indicative of some form of dyspepsia, many of the cases have undergone severe restriction in their diet, or the food may have been modified, with unfortunate results. The condition may persist for many months. In the most severe, death from hunger or from intercurrent infection may occur.

Treatment.

For a time to distract the infant's attention seldom fails, but always to carry the infant around after meals or to arouse its interest by means of rattles or musical boxes is apt ultimately to exhaust both nurse and child. Strauch achieved success by the simple method of plugging the nostrils, since the resulting mouth-breathing renders it difficult to express the column of fluid into the pharynx. This succeeded perfectly in one of my cases, in the others it failed. It is further recommended that the infant should always be placed upon the abdomen after a meal. Others have endeavoured to prevent rumination by forcible closure of the mouth. A cap and a chin-piece are connected by two side-pieces of webbing, each bearing a buckle, and after the feed the mouth is held securely shut by tightening the side-pieces. This again has proved a successful device in some, but not in all the cases in which I have tried it. Probably the most uniform success has been achieved by thickening the child's food to the consistency of a thick gruel. I have used successfully farina boiled with milk until it was thick enough to adhere to an inverted spoon. In infants after the seventh or eighth month it is often sufficient to anticipate by a month or two the change to a mixed diet and to feed them as the normal child would be fed at the beginning of the second year. Rumination of this sort is prevented, or at any rate made much more difficult, when solid replaces fluid diet.

Finally, it is well to emphasize that in rumination, as indeed in almost all the conditions of habitual vomiting considered in this lecture, the personal factor of the nurse is of supreme importance. Rumination, like aerophagy, like the vomiting due to idiosyncrasy for cow's milk, and like the vomiting of nervous unrest, is found most commonly among infants of psychopathic inheritance and in a psychopathic environment. Isolation, handling by a competent self-confident nurse, the reduction of emotional disturbance to a minimum, are all of the greatest importance if recovery is to follow. The nervous disturbances of infants, like the infective disorders of infants, are apt to display themselves for the most part by symptoms referred to the sensitive gastro-intestinal tract. The infant has indeed but one function highly organized and therefore capable of showing complex disturbance—the function of digestion. It is in disorder of that function that throughout infancy nervous instability, inherited or acquired, especially shows itself.

I have to thank Dr. G. W. Nicholson, Professor Adrian Stokes, Mr. Redding, Dr. Lindsay Locke, and Dr. Vertue for their great kindness in providing me with the microscopic sections, microphotographs, and radiographs with which these lectures were illustrated, some of which have been here reproduced.

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TREATMENT OF INOPERABLE CARCINOMA OF THE CERVIX UTERI WITH RADIUM:

DESCRIPTION OF THE MORE RECENT METHODS EMPLOYED.*

BY

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THE purpose of this paper is to demonstrate that the results of radium treatment in inoperable carcinoma of the cervix uteri are so promising that it is imperative that as many of us as possible should join in combined and organized research on these lines.

Medical opinion in this country is extremely sceptical of the value of radiotherapy, and I cannot help thinking that this is because so little systematic work has been done on the subject. I would ask the profession to keep an open mind, as much harm is done by the expression of very optimistic or very pessimistic views on a method which is, comparatively speaking, so new. Many people think of radium as a drug, of which there is only one dose and one method of administration, and that if this does not prolong the patient's life the treatment is of no value. Many years will elapse before we reach any final judgement on the value of radiotherapy, and meanwhile, in order to make progress, we must compare the value of the different techniques, not only as judged by complete cure of the patient, but also by lesser standards. These standards are: (1) histological; (2) rate of disappearance of symptoms, such as haemorrhage; (3) rate of disappearance of the local growth and healing of the malignant ulcers; (4) duration of the patient's life after treatment.

Next I would appeal to those working at this subject to make their reports on uniform lines, and, when mentioning the dose, to give the fullest details as to whether radium element is used or radium emanation, and, if the former, whether the number of milligrams relates to the salt or the element; the exact material and thickness of the filters; the form of the applicators; the exact number of hours during which the radium is applied; and as far as possible the distribution of the radium in relation to the growth. If emanation gas is used, additional notes should be quoted—namely, the number of millicuries at the commencement of the treatment and the number of hours. It is of little or no value to talk about milligram hours or even millicuries of emanation destroyed.

[The work here described has been carried out with radium kindly lent by the Medical Research Council.]

DESCRIPTION OF TECHNIQUES.

Speaking generally, there are two schools of technique—one which believes in external application only, the other which believes in burying the radium close to or within the growth. The arguments for the different opinions may be summarized as follows.

Those who advocate external application consider—

1. That any incision, even the introduction of needles, may disseminate the growth.
2. That the injured normal tissues may be affected by the radium to an undue extent, as it is well known that radium affects cells which are about to go into mitosis.
3. That the tissue extracts produced by injury to the normal cells may stimulate the growth of the tumour.
4. That the burying of needles may produce sepsis under conditions very suitable for the growth of organisms.

Those authorities who advocate the burying of needles do not consider that these objections are in any way comparable to the advantages of the greater intensity obtained by placing the needles near the growth, and, further, that if the radium is used from outside, the doses have to be so large that there is a considerable likelihood of damaging the skin and other intervening tissues. The Radium Institute of Paris is, on the whole, inclined to believe in external application. The Radium Institute of Brussels believes in buried radium. Most of the American institutes

* A paper read before the fifth British Congress of Obstetrics and Gynaecology, London, April, 1925.

believe in buried radium, and some of them use unscreened glass tubes by means of which the beta rays are brought into action. The Radium Institute, Stockholm, believes in external application. Opinion in this country is divided.

Vaginal Treatment by Surface Application.—The usual routine is as follows: The vagina is prepared by means of douches, but the growth is not cauterized or in any way interfered with. One or more tubes are placed in the cervical canal, containing in all approximately 50 mg. of radium element, with a filter of 0.5 mm. of platinum. In the vagina there are more tubes, heavily filtered with 0.5 or 1 mm. of platinum, and sometimes these have additional filters of cork or aluminium and rubber, to stop the secondary rays coming from the platinum filters and to act as spacers. The amount of radium contained in these vaginal tubes is 25 to 30 mg. of radium element, making 75 to 80 mg. in all. The exact details of the filters vary in different clinics. The duration of application also is a matter of opinion, some authorities advocating twenty-four hours, others as much as a week or even more. On the whole the tendency seems to be to lengthen the duration of exposure.

Extra-abdominal Application of Radium.—In addition to vaginal application large quantities of radium are sometimes used on the surface of the abdomen, placed at a distance from the skin. This method has been widely employed in America, where as much as a gram of radium is used at a distance of 10 cm. As an example of burying technique by the vagina, I will describe my own method of treatment.

Method.—The patient is doused for two or three days before the operation with weak lysol. At the time of operation she is placed under an anaesthetic in the lithotomy position, and the vulva and vagina cleaned with picric acid 3 per cent. in spirit. A microscopic section of the growth is then taken in every case in which the radium is applied for the first time. The needles are placed in and around the growth, keeping as far as possible about half a centimetre of tissue between each needle. The longer needles are pushed outwards as well as upwards into the base of the broad ligaments. The whole vagina is then packed with gauze soaked in flavine. The amount of radium I generally use is as follows: 8 large needles approximately 6 cm. long, each containing 3 mg. of radium element, filter 0.5 mm. of platinum; 12 or 13 smaller needles, each containing 2 mg. of radium element, filter 0.5 mm. of platinum; total number of mg. 48 or 50. These remain in place for 144 hours.

In my present series of cases the patient has a second vaginal application after an interval of four weeks.

Technique for Intra-abdominal Radium.—The great difficulty is to affect the deeper parts of the growth. With this in mind I carried out in one series the technique suggested by Daels of Ghent. This consists in putting the radium alongside the iliac glands, but extraperitoneal, and is carried out in the following manner:

The patient is put under an anaesthetic in the lithotomy position. An incision is made in the ischio-rectal fossa and blunt dissection carried out with the finger as far as the spine of the ischium. Another incision is made just to the inner side of the anterior superior iliac spine, and a blunt dissection carried out, the finger passing over the psoas muscle and external iliac vessels. A tube is then passed from the lower incision right through the pelvis to the upper incision, and through this tube a chain is guided, the tube being then removed and leaving the chain in place. One radium tube is attached to this chain, which is pulled on, and the desired depth can be obtained by counting the number of links of the chain remaining outside. The radium is moved each day, and entirely removed at the end of the third day.

This operation I carried out in 14 cases. Although some of these cases have done well I do not care for the technique, as it involves too much blunt dissection, and the radium is concentrated into one mass, and therefore does not conform with my ideal of uniform distribution throughout the growth.

The next method that I tried was that employed at the Radium Institute of Brussels—namely, the intraperitoneal method.

The patient is put in the Trendelenburg position and the abdomen opened. Needles are then placed in the back of the uterus and in the broad ligaments, and the rubber-covered wires holding them are brought out through the lower part of the abdominal wound. The whole pelvis is then packed with gauze (it generally requires about 8 yards of 6-inch gauze), and the end of the gauze brought out with the above-mentioned wires through the lower part of the abdominal wound. At the end of a week the gauze and wires are pulled out, the patient being given gas anaesthesia. I have performed this operation in ten cases.

Although some have done quite well I am not satisfied with the technique, and am at the present moment working out a new method, using a rubber plug to fill the pelvis.

Combined Radium and X Rays.—Until recently facilities at St. Bartholomew's Hospital for this method of treatment have been rather restricted, and my own experience of combining radium and x rays has been limited to a few patients treated in private by Dr. Finzi, two of whom have been very satisfactory indeed. Now that we have installed a deep x-ray plant purely for research we hope to undertake a large series of such cases.

Conclusion regarding Technique.—My own opinion is that any technique should aim at getting a comparatively small intensity evenly distributed throughout the growth, and applied for a comparatively long time.

DOSAGE.

The question of the best dosage is still *sub judice*. It is from the solution of this difficult problem that the final technique will be evolved.

Although it is impossible here to discuss in detail the physics of radium, yet there are one or two points to be remembered. The first of these is the fact that the intensity of radium obeys the inverse square law in the same way that light does. As an illustration it may be noted that the dose received by the fingers holding a tube of radium with a filter of 0.5 mm.

of platinum for half a minute is the same as if those fingers were exposed at a distance of one yard from the radium for a period of three and a half years; or, to put it in a more practical form, the tissues of the pelvis 2 inches away from the tube receive 10,000 times less irradiation than the tissues immediately surrounding it. In these circumstances, is it a matter for surprise that those people who only put one tube into the middle of the cervical canal do not prolong the lives of their inoperable cases? Another point to remember is the filter, which makes a considerable difference to the type of rays and intensity.

Units of Dose.—In order to understand the description of various techniques we must be quite clear about the expressions used to indicate units of dose. In using radium element in the form of a salt we should speak of x number of milligrams of radium element used for y number of hours, and then add the full description of the distribution and number of needles or tubes. When, however, emanation gas is employed the unit used is spoken of as a millicurie.¹ When emanation gas without its parent salt is used it breaks down rapidly, so that its activity declines by one-sixth every twenty-four hours. There are two ways of describing the dosage when emanation is used. We can say that the dose was x number of millicuries applied for y number of hours, and then work out by reference to a table the mean number of millicuries for the length of time of application. Or we can describe the number of

Skigram of needles placed in position per vaginam. The shorter needles grouped in the centre are encircling the cervix. The longer needles on either side are in the base of the broad ligaments.

¹ When a milligram of radium is sealed up for a time the amount of emanation gas becomes constant, and this equilibrium amount is spoken of as one millicurie, and can be measured by its effect upon an electroscope.

millicuries of emanation gas which have been destroyed during that time. For instance, if we put in 100 mc. and take them out after twenty-four hours, we shall have used approximately 16 mc. This latter method has the advantage that it can also be used for calculating the dose when radium element is employed. Whichever method is used it is still necessary to give details of the number of tubes, distribution, filters, etc.

Dosage in Relation to Biological Effect.—A great deal of work is being done in various laboratories to find out the exact action of radium on the normal tissues, and until the laws governing such action are known we clinicians can only grope about in the dark, trying by empirical means to find the most efficient dose. The first, and perhaps the most important, point to be decided is whether the biological results are proportional to the irradiation received; in other words, are the same biological results obtained by using 100 mg. of radium element for twelve hours as 50 mg. for twenty-four hours? That is, is it better to use a small dose for a long time or a large dose for a short time, or is it exactly the same thing? There is a certain amount of laboratory evidence that it is not the same thing, and in my opinion the clinical evidence is very much in favour of a medium dose, well distributed, applied for a very long time; in my last series of cases I have been using 50 mg. of radium element in twenty needles for 144 hours at a time, with distinct improvement in immediate results compared with my former series.

RESULTS.

The general public, and for that matter the majority of practitioners, will only judge results by the number of years the patient lives after the treatment, and although we all hope that eventually radiotherapy will be able to stand such a test in the case of inoperable carcinoma of the cervix, yet it is obvious that at first we must judge by the local and histological effects, for, as already mentioned, the more inaccessible parts of the growth go on living and continue to kill the patient as heretofore. That does not mean that radium has no effect on malignant disease; it merely means that we have not yet learnt how to apply it to the whole growth. My disinclination to judge the results of radium treatment by the years that a patient lives does not arise from a wish to vindicate radiotherapy. We at St. Bartholomew's took the matter up four years ago with absolutely open minds, and we judged the improvement or otherwise following the use of different techniques by:

1. The histological evidence from the uteri removed by hysterectomy following radium.
2. The rate of disappearance of symptoms.
3. The rate of disappearance of the growth and the healing of the malignant ulcers.
4. The duration of the patient's life after treatment.

Histological Evidence.

This histological work was all carried out by my colleague Dr. R. G. Canti. During the first two years of our research we paid particular attention to the histological findings after irradiation, and in two series comprising over 50 cases the amount of radium used and the technique were approximately the same, and we only changed the number of hours, the first series being for eight hours, the second for twenty-four. The conclusions that Dr. Canti came to were as follows:

(a) That the introduction of approximately 170 mg. of radium element into and around the cervical tissue for twenty-four hours is capable of causing a complete disappearance of the growth in 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.

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

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

(d) 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 the growth.

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

In one case, in which hysterectomy was performed as early as four weeks after the first application of radium, no growth was found in spite of a number of sections being cut and examined, and in the other hysterectomies (some of them performed at the end of a week, others after several weeks), if growth was found at all it was so affected as to make it impossible to believe that the cells would have been viable.

Disappearance of Symptoms and Signs.

In order to get the most reliable symptoms and signs by which to judge the effect of irradiation, we have chosen the three following: (a) haemorrhage; (b) ulceration; by this we mean malignant growth of an ulcerative type, in contradistinction to (c) the proliferating cauliflower type of growth.

An analysis of these symptoms and signs shows the following: Of 85 cases treated, all were quite inoperable except 11. Of these 11, 5 were borderline cases upon whom some people would undoubtedly have attempted operation, 6 were cases upon whom I myself would have operated had it not been for the general condition, or the fact that the patients themselves refused operation.

(a) *Haemorrhage.*—Of the 85 cases, in 5 no note was made of the symptom of haemorrhage after treatment. Of the remaining 80, in 68—that is, in 85 per cent.—haemorrhage ceased, either permanently or for a considerable time, which in itself is of benefit to the patient.

(b) *Ulceration.*—Of 68 cases in which ulceration was noted before treatment started, and in which a note was made concerning this condition after treatment, it was found that ulceration had disappeared entirely, either temporarily or permanently, in 43 cases—that is, in 63 per cent. In 25 cases ulceration did not disappear. In these 25 cases, as a matter of fact, it diminished for a time in some, but as the question of the size of an ulcer is always a matter of opinion this is not taken as any index.

(c) *Growth.*—In 37 cases in which growth (by this is meant the raised cauliflower type of growth, in contradistinction to malignant ulceration) was noted before treatment, this entirely cleared up in 26—that is, in 70 per cent. In 11 cases it did not disappear entirely, although in some it was diminished.

It was noted that both these last signs—malignant ulceration and malignant overgrowth—disappeared more quickly in those cases which had had applications of radium for long duration.

Duration of Life.

The figures relating to the cases treated at St. Bartholomew's Hospital are as follows:

Of 85 cases treated between May, 1921, and April, 1925, 74 were hopelessly inoperable, 5 were borderline, 6 operable but for various reasons were not operated upon, as already mentioned. Of these 85 cases, 31 are living and 54 have died. As, however, some of these living cases have only been treated for a few months, the real facts are better expressed by taking those cases which were treated between May, 1921, and May, 1924.

Of 58 inoperable cases, 10 are living after one year or more—making 18.9 per cent. Of these 10, 1 has lived for 43, 1 for 43, 1 for 40, 1 for 21, 1 for 19, 1 for 17, 1 for 14, and 3 for 12 months.

Of 4 borderline cases treated, 1 has lived for 16 months.

Of 2 operable cases treated within the same period, 1 has been living for 12 months. Taking these three classes comprising 64 patients, there are 12 living for 1 year or more—making 18.7 per cent.

Of the 54 cases who have died, 14 lived for one year or more, 1 lived for 36 months, 1 for 31 months, 1 for 26 months. All the 14 were very materially benefited for a considerable time, and there is very little doubt that their lives were prolonged. Of the remainder 27 were benefited and made more comfortable for a time, but there is no evidence that their lives were prolonged. Of the rest, to 8 the treatment seemed to do no good whatever, and in the case of 5 it is quite possible that it actually did harm. Of the 64 patients, therefore, all but 13 received some benefit—making 80.9 per cent.

Of the 21 patients living less than a year, 4 are doing badly and going downhill; the rest appear well.

It is impossible to quote all the statistics available, but the following figures give some idea of the prolongation of life in some of the well known centres.

Last year the Radium Institute of Paris published the following figures. Of those cases treated in 1919, 1920, and 1921, 226 cases of carcinoma of the cervix were treated solely by radiological methods. Of these—

Of 21 cases of recurrences following operation, 2 are free from recurrences (one was treated with x rays as well), 3 are living but have recurrences, 16 are dead. Professor Régaud dogmatically states that a preliminary hysterectomy causes radium therapy to lose all the anatomical conditions for its efficacy, and moreover is liable to scatter malignant cells, and is therefore a great mistake.

Of 114 inoperable cases, 15 appear to be without any recurrences, the longest being three and a half years and the shortest one year. This equals 13.2 per cent.; 12.4 per cent. were greatly benefited.*

Of 67 borderline cases, 24 are still living, the time since the beginning of treatment varying from one year to three and a half years—making 35.8 per cent.; 35.8 per cent. were greatly benefited.

Of 24 operable cases, 11 (45.8 per cent.) are still living without any sign of recurrences, for times varying from one to three and a half years. In another 25 per cent. the disease disappeared locally.

The statistics published by the Radium Institute of Brussels are roughly as follows:

Operable Cases.—Of 14 operable cases treated by radiotherapeutic methods, 73 per cent. were living and free from signs of growth at the end of one year or more.

Borderline Cases.—Of 24 doubtful cases, 12 were free from any signs of growth after one year or more—making 50 per cent.

Inoperable Cases.—Of 24 inoperable cases, 8 per cent. were living and free from any sign of growth after one year or more.

The figures from the Radiumhemmet, Stockholm, are:

Of the 181 inoperable cases treated, 16.6 per cent. were well after five years.

Of the 36 operable and borderline cases, 40.5 per cent. were well at the end of five years.

The following list shows the number of cases treated in various years at the Memorial Hospital, New York, and the number living in May, 1921.

<i>Inoperable Cases:</i>				Alive May, 1921.	
Of 15 cases treated in 1915	...	...	...	None	
" 24 " " " 1916	...	...	...	1	
" 41 " " " 1917	...	...	...	None	
" 41 " " " 1918	...	...	...	7	
" 69 " " " 1919	...	...	...	23	
" 92 " " " 1920	...	...	...	58	
<i>Borderline Cases:</i>					
Of 3 cases treated in 1916	...	...	...	2	
" 3 " " " 1917	...	...	...	2	
" 17 " " " 1918	...	...	...	5	
" 10 " " " 1919	...	...	...	7	
" 12 " " " 1920	...	...	...	8	
<i>Operable Cases:</i>					
Of 1 case treated in 1915	...	...	...	1	
" 3 cases treated in 1916	...	...	...	None	
" 3 " " " 1917	...	...	...	2	
" 4 " " " 1918	...	...	...	2	
" 9 " " " 1919	...	...	...	7	
" 14 " " " 1920	...	...	...	6	

RADIUM TREATMENT OF INOPERABLE CARCINOMA OF THE CERVIX.†

BY

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This communication is founded on a study of 40 cases of carcinoma of the cervix treated by the application of radium. The radium is supplied to the Cardiff Royal Infirmary by the Medical Research Council for research purposes, and inoperable cases of this disease have been treated in this manner since May, 1922.

Technique of Application.

The dose usually employed is 150 mg. of radium bromide, and it is inserted for twenty-four hours. Two tubes of 50 mg. each, sheathed in 2 mm. of platinum, are inserted into the cervical canal, and the others are distributed at the periphery of the growth according to the anatomical conditions. In some cases six tubes of 10 mg. each are inserted in a circle, but in other cases, when the condition is of irregular shape, the smaller tubes are inserted where they would appear to be most effective.

* In 1919 and 1920 every single case that could reach the institute was treated. Since then the inoperables have been selected slightly, as it was found that when very far advanced the treatment did more harm than good. The authors consider that x-ray treatment only is better for these cases than radium.

† A paper read before the Fifth British Congress of Obstetrics and Gynaecology, London, April, 1925.

Difficulties may be met with during application. In a number of cases the cervix had ceased to exist as a protrusion into the vaginal vault, and was represented by a foul, bleeding, friable ulcer, and in these it was often very difficult to get a satisfactory grip of the friable material with a volsellum. In some cases the cervical canal was difficult to find, especially where the growth was hard and excavated. It is essential, however, to find and explore the canal with a sound to exclude the presence of an unsuspected pyometra. This condition was present in 12 cases, in none of which was there any pyrexia or marked uterine enlargement. If pyometra be found the cervix should be dilated and the uterine cavity drained before radium is applied. In the cauliflower type of growth and in some others showing exuberant fungation the cervix is scraped prior to the insertion of radium. In such cases the radium should be inserted immediately after scraping, so as to prevent dissemination of the carcinoma cells.

After removal of the radium a vaginal douche should be given, and repeated night and morning for three weeks. This is recommended by Hayward Pinch, and is a practical necessity in the prevention of adhesive vaginitis, which developed in certain cases where douching was omitted and rendered future applications and investigation very difficult.

At the first and each subsequent insertion a specimen of the growth is obtained for microscopic examination. As the condition improves it becomes progressively more difficult to fix the cervix, to get a proper view, and to remove a piece for examination, as, in the process of "healing," the carcinomatous cervix becomes more and more retracted up into the vaginal vault until only a little cicatrized area is present there, with the vaginal walls often slack below it.

Contraindications.—The main contraindications to the use of radium may be classified under these headings:

1. The presence of pyometra. This is discussed above; drainage is required before radium is introduced.
2. The presence of inflamed appendages. Radium is apt to set up an acute exacerbation in such cases.
3. Vesico-vaginal fistula. If this is present when the case is first seen radium is inadmissible, as an acute cystitis may be set up. If fistula develops in the course of treatment no further application should be given.

Histological Changes.

The histological changes in the carcinoma cells were at first puzzling and difficult to interpret; but after familiarity with the appearances had been acquired the changes were found to be of a more or less uniformly degenerative character in a large number of sections examined at different periods after treatment.

The first change observed was enlargement of the cells and of the nuclei. It was found in a number of cases as early as the third day, and usually by the end of the first week. In the majority of cases the cell cytoplasm and nucleus did not take up the stain as deeply as before. Here and there atypical karyokinetic activity was seen, shown by splitting of the chromosomes, often in an irregular manner. Oedematous infiltration also was seen in the stroma; the changes in both situations were attributed to oedematous swelling due to a vascular reaction to the damage caused by the radium. True degeneration was usually well marked by the end of the second week. The nucleus was affected first; karyokinetic changes were no longer seen, the definite nuclear structure was lost and it stained darkly, showing little or no structure, and having an indefinite margin. The cytoplasm of the cell also underwent granular degeneration, and vacuolation occurred, while the cell walls stained faintly. By the fourth week degeneration was well advanced and the nuclei had either disappeared or were represented by dark structureless masses in the interior of the cells. Degeneration of the cytoplasm had also advanced; it stained irregularly, and vacuolation was well marked. In some cases what was left of the nucleus was seen to be pressed against the cell wall by a vacuole which occupied the rest of the cell. The cell walls were very faint or indistinguishable, so that areas were seen here and there occupied by an irregularly stained mixture of degenerated cytoplasm and nuclei with vacuolation—almost the appearance of degenerated syncytium. At about this period the stroma began to show reaction. Around the epitheliomatous columns lymphocytic infiltration was marked, together with an increase of vascularity and a return of oedema.

These changes progressed until about the sixth week, after which little more effect on the carcinoma cell was to be expected as a result of a single application. The reaction of the stroma now became the main feature, and in time a condition of fibrosis was brought about; it did not occur until the cellular degeneration was advanced, and is to be regarded as a process of repair bringing about what amounted to scar formation. In some