by a coronal section through the hinder part of the mid-brain, in a plane bounded dorsally by the posterior limit of the superior corpora quadrigemina and ventrally by the region immediately caudad to the corpora mammillaria. This section cuts off the greater part of the red nucleus from the body; if the transection passes above the red nucleus, the muscle tone remains normal. Rigidity persists as the plane of the transection passes caudally through the pons and medulla to the level of entry of the acoustic nerves and Deiters's nucleus. Thus the brain stem centres responsible for decerebrate rigidity clearly lie in the pons and medulla.

Summary.

1. Radium has made a notable contribution and has added stimulus to the general problem of cancer investigation.
2. Since it is an agent for local application only, it must not be regarded as an ideal cancer cure.
3. It has, however, increased the curability of cancer.
4. It has reduced the limits and the severity of many operative surgical procedures.
5. It has supplanted some surgical operations entirely.
6. It has relieved operative surgery of the responsibility for attempting the unreasonable or impossible, as a frantic effort, in a large and varied group of cases.
7. It has made possible a larger measure of palliative relief in advanced cancer.
8. Advancement in radium therapy depends upon the intensive co-operation of pathologist, clinician, and physicist.
9. The technical problems of application and dosage intensity must be calculated and made with the greatest possible care and precision.
10. The combination of radium emanation, α -radiation, and operative surgery offers far more in the average case of cancer than adherence to any one agent alone: they are complementary, and not competitive.

REFERENCES.

- ¹ Failla, G.: *Amer. Journ. Roentgenol. and Radium Therapy*, xx, No. 2, August, 1928, p. 128.
- ² Ewing, James: *Amer. Journ. Path.*, March, 1929, v, No. 2, p. 99; *Amer. Journ. Roentgenol. and Radium Therapy*, February, 1926, xv, No. 2, p. 95.
- ³ Schmincke, A.: *Beitr. z. Path. Anat. u. z. allg. Pathol.*, 1921, lviii, 161.
- ⁴ Regaud, C.: *Compt. Rend. Soc. de Biol.*, 1912, lxxii, 523.
- ⁵ Quimby, E. H., and Pack, George T.: *Radiology*, 1929, xiii, p. 306.
- ⁶ Martin, H. E., and Quimby, E. H.: *Amer. Journ. Roentgenol. and Radium Therapy*, 1930, xxiii, No. 2, p. 173.

In this experimental decerebrate rigidity there is a great increase of tonus in the extensor group of muscles, with reflex inhibition of tonus in the antagonistic flexors in accordance with the laws of reciprocal innervation. On being suspended, the animal hangs with its fore limbs thrust backward, with retraction at the shoulder-joint, straightened elbow, and some flexion at the wrist. The hand of the monkey is turned with its palmar aspect somewhat inward. The hind limbs are straightened and thrust backward; the hip is extended, the knee very stiffly extended, and the ankle somewhat extended. The tail is straight, horizontal, or stiffly curved upward. There is a little opisthotonos of the lumbo-sacral region, and the head is kept lifted up against gravity. Sherrington regards this rigidity as reflex standing—the result of release or removal of inhibition of the postural reflex; it can be abolished by section of the appropriate afferent posterior nerve roots.

Decerebrate Rigidity in Disease.

The problem is to ascertain what is the counterpart in man, in a physiological sense, of this experimentally produced rigidity.

Kinnier Wilson¹³ has carefully analysed and recorded conditions—the results of cerebral haemorrhage, meningeal inflammation, or intracranial tumours—in which there has been, coupled with the impairment of consciousness, tonic rigidity of the trunk and limbs. He considers that these clinical pictures minutely resemble experimental decerebrate rigidity. In many of these cases frequent exacerbations are superadded in the form of tonic or postural fits, accentuating and exaggerating the background of tonic posture. The cases fall into three groups: (1) decerebrate rigidity (or attitude) and tonic fits combined; (2) cases of decerebrate attitude without tonic fits; (3) cases of tonic fits without persisting decerebrate attitude. Hughlings Jackson⁵ described attacks of rigidity in cases of cerebellar tumour. Many of these cases showed also tetanus-like seizures, in which the patient exhibited opisthotonos with extension of the lower extremities and flexion of the upper extremities, but he considered that the causation of the two conditions was different. In Wilson's opinion the involuntary postures of a limb or segment of a limb in many forms of nervous disease, as well as the transient positions assumed in involuntary movements such as chorea and athetosis, are in reality simply parts of the complete decerebrate attitude.