A Paper ON THE TREATMENT OF CANCER OF THE RECTUM WITH RADIUM.*

BY

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RADICAL surgery for cancer involves some mutilation of the human body. The appeal which radium makes to both surgeon and patient is the hope of a cure without disfigurement.

In the case of the tongue, the larynx, the breast, this appeal is outstanding. Much has been accomplished to substantiate the claims of radium *versus* surgery in these situations, though they are not yet so firmly established as to be unassailable.

If radium treatment of rectal cancer can be raised to the same level, and if it can supplant radical surgery, it must be able to cure the disease without a permanent colostomy and to leave a rectum which can function. This ideal, though possible in certain instances, as I have shown, is a long way off. Nevertheless it is one to be aimed at, and justifies intensive research. It is generally recognized that the present methods of radical surgery for cancer of the rectum in its early stages cure a high percentage of cases, but they involve the stigma of colostomy.

SPREAD OF CANCER OF THE RECTUM.

The recent work of Dr. Cuthbert Dukes[1] on the spread of cancer of the rectum suggests that it is not necessary to excise the rectum completely and establish a permanent colostomy for an early carcinoma which has not penetrated the rectal wall. Dr. Dukes has shown on histological evidence, based on a hundred consecutive specimens of excised rectums, that lymphatic invasion does not occur until the growth has penetrated through the longitudinal coat, and, further, that the line of spread is in the main to the retrorectal space and upwards along the superior haemorrhoidals. So far as this series of cases can be relied on to represent the average, the lines of lateral and downward spread along the middle and inferior haemorrhoidals are negligible. These observations, if confirmed in a further series of cases, are of the utmost importance, and have an important bearing on treatment either by irradiation or by radical surgery.

LOCAL RESECTION FOR EARLY CARCINOMA.

If the growth can be removed freely by some form of local resection and the rectal passage maintained, this method may be justified on histological grounds, whether or not a temporary colostomy is required. The view, which has held ground for twenty years or so, that, however early the carcinoma, complete removal of the rectum and perirectal lymphatics is essential, must be reconsidered, and the methods of thirty years ago may perhaps be reintroduced.

Acting on these views, I have treated the last three cases of quite early mobile carcinoma of the rectum by local resection, one without a colostomy and two with a temporary colostomy. Time alone will show whether this procedure, based on histological evidence, is justified by ultimate results. It may be mentioned here, however, that the results of Harrison Cripps over twenty years ago, and Grey Turner in more recent years, show that end-results of operations, less radical than now usually considered necessary, are remarkably good.

Can radium treatment of an early carcinoma compete with a local resection which aims at avoiding a permanent colostomy? These three cases could have been dealt with quite easily and thoroughly by interstitial irradiation. Two of them were amenable to vaginal irradiation and the other to posterior barrage after resection of the coccyx. That these were not so treated, in spite of some successes in similar cases, is due to the fact that it was impossible to give any promise that radium would be successful.

IRRADIATION OF AN EARLY GROWTH.

Sufficient evidence has been obtained in my series of cases to show that an early growth of the rectum can be destroyed with radium without colostomy (or with a temporary colostomy) and without interference with the function of the rectum, though no observations are available, on a five-year basis, as regards recurrence. If, however, local resection with little or no immediate mortality, and without permanent colostomy, should replace radical excision for similar cases, it would be difficult to advocate radium in preference, because experience shows that adenocarcinomas vary considerably in radio-resistance and in their response to radiation, and so, unfortunately, the result which may be anticipated with radium in any given case cannot be predicted.

The ultimate result as regards function of the rectum after irradiation of a growth varies according to the degree of fibrosis which results, and whether a fibrous stricture follows or not. The smaller the growth dealt with the better the prognosis as regards stenosis. Small growths can be destroyed with little or no deformity of the lumen. The degree of fibrosis depends also on variations in reaction. An overdose may cause necrosis and excessive fibrosis with resultant stricture, but a correct dose may secure a perfect anatomical result. When this happens, new epithelium grows over the irradiated area, and it may be difficult on digital examination to recognize any abnormality of the lumen beyond a slight projecting ridge.

Alterations in the lumen of the rectum result from local resections, and fibrous strictures are very liable to follow, unless great care is exercised in avoiding sepsis during healing, and unless any tendency to stricture is checked by careful dilatation during convalescence. Thus, if a local resection is preferred to treatment by radiation, it is not certain that a permanent colostomy can be avoided.

When the operative risks of radical excision as distinct from local resections are considered, especially in cases where the risks are above the average, the arguments in favour of radium are more worthy of consideration. If adenocarcinomas, like squamous-celled carcinoma of the tongue, can be graded, as they have been by Broders, into radio-sensitive and radio-resistant, the arguments in favour of radium in selected cases may be enhanced.

Furthermore, if research should reveal some method of sensitization which can be relied on, there will be a wider field for the use of radium in preference to surgery. At the present time the number of cases dealt with in this class does not justify a too dogmatic opinion. The result in any given case depends on the delivery of an optimum dose, which is dependent on the correct amount of radium, the correct distribution, the correct filtration, and correct time of exposure.

Several unexpected failures have been encountered in the irradiation of early growths. Fortunately, in most instances, these failures can and have been made good by radical surgery, but unless it can be shown that preoperative radiation increases immunity against recurrence, patients so treated may have cause for complaint. Until a much larger series of early cases comes under review it is reasonable to assume that unexpected failures (such as two apparently similar growths treated on supposed identical lines, responding in one case well, in the other badly) may be explained in part by some error in technique, and not entirely by variation in radio-resistance.

TREATMENT OF AN OPERABLE GROWTH.

A small operable growth in the rectum below the peritoneal reflection and clear of the anal canal can, if it involves the anterior or lateral wall in the female, be attacked through the vagina. In the male the best approach is from behind, after removal of the coccyx. The rectum can be mobilized, so that the growth becomes accessible whether posterior, lateral, or anterior. The same approach is employed for the female if the growth is posterior. If the growth, though small, has commenced to ulcerate there is a risk of lymphatic spread; whether

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the posterior or vaginal route is employed the retrorectal space should be radiated.

If a very small growth is encountered and found to be malignant, and the mobility of the growth is such that it can be freely mobilized from the muscular wall, it may be treated with some confidence by the introduction of intrarectal seeds without surgical exposure and without glandular attack. Nevertheless, local resection without colostomy offers in all probability a more certain cure.

During the past five and a half years, up to the end of June, I have treated 121 cases of cancer of the rectum with radium. The majority of these have been regarded as inoperable, but lest it should be supposed that radium has been preferred to surgery, when surgery was indicated, it may be mentioned that over sixty cases have been submitted to radical surgery during the same period, and a considerable number have been submitted to colostomy *only*, owing to the presence of secondary visceral deposits.

A few quite small early carcinomas have been treated by intrarectal seeds, or by vaginal irradiation with needles, with complete success, and without colostomy. Others, more advanced but still operable, have been apparently cured either by a posterior barrage or by vaginal irradiation, or a combination of the two, some with a preliminary colostomy and others without.

On the other hand, as already stated, some of the operable cases which seemed to offer every prospect of cure have responded indifferently, and have been submitted to excision at a later date. Undoubtedly, some adenocarcinomas are more resistant than others. The rapidly growing adenocarcinoma in a young person is more radio-sensitive than a slow-growing growth in an elderly patient, and is also more liable to recur after resolution.

The number of cases definitely regarded as operable which have been submitted to radiation is too small, and the length of time that these have been under observation is too short to enable me to form any very definite opinion as to end-results. Excellent results have to be set off against unexpected failures, and at the present time it seems impossible to predict the immediate result in any given case. Even in those patients who remain well without colostomies, and with apparently healthy rectums, the question of future recurrence is still *sub judice*, and on a less secure foundation in all probability than after a local resection.

Difficulties.

The obstacles to efficient irradiation are:

1. *Anatomical Difficulties.*—In the case of the tongue or breast it is comparatively easy to secure a complete barrage of the growth; the outlines are visible, and the lymphatic areas are reasonably accessible. In the case of the rectum, unless the growth is small and low down, there are great obstacles to a complete barrage both of the growth and of the lines of lymphatic spread.

2. *Radio-resistance.*—Experience seems to indicate that columnar-celled carcinoma is more radio-resistant than other types. Anatomical difficulties are no doubt responsible in some measure for the failures recorded and for the unfavourable views which are held on the radio-resistance of this type of growth. My experience leads me to believe that the dosage required to secure complete retrogression of columnar-celled carcinoma is very near the margin of tolerance of the healthy tissues. Consequently radium burns are difficult to avoid and beta-radiation must be reduced to a minimum.

Filtration.

Most of my work has been done with filtrations of 0.5 or 0.6 mm. platinum. Recently I have been using 0.8 mm. in some cases, and I intend, when an increased supply is available, to use only this filtration for rectal carcinomas for the present. If necrosis results, perforation of the rectal wall and sepsis are liable to follow, and even if a cure follows, the period of convalescence is a very long one. By increasing the filtration so that all primary beta rays are excluded, it is possible to employ a much larger dose of radium than with either 0.5 or 0.6 mm. filtration without risk of necrosis.

I like to leave the radium in for ten days in the hope that every cancer cell will be exposed to radiation of a constant intensity during a period of mitosis. Uniform intensity cannot be obtained with radon; this is a great disadvantage in the use of seeds, which in other respects have so many technical advantages.

Effect of Chronic Sepsis.

It sometimes happens that an operable growth which has been treated without a colostomy retrogresses up to a point and then appears to remain stationary owing to chronic sepsis. This is illustrated by the case of a woman with a growth on the anterior wall of the rectum treated at St. Mark's by vaginal irradiation without colostomy. Response was inadequate, and a second treatment was carried out by vaginal irradiation both with needles and with intrarectal seeds two months later. No apparent appreciable change followed after three months, and I excised the rectum. Dr. Dukes reported that in his opinion the case would have been completely cured if it had been left a little longer, because there was practically no carcinoma active and the few carcinoma cells found were disintegrating. The general microscopic characters were those of a chronic inflammatory ulcer. Before treatment a section showed that the growth was a typical adenocarcinoma. It is probable that this case would have been cured with radium in reasonable time if a colostomy had been done in the first instance.

Reaction of Rectal Growths to Radium.

One of the disadvantages of radium treatment combined with surgery consists in the length of time (often two months and more) which these growths usually take to retrogress and disappear. While evidence of growth remains, there is uncertainty as to the end-result. When all visible growth has gone, a varying amount of fibrosis remains. Uncertainty as to whether any growth remains in the interstices of these fibrous nodules cannot be avoided.

Further, when operative exposure from behind has been the method employed, the wound usually takes as long to heal or longer as compared with a radical excision. A long operative convalescence can be patiently endured if the prospect of cure is assured, but not so if the prospect remains uncertain throughout.

For the early accessible growth there is much to be said for vaginal or intrarectal (or perirectal) irradiation without surgical exposure. If this fails, surgery can follow without delay. Healing is not inhibited after irradiation, provided that the interval between irradiation and operation is not long enough to allow marked fibrosis and consequent diminution of blood supply.

It seems impossible to avoid the conclusion that with the experience available the results which may be anticipated are too uncertain to justify preference for radium to surgery *for the operable case* involving the perineal portion of the rectum (exclusive of anal carcinoma), unless surgery is refused or contraindicated on general grounds.

The operable cases which have been considered so far are the early carcinomas situated below the peritoneal reflection which are easily accessible to interstitial irradiation on the one hand and to local excision on the other.

Two other classes of operable growths remain for consideration: (1) Those which are above the peritoneal reflection and must, if treated surgically, be submitted either to perineal or to abdomino-perineal excision with colostomy, or, if treated with radium, cannot be satisfactorily dealt with except by transperitoneal attack. (2) Operable cases of squamous-celled carcinoma of the anus.

Supraperitoneal Growths.

During the past three years I have employed radium (both needles and seeds) by the transperitoneal route: (*a*) to barrage the upward line of lymphatic spread along the inferior mesenteric vessels at the same time as colostomy is performed as a preliminary to radical excision; (*b*) to attack the fixed inoperable growth which is situated above the peritoneal reflection, or to deal with the upper part of a growth which lies partly above and partly below

the peritoneum; (*c*) to attack an *operable* growth above the peritoneum in a patient who is considered too old or too unfit to stand an abdomino-perineal excision, and whose growth is too high for perineal excision.

Transperitoneal irradiation is a far more risky procedure than perineal irradiation. Radium causes a variable amount of inflammation of the peritoneum, often with effusion of fluid in the area attacked, and if this area is not protected from the small gut and drained there is a risk of paralytic ileus and general peritonitis, or of adhesions. Further, if the lumen of the bowel is penetrated by a needle and a track is established between the lumen and the peritoneal cavity as the result of radium necrosis, there is a considerable risk of general peritonitis.

Experience has shown that the use of radon seeds within the abdomen causes much less disturbance to the peritoneum than radium needles, and is a safer procedure, but so far the end-results have not been so encouraging. In my experience this observation applies to most other regions treated with radon. The radon seeds can be left *in situ*, and have not apparently caused any harm. The removal of the needles often calls for a second anaesthetic.

(*a*) The use of radium within the abdomen as an adjunct to radical surgery seems rational, but it is not possible at the present time to assess its value. When colostomy is performed as a preliminary to perineal excision, the liver, meso-rectum, meso-sigmoid, and iliac regions are first examined. When no glands are detected and the growth is freely movable and obviously an early one, radium is not used. If glands are palpable, radon seeds are inserted along the meso-rectum beside the glands. If no glands are felt, but the growth is more advanced, though considered operable—that is, a borderline case—the mesentery is barraged. Seeds containing 1 millicurie, filtered with 0.5 mm. of platinum, are usually employed within the peritoneum and are not removed. A certain amount of plastic inflammation follows, and radium (or radon) should not be used if an abdomino-perineal or an abdominal resection is contemplated afterwards.

(*b*) The use of radium within the abdomen to attack a growth in the upper part of the rectum or the lower portion of the sigmoid when the growth is regarded as inoperable is certainly justified, if only by one excellent result in which a growth attached to the bladder and fixed to the sacrum was successfully treated with radium needles. This patient remains well and free from all symptoms nearly three years after treatment. His bowels act normally; no growth is visible; he has no colostomy. Several similar cases have been helped enormously and the lives of these patients undoubtedly prolonged by the use of radium combined with colostomy. In some of these cases the growth does not completely retrogress but becomes quiescent, and the patient gains in weight, improves in general health, and is personally much impressed with the benefits received.

(*c*) The cases treated by transperitoneal radiation and regarded as operable (*qua* the growth) have been, with one exception, regarded as too old or too unfit for radical surgery. None of these has been under observation long enough or shown sufficient evidence of retrogression to suggest a cure.

Squamous-celled Carcinoma of the Anus.

This condition stands on a somewhat different footing to adenocarcinoma of the rectum. Early cases which have not infiltrated deeply into the ischio-rectal fossa, surrounded the anus, or invaded the inguinal glands, can, I think, be promised an immediate initial cure with interstitial radiation, combined, in some instances, with surface radiation. The question of permanent cure cannot yet be answered. So far results in these cases have been excellent, with one exception, in which recurrence followed an apparent cure. This was the first case of the kind treated (1925). Recurrence occurred wide of the original growth, and it is probable that the periphery of the growth was inadequately irradiated.

There are distinct advantages in the use of radium in these cases over surgical excision. Radical removal of an anal growth involves removal of the sphincters and a colostomy, whereas with radium, in most early cases, complete restoration of rectal function can be secured and a colostomy avoided. I can state with confidence that a squamous-celled growth involving the anal canal should be treated with radium in preference to surgery, at any rate in the first instance.

THE INOPERABLE CASE.

Individual standards as to operability vary, so that the borderline case cannot be defined, but there is general agreement in defining the advanced inoperable case—the large fixed annular growth which has infiltrated through the rectal wall in all directions.

How far can these cases be helped with radium? We all recognize that in the absence of liver metastasis both the general and the local condition of the patient improve in the majority of cases after a colostomy has been performed. If colostomy is followed by irradiation, it may not always be easy to say whether the improvement is the result of irradiation or colostomy, or both. My experience has shown, even in cases which have been submitted to colostomy some time previously, that rapid and marked general improvement follows irradiation, even in the absence of any marked local changes. In a small percentage of these cases the growth ceases to be active, and if it has been effectively barraged it is destroyed and transformed into a fibrous stricture. In one such case the patient remains well and free from evidence of growth four years after radiation.

The outstanding problem is to secure adequate and uniform radiation. To effect this a combination of methods is often necessary, and frequently more than one treatment is required.

At the time of colostomy, if the growth extends above the peritoneal reflection, it is essential to treat this portion from the abdomen either with radon seeds or with radium needles; the former is safer, and the latter I think more efficient. The meso-rectum is treated at the same time. Subsequently, if the growth is also infraperitoneal, this portion is dealt with in a variety of ways, according to the extent and situation of the growth, either by posterior barrage, vaginal irradiation, intrarectal seeds, or by a combination of these methods, sometimes with the assistance of the intrarectal tube.

Very large and advanced growths should not be dealt with by the posterior open operation. The risks of perforation and secondary sepsis are considerable, and the prospects of cure too remote. These cases often get great relief from perirectal and intrarectal attack. I have described these methods fully elsewhere.[2]

One example of combined treatment may be cited.

A masseur, aged 36, came under observation in October, 1928, with a very large annular cauliflower growth, which was mainly infraperitoneal and completely filled the rectum. It was evident that growth had been very rapid. The patient had quickly lost weight and looked very ill. Colostomy was performed and abdominal irradiation with needles was applied to the upper portion of the growth; three weeks later perirectal radium needles and intrarectal seeds were used, the total dose of the combined treatment being 11,000 odd mg. hours. Ten weeks later the anterior portion of the growth was given another 4,000 mg. hours with seeds introduced through the skin.

At the present time, more than 18 months after treatment, the patient is remarkably well, having gained several stone in weight. The rectum is extensively fibrosed, and it is not possible to say if any growth remains.

The prognosis of a rapidly growing cauliflower growth in a man of 36 is extremely bad, and I am certain that this patient would not be alive and well to-day without radium.

Conversion of Inoperable into Operable Growth.

In several instances an inoperable case has been treated with radium with such marked improvement that a radical excision has been carried out subsequently. I may mention two cases in which a perforation through the posterior vaginal wall was present at the time of irradiation. In both cases the perforation healed, the growth becoming smaller and less fixed. Both patients are in good health after excision, and one has survived four years.

THE BORDERLINE CASE.

In view of these experiences it would seem that the borderline case—that is, the doubtful case as regards radical operation—provides a useful, perhaps the most useful, field for irradiation. A cure may result from irradiation, or the local condition may be so improved that radical surgery becomes possible.

RECURRENCE FOLLOWING RADIATION.

In all branches of surgical irradiation it happens, unfortunately, that cases of apparent cure relapse, or that a tumour shrinks to small proportions and then resumes active growth. Such results no doubt will become less frequent with increased experience. So far as my own experience goes, a recurrence is more likely to follow the use of radon seeds than needles; it is probable that the diminishing intensity of radon, as opposed to the constant intensity of radium, is the causal factor. It may be possible to overcome the factor of diminishing intensity by reinforcement—that is, by adding additional radon seeds at short intervals, which can be done in certain situations, especially when general anaesthesia is not required. Another method is to combine intrarectal seeds with perirectal needles, a method which minimizes the loss of intensity, though it does not give a uniform intensity. In several instances, when retrogression of the tumour has appeared to be complete (or nearly so) and recrudescence has followed, irradiation has been repeated (in a few cases more than once), but in most instances the result has not been very satisfactory.

Without doubt, primary irradiation increases radioresistance to secondary radiation. Relapses following apparent success become more noticeable as the number of cases increases. It is evident that if we are to make further advance we must improve technique and explore the possibilities of radium in combination with x rays, lead selenide, etc., more fully.

CONCLUSIONS.

1. In young people, in increasing ratio from the age of 40 downwards, rectal carcinomas grow rapidly, metastasis occurs early, and the end-results of radical surgery are not good. An actively growing carcinoma in a young subject responds well to radium, and far better than a slow-growing carcinoma in an elderly subject. End-results in comparison with surgery are not available.

2. If a growth is adequately barraged with radium and shows little evidence of retrogression after two months, it is probably useless to repeat irradiation. On the other hand, if the growth responds to radium and readily retrogresses, though it fails to disappear completely, further irradiation is indicated on the ground that the dose has been insufficient in respect of amount, time, or distribution.

3. Secondary irradiations are less likely to produce a good final result than an adequate primary irradiation, and are more prone to produce pain of a neuralgic type, which may be very severe and last for long periods.

4. When the growth has been exposed by open operation, an overdose may result in perforation of the bowel with secondary sepsis, and when healing takes place be followed by excessive fibrosis and consequent stricture.

5. The criteria of a correct dose are absence of sepsis, a well-marked radium film, rapid resolution of growth, restoration of normal epithelium, and limited fibrosis.

6. Radon is less efficient than radium, but is valuable within the abdomen and within the lumen of the rectum.

7. Apart from the possibilities of cure, radium has its value in improving both the local and the general condition of an inoperable case, so that in some instances operation with prospect of a cure becomes possible. In cases of local recurrence it is an asset of great value, especially if the recurrence is treated early. It gives hope to those who are beyond surgical help, and in moderate doses has a remarkable tonic effect on the general health.

8. For epithelioma of the anus radium is in all probability more efficient than surgery.

9. The treatment of cancer of the rectum with radium is still in the nursery stage. Time will show whether selection, combined with increased experience and skill, will vastly improve results in radium therapy, or will reveal that radium is too capricious a master and too seldom a servant to be reckoned with as a serious fighting factor in the campaign against cancer.

Research on radio-resistance and methods of sensitization is an urgent need. It is not enough to say: "Here is a cancer of the rectum; let us excise it or let us use radium." We must have an index of sensitivity and a corresponding dose index, and we must develop a technique that allows no uncertainty in the application of the indicated dose. For help on these lines we must look to the physicist, the biochemist, and the pathologist.

When we consider how long it has taken to develop the high technical standard which now exists in abdominal surgery—so high that Lord Moynihan has said we can hardly hope to advance it much further—we ought not to be downhearted. Medicine in recent years has advanced by leaps and bounds because the biochemist has come to the aid of the physician. Is it too much to hope that the "big five"—medicine, surgery, pathology, biochemistry, and physics—will by team work enable the radium worker to conduct his practice on a strictly scientific basis rather than empirically?

We must not be blind to the fact, however, that radium is no panacea for cancer. It has very definite limitations, which need emphasizing. We know that brilliant results can be secured with radium in a small percentage of cases. Can we doubt that further research, increased experience, better technique, and greater skill will reduce the failures and add to the successes?

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RADIUM AND SURGERY IN CANCER OF THE TONGUE.*

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CANCER of the tongue embraces one of the largest groups of epidermoid carcinoma. For the purpose of discussing this common form of tumour process it may well be taken as illustrative of practically all types.

Anatomically, growths of the tongue range from the most superficial papillary outgrowing processes to the deeply infiltrating neoplasm, with little by way of surface manifestation to call attention to it before it is entirely out of bounds. Depending upon the location, it may be most accessible or it may be practically impossible of technical approach. When cancer is superimposed upon chronic inflammatory processes, notably leucoplakia, luetic glossitis, or both, the anatomical changes may be such as to alter the normal course and type of growth, and to present added complications from the therapeutic standpoint as well.

Practically every histological type of epidermoid carcinoma is encountered in the tongue, from the papillary squamous-cell growth to the invasive infiltrating tumour of like cellular structure, and from the fully differentiated adult type to the totally anaplastic transitional cell structure. Tongue cancer is influenced by all of the various factors of dental and oral hygiene. The chronic irritation of irregular teeth or dentures is a well-recognized contributory cause in the development of lingual growths. The bacterial flora of the ill-kept mouth exerts a profound influence on the otherwise normal course of a growth, if, indeed, it does not actually contribute towards its development.

There is a consensus of opinion that tongue cancer affords an average cross-section of therapeutic results in comparison with intra-oral cancer in general. It is the purpose of this communication to emphasize particularly two points: (1) the combined use of radiation and operative surgery offers several advantages in the treatment of

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