Observations

ON

FIFTY CASES OF CARCINOMA OF THE CERVIX
TREATED WITH RADIUM.

BY

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NATURE OF THE RESEARCH.

In June, 1921, the Medical Research Council offered to lend St. Bartholomew's Hospital 324 mg. of radium bromide, to be used solely for the purpose of research.

The hospital authorities gladly accepted this offer, and formed a Radium Committee, which decided that one of the investigations to be carried out should be "the study over a prolonged period of the clinical and pathological changes produced by the action of radium, applied locally, in cases of carcinoma of the cervix." The object of the present paper is to record the results of the work done in this connexion during the last eighteen months.

In carrying out this research, both as regards clinical and histological observations, it was decided not to attempt more than to record the changes produced in the local condition and in the chief clinical symptoms, together with those histological changes which were easily recognizable and lent themselves to more precise classification.

Irradiation of Cervix.

Radium.—The radium available consists of the following:

(1) Two platinum tubes with walls 0.5 mm. thick containing respectively 53.1 and 54.2 mg. radium element. The outside dimensions of the tubes are 4 mm. in diameter and 34.8 mm. in length.

(2) Thirteen platinum needles with walls 0.4 mm. thick, each containing on the average 5.1 mg. radium element. The average outside dimensions of the needles are 1.8 mm. in diameter and 23.5 mm. in length.

(N.P.L. measurements corrected for platinum containers.)

The two tubes, filtered with aluminium, are placed end to end in the cervical canal, and the thirteen needles inserted into the cervical tissue at some distance from the canal and in a circle round it. On a few occasions, the needles before insertion were dipped into sterile Indian ink and allowed to dry. This procedure serves to leave a mark along the track of the needle.

Dosage.—The cases are divided into two series. In the first the quantity of radium element varied between 133.3 and 173.6 mg. radium element, the duration of exposure being eight hours. In the second, with one exception, the amount of radium element was 173.6 mg. and the duration of exposure was twenty-four hours.

Filters.—The filters employed in the case of the tubes consisted on most occasions of (1) a platinum container, which is 0.5 mm. thick; (2) a covering of aluminium; in the case of the needles, on all occasions the platinum container, 0.4 mm., was the only filter.

Sterilization of Radium and Filters.—This was carried out by boiling, the use of soda being avoided.

Irradiation of the Iliac Glands.

To this end the technique of Daels (of Ghent) was employed. For details of this operation, see a short paper written by one of us (M. D., *Proceedings of the Royal Society of Medicine*, 1922, pp. 67-70.)

HISTOLOGICAL INVESTIGATIONS.

Method.—In undertaking the histological investigations it was considered essential to examine sections of the growth before irradiation and as often after irradiation as circumstances would permit, so that comparative observations could be made from time to time. Owing to the anatomical situation of the lesions there was no difficulty in obtaining at frequent intervals fair-sized portions of the material for examination in the form of "snippings." Further, we

were able to obtain from some of these cases the whole uterus, appendages, and glands by operation, or, as in two cases, at autopsy.

Technique.—Formalin was employed for fixation in the earlier cases, but later Zenker's fluid was substituted. Efforts were directed to placing the material in the fixative as soon after it had left the body as possible, and to cut it up into as thin slices as could conveniently be made. Sections were embedded and cut in paraffin, the usual technique being employed. As a routine staining, haematoxylin and eosin were used, but where special nuclear detail was required, the sections were stained with iron haematoxylin.

Results of Histological Examination.

In order that we might arrive at conclusions with the least possible bias, we made a careful analysis of our protocol, which was compiled without preconceived ideas as the sections came to hand.

I. Eight-Hour Series.

The observations in this series were made on cases examined at different times from one to sixty-two weeks after first irradiation (see chart); the majority of cases having more than one such application, and the dose varying between 133.3 and 173.6 mg. of radium element. The series comprises 14 cases of squamous-celled carcinoma. Of this number, 9 were examined both before and after treatment and are included in the chart. Growth was present in 8 after irradiation, and in the remaining case of the 9 (No. 8) a few cells of doubtful nature were found. Of the 5 not included in the chart, 2 were not examined before irradiation, and 3 did not present themselves for examination after treatment.

The material after treatment was obtained by hysterectomy in three (Nos. 5, 13, and 15) and at autopsy in two (Nos. 1 and 6), and by snippings in the remainder. Seven out of the nine received one irradiation before the second observation, and two (Nos. 2 and 8) received two irradiations, one of the latter being the case in which the only possible evidence of carcinoma was a few cells of doubtful nature.

Characters of Growth and Surrounding Tissues.

Certain of the main characters of the growth are mentioned here for comparison with the twenty-four-hour series, and will be found in more detail under that heading.

Cell Division.—In this series, 5 cases showed mitosis after irradiation; in 2 of these mitosis appeared more abundant than before; in 2 other cases mitosis had apparently disappeared after irradiation.

Large Nuclei.—These were seen in 3 cases, in one of which they were present before irradiation.

Small Round-celled Infiltration.—This was always found at the spreading edge of growth before and after irradiation, except in one case (No. 15) where it was absent after treatment.

Fibrosis.—This is not a marked characteristic in this series.

Encapsulation of new growth was not found in this series.

II. Twenty-four-Hour Series.

The observations were made on cases examined at different times up to forty-nine weeks after irradiation. The full quantity of radium was given on almost every occasion, the number of applications being two or more in the majority of cases (see chart). The series consists of 34 cases of squamous-celled carcinoma and 2 of columnar-celled carcinoma (Nos. 47 and 54), in which sections were taken both before and after irradiation. In addition, there were 2 cases in which no sections were taken before irradiation; and in 3 cases no sections were taken after irradiation, and thus are of no histological value.

In the 34 cases of squamous-celled carcinoma we were unable to find any growth after treatment in 22, and found growth in all stages of degeneration in the remaining 12. Two of these latter, however, contained bodies, for the most part structureless, but which appear to be the remains of new growth cells.

Twenty-two Cases in which no New Growth was found in the Cervix after Treatment.

From these the material was obtained by hysterectomy in 7 (Nos. 26, 27, 34, 36, 37, 45, 57), sections being cut at different levels. Four of these 7 cases were irradiated twice before the hysterectomy was performed, and 3 were treated once only before operation. In the remaining 15 cases, the material was obtained by "snippings"—in 14 cases after one irradiation, in one case after two irradiations.

Twelve Cases in which Growth was present in the Cervix after Treatment.

Growth was found to be present in 12 cases, but, as will be seen later, the amount of growth was considerably reduced. Further, the general microscopic appearances of the growth differed markedly from that of the original, and in some cases it was barely recognizable as such (Cases 22, 23, 33). All these 12 cases, with 3 exceptions, received one irradiation. Of the 3 exceptions, one (No. 24) received two doses before the second observation was made, the other 2 cases (Nos. 33 and 48) received one dose before the second and third observations respectively. Of these 12 cases, the material was obtained by hysterectomy in 4 and by "snippings" in 8.

Characters of Growth and Surrounding Tissues.

After irradiation, cases have been observed on the first day (that is, at the time of removal of radium), also on the second, fourth, and seventh days, and henceforward at varying intervals up to forty-nine weeks.

In the sections taken on the days immediately following irradiation considerable changes were noted. In some cases these were more marked than in others, probably owing to the proximity of the source of irradiation. In a section taken immediately after removal of radium the appearances were not dissimilar to those in the section taken before treatment—namely, normal mitotic figures were present in small numbers, and degenerate mitoses were occasionally seen. In a section taken on the third day, mitotic figures were much more numerous, normal prophase and metaphase were frequently seen, together with undoubted mitoses showing an irregular arrangement of chromosomes and occasionally multipolar-spindle figures. These changes were still more marked on the fourth day, when there was hardly a cell which did not show abnormalities of one kind or

another. These abnormalities consisted of (a) Abnormal mitosis, (b) Necrosis, (c) Increase in size of the cell.

(a) *Abnormal Mitosis.*—No normal mitoses were seen; almost 50 per cent. of the cells showed absence of nuclear boundary and of these a large number showed degenerative mitoses. Prophase was occasionally seen, metaphase was abundant, but the later stages of division were not observed. Multipolar division was present, though not frequent, but cells showing granular and fragmented chromosomes were seen in large numbers. Some of them showed well formed spindle figures, but others showed only occasional scattered threads, the nature of which was doubtful, and we were unable to decide whether these latter cells were undergoing mitosis or were in a process of dissolution, especially as the

cytoplasm of some of them was broken into droplets. In other cells, the chromosomes had almost entirely disappeared, the spindle figure alone being seen.

(b) *Necrosis.*—In some areas the tissue as a whole had undergone coagulation necrosis, there being complete loss of power to take up nuclear stain, while the general structure of the tissue was maintained. These areas, we believe, were in close proximity to the radium.

(c) *Increase in Size.*—The remainder of the new growth cells showed some increase in size compared with those in the original growth, and further, their nuclei were enlarged.

Later Changes.

From the seventh day onwards no mitoses of any kind were observed, an observation which would seem to be of considerable importance. The nuclei appeared to be broken up, the chromatin being distributed in the cytoplasm as droplets or irregular particles;

in some cells, however, nuclear staining was no longer visible. After the first six weeks breaking up was less frequently seen, but when it did occur the nuclei occasionally assumed irregular and angular outlines, staining indifferently and unevenly, their appearance being more like that of an inorganic than of a biological substance.

In certain cases observed at a still later date the nucleus was no longer distinguishable, but masses of unorganized material, often concentrically laminated, were seen. These masses usually take up haematoxylin to a moderate extent. They are stained deep blue by a well matured Nile blue solution and red with mucicarmine, especially with regard to their outer laminations.

CHART OF HISTOLOGICAL CHANGES.																													
Case No.	Weeks after First Dose—																												Method of Obtaining Section.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	...	49			
<i>Squamous-celled Carcinoma : 8-hour Series.</i>																													
1												(X)																P M	
2																												P	
4						2																				0 ₃		S	
5	0															(X) ₃												S	
6																												S	
8		(X)																										P M	
13	(X)		2																									S	
15	0																											H	
16											(X) ₂																	S	
<i>Squamous-celled Carcinoma : 24-hour Series.</i>																													
14																												S	
17																N ₂												S	
18																												S	
20																												S	
22																												S	
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56																												S	
57																												S	
<i>Columnar-celled Carcinoma : 24-hour Series.</i>																													
47	X																											S	
54						X			X																			H	

N.B.—Some cases are omitted from the above series because the patient refused further examination, and a few because no section was obtained before treatment.

Explanation of Signs.—O = No change found. (X) = Slight changes found. X = Marked changes found. [!] = Growth scarcely recognizable. N = No growth found. P M = Section obtained post mortem. H = Section obtained from hysterectomy. S = Section obtained from snipping. The small figures 2 and 3 denote date of second and third doses respectively. For amount of radium used see text.

Large nuclei were observed in 3 cases and were usually accompanied by a great increase in the amount of cytoplasm. They were deeply staining and had irregular and often "blurred" outlines. Although such nuclei are occasionally observed in untreated growths, and were undoubtedly seen in one of these cases, yet there is no question that they occur much more frequently after irradiation.

Small round-celled infiltration to a greater or less amount was always found before irradiation at the spreading edge of the growth or between the finger-like processes. In sections taken nine weeks after treatment it was still found, but later than this was no longer present. It is remarkable that the absence of small round-celled infiltration seems to correspond with the presence of the later type of nuclear change mentioned above.

Polymorphonuclear cells were usually found in a breaking down core of a growth, whether it had been irradiated or not. They were seldom seen at the spreading edge of the growth, except in relationship to an ulcerated surface. Occasionally polymorphonuclear cells were seen included in a new growth cell before irradiation, but on three occasions, varying from three to five weeks after treatment, this intracellular invasion was a prominent feature.

Fibrosis was found to be increased in all cases after treatment, especially near the position previously occupied by the radium, as shown by the Indian ink preparations. In the early stages there is a greater number of fibrous tissue cells between the muscle fibres independently of the proximity of new growth. As time continues muscle strands are less frequently met with and may be seen separated by masses of fibrous tissue fibrils. In the later stages no muscle at all, nor nuclei of any cells, are seen, but the micro-anatomical structure of the uterus and its vessels—the latter being by this time thrombosed—is to be seen formed of a quantity of dense fibrous tissue in which relatively few elastic tissue strands are incorporated.

Encapsulation.—There was little or no attempt at the formation of fibrous capsules round the growth before irradiation. This was also the rule after irradiation in those cases observed before the eighth week; but in five cases observed on six occasions—at the eighth, ninth, tenth, fifteenth, and forty-ninth weeks respectively—there was a definite sheath of fibrous tissue encircling the growth islets. It is not clear whether this formation is a purposeful reaction on the part of the tissues or whether it is simply a mechanical arrangement of the fibres. It is to be noted that this period corresponds with the later type of nuclear change, and with the absence of small round cells.

Columnar-celled Carcinoma.

Columnar-celled carcinoma was found in two cases of the 24-hour series. These were irradiated on one occasion only before hysterectomy. Growth was found in these two cases five weeks and nine weeks respectively after irradiation. In both cases the amount was much reduced, and in the second case to such an extent that it was only found in small isolated islets after several sections had been searched. The changes were of a similar nature to those found in the squamous-celled carcinoma.

ANALYSIS OF CLINICAL RESULTS.

A concise presentation of the clinical aspects of the cases seems to the authors to be a matter of some difficulty, for while a complete clinical note of each case might be of great value to those who are directly interested in irradiation, yet this is so cumbersome that it was considered that an analysis would be more acceptable to the majority of readers.

The analysis is based upon the effect of irradiation on the four cardinal signs and symptoms—that is, haemorrhage, discharge, ulceration, and induration—and also upon the effect on the length of life and general comfort of the patient, so far as can be estimated at the present juncture.

As the immediate object in view is to show the effect of irradiation on the cervix, those cases in which hysterectomies have been performed are necessarily omitted from this analysis, but are included in the histological investigations.

Analysis of 8-hour Series.

Reviewing first the 8-hour series, we find that there were 14 cases treated, and of these 5 had hysterectomies performed, leaving 9 inoperable cases for analysis, but detailed information of subsequent history could not be obtained from 3 of these.

Length of Life.—Of these 9 cases, 2 (Nos. 4 and 3) have been treated for twenty and eighteen months respectively, and are still living. One of these cases (No. 4) is extremely well, and able to do her daily work; in her own words, she "has taken on a new lease of life." On vaginal examination it is found that the walls have become densely adherent, making it impossible to see the cervix. Per rectum there is some thickening to the left and to the front of the rectum. It is doubtful whether this is fibrous tissue or new growth. This patient, however, was found to have a fresh nodule of growth in the vagina after fifteen months. This was treated with 66.3 mg. of radium element for 24 hours, and at the same time deep irradiation was done by Daels's method. The second patient (No. 8) was very much improved for fifteen weeks, but is now not doing well, and when last heard of was rapidly going downhill. Of the remaining 7, 1 lived three, 1 sixteen, and 2 nine months respectively; 1 died of septicaemia within a few weeks of the insertion of radium, and 2 were notified as having died about four months after treatment began.

Haemorrhage.—Of the 5 cases in which this symptom was noted, haemorrhage ceased entirely after treatment in 4, and in 1 the amount was diminished.

Vaginal Discharge.—This cleared up entirely in 1 case, and was diminished in 4.

Ulceration.—This cleared up entirely in 2 cases, was diminished in 2, and remained the same in 1.

Induration.—It is always difficult to gauge how much of the induration present is growth and how much fibrous tissue caused by infection or as a result of treatment. In no case has the induration entirely cleared up, but in 1 case it was markedly diminished, in 2 somewhat diminished, in 1 somewhat increased, and in 1 remained the same.

Summary.—Two cases were decidedly improved, 2 cases slightly improved, in 4 cases there was no alteration, and 1 case died shortly after treatment.

Analysis of 24-hour Series.

Reviewing now the 24-hour series, one finds that 41 cases were treated, and of these 13 had hysterectomies performed, and 2 of the remaining cases have been treated so recently (within three months) as to be of no value in discussing results. This leaves 26 inoperable cases for analysis in detail.

Of these 26, 10 have died, 1 could not be traced, 15 are still living after periods varying from four to sixteen months, and in 7 of these treatment was commenced more than twelve months ago. Of these 15, 4 are deserving of special remark. One (No. 49) was treated with deep x rays by Dr. Finzi after one application of radium. Another (No. 23) is extremely interesting. After one application, she was considered to be too advanced for further treatment. It was, therefore, a very great surprise to find that six months later she had entered another department of the hospital and had undergone an operation for gall stones. Some months after the treatment she developed a vesico-vaginal fistula, the edges of which are at the present time composed of healthy-looking epithelial tissue. She is still alive more than twelve months after treatment and appears to be in good health. One case (No. 21) is still living after sixteen months, and feels extremely well; the local condition shows the vagina walls to be somewhat adherent, but on separating these the cervix is revealed as an atrophied nodule of fibrous tissue. There is some induration in the fornices. Another (No. 17) has been under treatment for thirteen months, is extremely well, and doing her daily work. Of the remaining 11, the majority were markedly improved for a time, but some now seem to be on the downward grade. Of the 10 who died the term of life after treatment varied up to fourteen months. In nearly every case the patient had a considerable amount of growth in the parametria.

tissue and glands, which in 2 cases caused intestinal obstruction.

Haemorrhage.—This symptom almost invariably yields to treatment, and we find that it usually ceases within a week or so of the first irradiation. It ceased entirely in 22 of the 25 cases; in 2 others it was absent for a time but recurred. In 1 case it was diminished.

Vaginal Discharge.—In 11 cases discharge disappeared entirely; in 2 it ceased but recurred, and in 12 it was not diminished.

Ulceration.—In 10 cases ulceration cleared up entirely; in 2 it disappeared entirely but recurred; in 6 cases it was diminished, but never entirely disappeared. No change took place in 7 cases.

Induration.—Induration was markedly diminished for a time in 1 case. This was the one referred to above, which was treated by Dr. Finzi by means of deep x rays. Induration was slightly diminished in 3, markedly increased in 3, and not altered in 17. In 1 case it was markedly diminished for a time but increased later.

Summary.—Of the 25 cases traced, 13 are still living, and 3 remain well after more than a year. Definite improvement was made in 13 cases, slight improvement in 10; in 1 treatment seemed to have no beneficial effect whatever, and in 1 pain was actually increased.

DISCUSSION OF RESULTS.

The present-day knowledge concerning the action of irradiation and results hitherto published appear to the writers to be quite inadequate to justify any discussion as to the relative merits of this form of treatment as compared to operation, and the majority of people in this country agree that at present radical operations should be performed for carcinoma of the cervix wherever that procedure is possible, whether or not irradiation is employed in addition. Nevertheless, the most optimistic of surgeons cannot but deplore the small number of cases that can be said to be cured, considering the prevalence of the disease. It is therefore essential that we should no longer resign ourselves to this hopeless state of affairs, but should investigate fully any method which offers hopes of bettering the present conditions. It must be remembered that the treatment by irradiation is, comparatively speaking, in its infancy, and therefore, in spite of the promising nature of the results so far obtained, we must not, at present, expect to effect permanent cures. As has been seen, certain changes, such as the local disappearance of the growth, cessation of haemorrhage, diminution of discharge, and healing of the ulceration, have been observed, striking differences having been noted between the 8- and 24-hour series. These facts promise to be of value in helping to discover the laws governing the biological effect of irradiation, without the knowledge of which it is extremely improbable that any true progress in the treatment is likely to result.

Histology.

Before discussing the histological results in detail, it is necessary to bear in mind certain preliminary considerations.

First, it is usual to find in untreated carcinoma a greater or smaller number of cells undergoing degenerative changes; but whilst it might seem that these changes would vitiate the conclusions arrived at on the effect of the irradiation, yet a careful comparison of the sections before and after treatment will leave no doubt that these are due to the radium.

Secondly, a series of "snippings" in any one case may differ from one another, because the conditions of sepsis, blood supply, distance from the situation previously occupied by radium, and relation of surrounding tissues are not the same for each successive piece taken. Nevertheless, if all the changes observed trend in the same direction, it is impossible to believe that they are due to any such chance causes. Further, in the 8-hour series no striking differences were observed after treatment, except in one case, whereas in the 24-hour series a very different state of affairs exists.

Thirdly, in those cases where growth is absent after treat-

ment it is possible that it may not have been included in the material obtained. The fact, however, that growth was always present after treatment in the 8-hour series (except possibly in one case), and absent in over 60 per cent. of cases in the 24-hour series, makes it extremely improbable that this can often have occurred.

The quantity of radium in most of the cases has been kept a constant factor. The time of application has been eight hours or twenty-four hours in the two series respectively, so that the amount of irradiation of the tissues in the two series is in the proportion of 1 to 3. Marked differences were obtained in the two sets of cases, and we are of opinion that irradiation for eight hours is wellnigh useless, even if repeated on as many as three occasions; whereas even one exposure for twenty-four hours has a very marked effect, and has not infrequently led to the complete local disappearance of the growth.

Although it is impossible to obtain accurate measurements of the energy at any one point in the pelvis, owing to the method of distributing the radium, yet it is obvious that the energy received by all parts of the cervix must be of very great intensity compared to that received by the iliac glands, where the action of the inverse square law comes into play. Consideration of these facts explains why no growth can be found in the cervix, but is present and apparently unaffected in the iliac glands.

The only change after treatment which can be shown to have any degree of constancy in the 8-hour series is the appearance of large cells containing large deeply staining nuclei with irregular outline. This has been seen only in the first and second weeks after irradiation, and is probably to be regarded as a degenerative process.

In the 24-hour series the most striking change is the disappearance of the growth from the cervix in over 60 per cent. of cases of squamous-celled carcinoma. As is to be expected, this does not take place immediately; the earliest date on which it was observed was three weeks after irradiation, and this was in a case where the whole uterus was examined. It is not possible to say how long carcinoma cells can persist after treatment, but it is interesting to note that evidence of new growth debris was present in a section taken forty-nine weeks later. In those cases where new growth can yet be found, it is present in greatly diminished amount and shows marked degenerative changes. Consideration of these cases leads us to frame a tentative hypothesis of the stages through which the cell may proceed to its doom.

In discussing the sequence of events it is necessary to bear in mind the physical conditions present in the irradiated area. The cells closest to the radium receive the greater amount of energy, and those further away receive less, both because of the increase in distance and because a certain amount of energy has already been absorbed. When a large amount of radium such as we have used is left *in situ* for twenty-four hours it seems as if the radiations were sufficient to cause immediate death of all the cells in close proximity, thus giving rise to the picture of coagulation necrosis, which in turn disappears within a few days as the debris is removed. In the zone beyond this the irradiations do not seem to have an immediate lethal effect, but about the third day the cells show a breaking up of the chromatin into droplets accompanied by an enlargement of the cell itself, and sometimes by a breaking up of the cytoplasm into a number of small masses. Still further beyond this zone a large number of cells show marked activity on the third and fourth days. Mitoses are much more frequent than in the original growth, but they are almost entirely of a degenerate nature. They may be multipolar or may show granulation and fragmentation of the chromosomes, or the chromatin may have disappeared from the cell leaving only the spindle figure. The observations on which we have based this hypothesis of the stages in the first four days is in accordance with those published by A. Lacassagne and O. Monod (*Arch. Franç. Path. Gén. et Exp.*, 1922, Fasc. I, p. 28), but we are not so far in entire agreement with regard to his interpretation that the *principal mode* of death is degenerative mitosis. When discussing the matter with M. Lacassagne, he pointed out that there

was a considerable difference in the technique of irradiation employed by him, which fact may account for our interpretation. We are, however, further investigating the changes that occur within the first few days.

From the seventh day onwards there is apparently no attempt at multiplication by mitosis, and we have no evidence that multiplication in any form takes place. The nucleus, on the other hand, assumes strange forms; there is often an increase in size accompanied by an increase in cytoplasm and sometimes very large forms are seen. The outline is irregular and the nucleolus is often deeply stained. Later mottling or even vacuolation (sometimes the vacuoles are of large dimensions) is seen, followed in some places by a gradual loss of staining power whilst the nuclear form is still maintained. The cytoplasm itself is usually increased in quantity, and occasionally shows vacuolation. The tissues around are heavily infiltrated with small round and plasma cells, as before treatment, and in addition there is usually an increase in the amount of fibrous tissue. These appearances last up to six or eight weeks, towards the end of which time the cells, if they have not already disappeared, become difficult to find owing to their paucity. After this stage it seems that the cells entirely vanish from the tissue, except in a few cases where another process seems to be at work, which for want of a better expression we have termed "embalming." Whereas in the former case the cells seem as if they were dissolved and their remains removed, in the present case they appear to remain collected together in their original alveolar forms. The nuclei are sometimes to be recognized by their spherical outline and staining properties, but generally, and especially in the later observations, no nuclear structure is to be seen, and the islets consist of an unorganized mass, often concentrically laminated. These can only be regarded as remains of new growth because (1) they are bodies entirely foreign to the normal cervix; (2) they can be traced in a series of cases through the various stages from unquestionable carcinoma. In this embalmed state there is an entire absence of round-celled and plasma-celled infiltration around, suggesting that the growth is no longer capable of causing cell reaction, and is dead. The islets are often embedded in a mass of dense fibrous tissue or may have muscle tissue in close proximity, but usually there is an attempt at fibrous tissue encapsulation round them. From their staining properties these masses appear to be heterogeneous, but there is evidence that their outer portions contain myxomatous material.

Judging from the observations in one case which was examined fifteen and forty-nine weeks after irradiation, it would seem that when once the cells have reached this advanced stage these masses appear to be relatively permanent.

CONCLUSIONS.

Clinical.

1. These are in accord with the general experience of others in recent years, that in the majority of cases patients suffering from carcinoma of the cervix cease to have hæmorrhage, vaginal discharge, and ulceration after treatment with radium. Further, that in some of those cases which are inoperable, life is prolonged and the patients are enabled to lead useful existences. It would be premature at the present juncture to talk of cures.

2. That the preliminary application of radium in those cases which are operable causes the disappearance of fungating growths or ulcers, so that the risk of infection and of implanting new growth from the cervix at the time of incising the vagina wall is markedly diminished.

3. There is no doubt that the application of 173.6 mg. of radium element for twenty-four hours is markedly more efficient in bringing about this result than the same amount applied for eight hours, even when the latter is given on as many as three occasions.

4. That since histological evidence of the efficacy of Daels's method of irradiation of the pelvic glands is impracticable its value is still *sub judice*, as it depends upon clinical evidence.

Histological.

1. That the introduction of 173.6 mg. of radium element into the cervical tissue for twenty-four hours is capable

of causing a complete disappearance of the growth from the cervix within a few weeks, whereas the same application for eight hours produces little or no effect in the quantity or appearance of the growth.

2. That definite series of changes in the carcinoma cells can be demonstrated after irradiation, leading up to the destruction of the cell.

3. That little or no effect has been produced in affected iliac glands when the cervix is irradiated.

4. That as changes in the malignant cells take place before the formation of fibrous tissue, the latter is not the causal agent in the disappearance of growth.

5. That the carcinoma cells are more vulnerable than the uterine musculature, but that in the latter local atrophy and fibrosis take place at a later date.

Our thanks are due to the Medical Research Council and the Radium Committee of St. Bartholomew's Hospital for the facilities given us in carrying out this research; to Dr. Williamson and Dr. Barris for allowing us to irradiate some of their cases and to include them in this series; and to many others for their valuable assistance, but especially to Dr. T. S. P. Strangeways for the whole-hearted manner in which he has given us his assistance and advice.

Memoranda :

MEDICAL, SURGICAL, OBSTETRICAL.

THE TONGUE SYMPTOM IN ABDOMINAL SEPSIS.

I WOULD like to call attention to a symptom which I have been accustomed to seek in all cases of abdominal disease, and which has not once failed me during many years of practice. I refer to a definite smell in the tongue, which I find present in all cases where pus is present in the peritoneal cavity. I do not refer to the smell of the breath but of the tongue itself. I find the smell varies from the distinct smell of pus to an actual faecal odour, sickening to the observer.

I am unable to find any reference to this symptom in books on surgical diagnosis, but have notes on cases extending as far back as twenty-five years in which I have used this symptom and verified its accuracy by operation. We know how rapid is the absorption from the peritoneum, and it appears to me that the tongue gives the first indication of this absorption. Among many cases of which I have notes I mention only three.

Case 1.—A female child had pain in the appendix area, and was sent into a nursing home at once. The temperature was not raised. There was slight rigidity of the abdominal walls. No vomiting. I noted that the tongue smelt very offensively. Operation at once. Perforation of adherent appendix, with offensive fluid in peritoneal cavity.

Case 2.—Adult, male. History of two days' illness. Pain not severe. Slight rigidity of abdominal walls. Temperature raised. Tongue smelt faecal. Operation at once. Appendix gangrenous; pus and gas in the peritoneum.

Case 3.—Seen in consultation. Adult female. History of obscure pain in left side of pelvis. Definite swelling extending upwards for three inches above iliac crest. Per vaginam tense swelling to left of uterus. The tongue very offensive. Gave advice for immediate operation as I was sure that there was pus in the peritoneal cavity. Operation two hours later. On opening the abdomen in the middle line we found a large collection of pus walled off. The pus had originated in the left broad ligament and ruptured into the peritoneal cavity, becoming walled off by adhesions. Over twenty ounces were evacuated. Recovery was uneventful.

I have tried testing this symptom by getting the patient to gargle and wash out the mouth, but in every case the smell of the tongue remained. In most cases I have noted that the tongue was not covered with fur; usually it is dry and beefy-looking.

I would be very interested to know if others have observed this symptom, which I have learned to rely upon with much confidence.

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