

essential character of the individual tumour and the degree of invasion of the lymphatic system of the part in each individual case. If the upper axilla be involved as well as the lower, the prognosis is the more doubtful; if there be obvious infection of the skin, especially in the form of detached separate nodules near the seat of the disease, the prospect of long immunity from recurrence is very slight, however large an area of skin be sacrificed, while if the disease is apparent in glands above the clavicle, I always now decline to operate. Still the extent of the operation is, undoubtedly, a certain factor in our results. I have mentioned the fact that long-continued good health and apparently permanent cure sometimes, in former days, followed removal of the breast alone; but the much more frequent experience of such encouraging results after the more extensive procedure of also clearing out the armpit has been very marked indeed. While preparing this paper I have either personally seen, or communicated with the medical attendants of, ten patients who remain quite well after operations performed seven years ago and upwards for mammary cancer, verified after removal by microscopic examination. The list only includes one hospital patient, as such patients, for the most part, quickly disappear from one's view, and I have made no search at all amongst former patients, whether private or hospital. These ten to whom I refer chance to have remained within the area of my own knowledge and observation. The periods of time which have elapsed since operation in these cases are respectively thirteen years, twelve years and four months, eleven years and eight months, ten years and eight months, ten years and six months, nine years and one month, nine years, seven years and ten months, seven years and three months, and seven years. In all of these cases the contents of the axilla were removed, but in none were the pectoral muscles interfered with. I believe it would, at any time, have been impossible for a surgeon of thirty or forty years ago, who removed the mammary gland alone, to have made a statement similar to this. Nowadays there are large numbers of surgeons all over the world whose experience of results is of exactly the same character; and this, no one will dispute, is due to the more extended nature of the operation. Whether or not the routine practice of removing the pectoral muscles will mark a corresponding advance is doubtful; but I think it should be followed, in the absence of anything to contra-indicate it, since we must do everything we can to be in advance with our operation of any existing dissemination of the disease; and, in any case, the removal of these muscles makes the clearing out of the axilla much more easy and satisfactory, while their absence is hardly at all disabling as regards the future usefulness of a woman's arm.

## REFERENCES.

<sup>1</sup> *Études sur la Tuberculose*, Paris, 1887. <sup>2</sup> *St. Bartholomew's Hospital Reports*, 1869, vol. v.

## A Lecture

ON

## THE NATURAL CURE OF CANCER.\*

BY

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ON two previous occasions, when I had the honour of occupying this chair, I presented a view of the mode of dissemination of cancer which I had worked out in the laboratories of the Middlesex Hospital. Under the name of the permeation theory, this view met with wide acceptance. In America it has recently found distinguished advocates in Professor W. S. Halsted, Dr. W. B. Coley, and Professor Rodman, and it has been confirmed in the laboratories where it originated by the work of Dr. Victor Bonney and that of Mr. Cecil Rowntree.

My reasons for mentioning these facts are two in number: First, that, although the permeation theory has met with wide intellectual acceptance, its intensely practical bearing on the surgery of every variety of cancer has

not yet been generally realized. In the second place, much of what I have to say to-day is a corollary of the permeation view of dissemination, and it is necessary to show that I have warrant for assuming its truth.†

Since the severance of my official connexion with the Cancer Research Laboratories of the Middlesex Hospital upon my appointment to the surgical staff of the hospital in 1906, my researches have been extended to stomach cancer, with the aid of a grant from the Imperial Cancer Research Fund. On a future occasion I hope to have the privilege of bringing forward my results in regard to gastric carcinoma.

In the literature of carcinoma there are embedded a number of scattered observations, usually referring to single cases, which show that under certain circumstances the disappearance of cancerous masses of macroscopic size may occur spontaneously. In a few cases all clinical evidence of the disease has in this way disappeared, and a natural cure seems to have been brought about.

Occurring in what is usually regarded as the type of a steadily progressive malady pursuing its undeviating course to a fatal event, these facts have appeared strange and anomalous to most of the authors who have recorded them. Their possible significance in respect to the cure of cancer, a significance which it would be difficult to overestimate, has been referred to by Mr. Pearce Gould, who, in a lecture on "Cases Illustrating Repair in Cancer of the Breast,"<sup>1</sup> pointed out that "we are justified in speaking of repair in cancer, even in its advanced stages," a conclusion which "justifies—nay, compels—a belief in the possibility of the cure of cancer, and gives us an indication of the direction in which a cure is to be sought."

In this lecture I propose to consider, as fully as time and a difficult and elusive subject will allow, the facts which bear on the natural cure of cancer.

I hope to show that, as I have stated elsewhere, "the progress of a cancer is normally accompanied by retrogressive or curative processes"<sup>2</sup>; that the recorded cases of natural repair in cancer, far from being anomalous and exceptional, merely illustrate more strikingly than usual the natural laws which govern every case of the disease. The order of Nature admits of no real anomalies, and is often best brought to light by the close study of apparent exceptions.

## AN UNRECOGNIZED LAW OF CANCEROUS GROWTH.

The unrecognized law of cancerous growth which I wish to establish may be stated as follows:

*Every aggregation of carcinoma cells has a definite life-cycle, and, after increasing in size for a varying period and at a varying rate, tends spontaneously to undergo degenerative and fibrotic changes. These changes extend from the centre of the mass centrifugally to its periphery, lead to its shrinkage, and terminate in the replacement of the aggregation of cancer cells by a fibrous scar.*

In other words, the natural history of a cancer is one of centrifugal growth followed by centrifugal death. It is obvious that the postulate thus stated cannot be completely proved, if only because at the time death occurs the life-cycle of many—and in some cases of all—of the deposits will be incomplete. The most I can hope to do is to produce a certain amount of positive evidence for my proposition, to meet certain possible objections, and, above all, to show that its acceptance drills into order a ragged regiment of apparently anomalous facts, provides a trenchant weapon of criticism for deciding the value of cancer cures, and offers an explanation of the vogue which almost any cancer remedy may for a brief space attain.

To avoid misconception it will be well at the outset to state that the natural cure in cancer is a local and not a constitutional process, and that as a rule it closely follows up, without overtaking, the centrifugal spread of permeation, and so fails to arrest the march of the disease. It is certain that in some cases its vigour is sufficient to strangle the growth in an early stage, or to reduce it to impotence for a long term of years, but as a rule the natural processes of cure go on contemporaneously with

† The permeation theory is beginning to gain adherents on the Continent. At the Congress of the International Society of Surgery, held at Brussels in September, 1908, Professor A. Depage, in opening the discussion on breast cancer, said: "Les recherches récentes de Handley et sa théorie de perméation nous ouvrent en ce moment des horizons nouveaux."

\* Delivered before the Royal College of Surgeons of England.

the active advance of the disease in other parts of the body further removed from the primary focus.

#### *Apparently Complete Spontaneous Cure.*

Velpeau believed that the spontaneous cure of cancer never occurs, and although since his time several cases of the kind have been recorded, the disappearance of a cancer which has clinically reached its full development has never yet been absolutely demonstrated by a complete necropsy with a negative macroscopic and microscopic examination of the tissues for cancer. A few examples may be given.

#### CASE I.

The best known of these cases is that of Mr. Pearce Gould.<sup>3</sup> There is no need to repeat its details fully. In 1890 the patient had her left breast removed for a "typical scirrhus," microscopically diagnosed. In 1895 she was emaciated and dyspnoic, with numerous secondary skin nodules, large axillary and supraclavicular glands on both sides, and a cancerous fracture of the neck of the left femur. Between March and November, 1896, the skin nodules shrank, and were converted into keloid scars, the glands disappeared, the fracture united, and all evidence of growth had disappeared. By 1899 all the scars had become soft and supple, and the general condition had further improved. Unfortunately the patient has not reported herself since about 1906.

#### CASE II.

Dr. G. Mackay<sup>4</sup> records the case of a woman of 37, who had her breast removed for a microscopically-diagnosed scirrhus. Recurrence took place a year later, locally in the opposite breast, and extensively in the lymphatic glands. Double hæmorrhagic pleurisy, with dysphagia and severe dyspnoea, next came on. From this point improvement began; the pleuritic effusion was absorbed, and all the secondary growths disappeared. Dates, however, and subsequent history are not given.

#### CASE III.

A woman, aged 56, now in the cancer wards of the Middlesex Hospital, under the care of Mr. Bland-Sutton, had a portion of the right breast removed for cancer at Chichester in 1894. Operations for recurrence in the breast and axilla were performed in 1896 and in 1903. The nipple still remains, and, indeed, most of the breast appears to be intact. That the disease was not entirely cured by the operation was shown by the development of a brawny arm in 1905, two years after the last operation. No other evidence of cancer remains, and it seems fair to consider this case as much one of natural as of operative cure.\*

#### *Atrophic Scirrhus.*

The apparently complete disappearance of a cancer in the acme of its career of dissemination is one of the rarest events in medicine, but cases are by no means exceptional in which from the beginning the natural processes of cure oppose a stout resistance to the growth. Such appears to be the true nature of cases of atrophic scirrhus. These cases include the best examples of the complete natural cure of cancer. In the most marked form of atrophic scirrhus a puckered scar, to which the skin may become attached, slowly forms in the breast. The whole breast becomes somewhat shrunken and the nipple indrawn, but no definite tumour makes its appearance. The disease in this form is usually painless, and the patient's attention is only attracted by local puckering and adhesion of the skin. Two such cases have recently come under my observation. In such cases the patient may die of some other disease, or, after many years, local ulceration or dissemination may terminate the case. It is not improbable that certain chronic ulcers of the stomach, accompanied by great fibroid thickening, are really extinct carcinomata. For every cancer which reaches its full clinical development, even as an atrophic scirrhus, it may be that a hundred are strangled in the process of birth and while still in the microscopic stage. Cases of typical atrophic scirrhus pass by imperceptible gradations into what is known as "ordinary scirrhus."

I recently had the opportunity of seeing, with Dr. Lockhart Stephens, of Emsworth, a woman 80 years of age, still hale and vigorous, who was operated upon twenty-eight years ago by Dr. Snow for cancer of the breast, and at intervals since for local recurrence. The growth was in the left breast and a considerable portion of the gland still remains. No palpable growth can be felt anywhere. She suffers, however, at intervals from swelling and fullness of the supraclavicular triangles, probably due to difficulties in the circulation of lymph produced by partial obliteration of the lymphatic vessels. She also complains

\* Note, October, 1908: This patient has since died with internal secondary growths, the probable ultimate fate of most cases of the kind under consideration.

greatly of pains in the head, and of rheumatic pains elsewhere. It appears certain that the process of permeation is still smouldering along her lymphatic vessels, for at intervals transient nodules appear in the scalp, and the subcutaneous tissues of the forehead are rough and granular to palpation, an indication of the fibrosis of the permeated lymphatics.

Without wishing to detract from the credit which is due to the surgeon, I think this case should be regarded as one of natural rather than of operative cure. More accurately it might be regarded as a kind of stalemate, in which the forces of the cancerous growth and the reparative processes are balanced with the utmost nicety, for the growth does not appear to be completely arrested even yet.

Leaving these cases of clinically more or less complete cure, we may now consider for a moment the records of partial or local cure, as evidenced by the disappearance of macroscopic deposits of cancer.

#### *Subcutaneous Nodules.*

The earliest observer of the spontaneous disappearance of skin nodules appears to have been Mr. Howard, the originator of the Middlesex Hospital cancer wards. In his *Notes and Observations*, published in 1792, he says, speaking of a case of bilateral breast cancer:

The tumours commence as small, reddish, slightly-elevated, shot-like indurations of the skin, which enlarge until they attain the size of a pea, when they ulcerate, and afterwards not infrequently heal. . . . The mammae were formerly voluminous, but have dwindled down until they are perfectly flat over the chest.

In 1867 Mr. Charles Moore noted, at the Middlesex Hospital that subcutaneous nodules can be destroyed by injecting them with glacial acetic acid, but that some weeks later they may reappear. In recent years the spontaneous disappearance of subcutaneous nodules has been recorded by observers too numerous to mention by name.

Even before the disappearance of skin nodules, and while they form little tumours still definitely raised above the surface, I find that the nodules may consist entirely of fibrous tissue, from which all trace of cancerous epithelium has vanished. This stage of fibrosis doubtless indicates approaching disappearance. Skin nodules frequently ulcerate in the later stages of the disease, and the ulcer may heal, as sometimes happens to an ulcerated primary growth.

#### *Epitheliation of Cancerous Ulcers.*

Mr. Pearce Gould in 1900 recorded two cases of partial healing of a cancerous ulcer by the spread of normal epithelium over it. In a third case a large ulcer, due to malignant disease of the right breast, completely healed up. The patient died a month after the process was complete, with deposits in the lungs and liver. It is to be noted that the cicatrization of cancerous ulcers does not seem to delay the fatal event of the case.

#### *Union of Cancerous Fractures.*

This is not a very rare, though doubtless an exceptional, event. Several cases occur in the records of the Middlesex Hospital for the last thirty years. In one case fractures of both humeri, of the left clavicle and the left femur, had united, while ununited fractures of three metacarpal bones were present.

#### *The Shrinkage of Spinal Metastases.*

Professor Osler<sup>5</sup> has recorded two cases of spontaneous relief from paraplegia due to the pressure of spinal metastases.

#### *The Shrinkage of Cancerous Lymphatic Glands.*

This important question has never yet been fully studied, but there is reason to believe that the successful cancerous invasion of a lymphatic gland is frequently preceded by fruitless attempts at invasion, and that lymphatic glands possess considerable power of destroying cancerous epithelium. I have examined sections of enlarged glands in connexion with a primary growth of the uterus which consisted almost entirely of fibrous tissue. In a case of breast cancer in a late stage I have observed an intermittent enlargement of the axillary glands on the side opposite to the growth. On some

occasions these glands were as large as almonds, while on other intervening occasions they were quite impalpable.

Dr. Bonney has lately studied the precarcinomatous changes which occur in lymphatic glands. He finds that enlargement of the gland precedes the access to it of carcinomatous epithelium. Microscopically the enlarged gland shows abnormally large germinal areas, with a great increase in the number of lymphocytes present. Plasma cells appear in large quantities in the stroma and capsule of the gland. The exact significance of these important observations is at present doubtful.

So far I have brought before you the vestiges of repair in carcinoma as traced in the literature of the subject, but I have produced no evidence to show that this repair is a normal event. This gap in the evidence must now be filled in so far as it is possible to do so.

#### A.—THE MICROSCOPIC EVIDENCE FOR THE CONSTANCY OF REPAIR IN CARCINOMA.

##### *Perilymphatic Fibrosis.*

My investigations on breast cancer have shown that the permeation of a lymphatic is normally followed by a curative process of fibrosis. The cancer cells, which at first fill the lymphatic without distending it, by their continued proliferation finally burst the tube of endothelium within which they are enclosed. Around the split lymphatic some extravasation of blood usually takes place, and a dense aggregation of lymphocytes appears. Soon the lymphocytes are replaced by young fibrous tissue, which forms an adventitious sheath for the cylinder of cancer cells set free from the burst lymphatic. This newly-formed fibrous tissue contracts upon the degenerate cancer cells, and they ultimately entirely disappear. The original lymphatic is now represented by a solid thread of fibrous tissue, and the process of natural cure is locally complete.

Figs. 3 and 4 represent this change diagrammatically. Inside the microscopic growing edge G G G the lymphatic plexus is represented merely by a network of fibrous threads.

##### *Perilymphatic Fibrosis in Stomach Cancer.*

In stomach cancer the difficulty of following out the various stages of permeation is enormously increased by the unstable nature of the cancer cells. The cells of a gastric carcinoma exhibit the utmost readiness to undergo complete mucoid degeneration. This difficulty, however, has in the end proved to be an advantage. In breast cancer it was impossible, except by inference, to trace the process of perilymphatic fibrosis beyond the stage in which cancer cells clearly recognizable as such are still present in the new-formed fibrous tissue. In stomach cancer, however, I have succeeded in following up the process beyond the stage of the disappearance of recognizable cancer cells. Fortunately there exists a stain—mucicarmine—which dyes mucin a bright red, while it has little or no affinity for any other tissue or material. The use of this stain promises to be of the greatest possible use in the investigation of gastric cancer. So far I have only used the stain for investigating the spread of stomach cancer in the deep fascial lymphatic plexus of the abdomen, to which the growth often obtains access near the navel. The drawing which I show you represents a section of one of the minute areas of young fibrous tissue, evidently of new formation, present upon the deep fascia near the umbilicus. My belief that this and similar areas represented the complete fibrosis of permeated lymphatics would have remained an unconvincing speculation. But mucicarmine brought out minute points of granular debris, stained a bright red, in the centre of the young fibrous tissue, and guessing was thus replaced by the strongest evidence. For it is certain that none of the normal structures of the deep fascia contain sufficient mucus to give a reaction with mucicarmine.

Thus, although in stomach cancer it has hitherto proved impossible to demonstrate all the stages of permeation in a nicely-graded series, such as I have shown in breast cancer, yet a gap in the evidence has been filled. The latest stage of perilymphatic fibrosis, in which cellular destruction is complete, remains no longer a mere inference, but can be shown actually to occur. The vanished cells of stomach cancer, unlike those of breast cancer, leave for a time a characteristic residue which enables

their former presence to be shown by means of a definite micro-chemical reaction.

In this process of perilymphatic fibrosis there exists therefore a definite and unmistakable instance of the natural cure of cancer by purely local processes which form a normal part of the pathology of the disease.

The destruction of cancerous emboli in the arterioles of the lungs, first demonstrated by M. B. Schmidt, is another instance of the local cure of cancer on a microscopic scale, but time will not allow me to enter into the details of the process.

#### B.—THE MACROSCOPIC EVIDENCE FOR THE CONSTANCY OF REPAIR IN CARCINOMA.

So far the evidence brought forward to show the constancy of repair in carcinoma has been of a microscopic character. But a recent study of repair on its macroscopic side has driven me to the conclusion that reparative processes are just as active and normal in the primary growth and in its satellite nodules on a macroscopic scale, as on a microscopic scale in the blood and lymph vessels. In the large aggregations of cancer cells the process of repair is later in beginning, and longer in its completion. The patient may die while it is still in its earliest stage, so that in some cases it may be difficult or impossible to demonstrate any sign of it. Its primary cause is a degeneration of the cancer cells, the result of a breakdown in their nutrition.

In carcinomata whose cells possess a high degree of proliferative power, the life of the patient is destroyed while the cancer is still in the early stages of its life-cycle. At the other end of the scale, in carcinomata of low proliferative power, the patient may possibly survive the carcinoma. Between these two extremes all gradations are met with. Expressed in clinical language these gradations are known as:

1. Medullary carcinoma.
2. Scirrhus.
3. Atrophic scirrhus.

Medullary carcinoma is a carcinoma of high proliferative power, occurring in young subjects, whose connective-tissues are vigorous and highly cellular. A large mass of growth is rapidly produced, and the patient dies in the early or evolutionary stage of the life-cycle of the carcinoma.

The typical scirrhus is a carcinoma of moderate proliferative power. The patient dies in the involutory stage of the carcinoma, but before its life-cycle is complete.

Atrophic scirrhus is a carcinoma of low proliferative power, occurring in old people, whose connective tissue is poor in cells. In its perfect form the life-cycle of the carcinoma is completed during the life of the patient.

##### *Ulceration of the Primary Growth.*

Almost invariably a primary carcinoma undergoes ulceration in the later stages of the disease. The ulceration begins at the centre of the growth and extends centrifugally into its peripheral portion. These facts are among the very elements of cancer pathology, and perhaps for that very reason no explanation of them has been attempted. From my point of view the constant occurrence of ulceration is of deep significance as showing that the death of the oldest portion of the primary growth is a normal event, and that the duration of any local aggregation of cancer cells is a strictly finite one.

##### *Macroscopic Repair in Cancer a Centrifugal Process.*

We have already seen that perilymphatic fibrosis closely follows up the centrifugal spread of permeation—that is to say, it is itself a centrifugal process—starting at the infiltrative margin of the primary growth, and extending in the lymphatic plexuses after the fashion of a ripple. The destruction and repair of large aggregations of cancer cells obeys a similar centrifugal law. Both in the primary growth and in each of its satellite nodules degeneration and repair commence at the centre of the mass and spread to its circumference.

##### *Centrifugal Repair in a Secondary Nodule.*

In certain of the secondary nodules of carcinoma no intranodular stroma makes its appearance, and the nodules in consequence only attain a very limited size. Such nodules afford the best material for the study of

repair in secondary deposits. The first indication of repair is that the central cells begin to exhibit degenerative changes. The cell body swells and becomes vacuolated. The nuclei begin to shrivel and lose their power of taking up stains. The whole centre of the nodule may undergo liquefaction. The peripheral cells of the nodule, those which abut directly upon the connective-tissue cells, retain the appearance of full vitality.

The next change is the appearance in the centre of the nodule, among the degenerate cancer cells, of a lymphocytic infiltration, which, however, is not a constant event. Still later, when degeneration has extended to the circumference of the nodule, the lymphocytes give place to a mass of connective-tissue cells, vascularized by new capillaries. Umbilication of the secondary nodule now occurs, owing to the contraction of this central mass of fibrous tissue.

The nodule may continue to spread at its margin, but finally the whole mass of cancer cells, becoming degenerate throughout, is replaced by a fibrous scar in which no cancer cells can be seen.

By the courtesy of Dr. Haaland, of the Imperial Cancer Research Laboratories, I am enabled to show you that similar changes may take place in the secondary deposits of mouse carcinoma. This slide shows a secondary nodule in the lung of a mouse, with advanced central degeneration, and infiltration of the degenerate portion by lymphocytes.

In the large secondary nodules, which present an intranodular stroma, the processes of repair cannot be so conveniently demonstrated, but they are essentially the same. Central degeneration is followed by fibrosis of the degenerate portion, and the nodule consequently becomes umbilicated like a sucked orange. In old metastases, such as this from the liver of which

I show you a photograph, the central portion presents no evidence of cancer, and consists simply of dense fibrous tissue.

#### *Centrifugal Spread of Repair as Affecting Groups of Secondary Nodules.*

It has already been shown that the microscopic processes of repair in cancer spread in a regular centrifugal manner away from the point of origin of the primary growth. It might reasonably be suspected that, taking a group of macroscopic nodules, the same centrifugal spread of the process of repair would be noticeable, for the secondary nodules near the primary growth are necessarily older than those further away. Indications of the centrifugal spread of repair, as affecting groups of massive nodules, are not hard to find. For instance, in this photograph, which shows subcutaneous nodules round a breast cancer, the nodules in the immediate neighbourhood of the breast are large, confluent, and ulcerated, while those further away are smaller, and have not yet reached the stage of ulceration. But it is very difficult to obtain convincing evidence of the completion of this centrifugal process of repair in groups of nodules, owing to the anatomical complexity of the lymphatic system.

Conclusive observations can only be secured provided that it is possible to watch the spread of permeation and nodule formation in a lymphatic plexus of extensive area, accessible to observation and lying in a single plane, and provided also that the cancer obtains access to this plexus

at a single definite point from which its centrifugal spread commences.

In rare cases of stomach cancer these exacting conditions are fulfilled. In some cases of gastric carcinoma I find that the growth penetrates the abdominal wall at a point in the middle line just above the umbilicus. At this point permeation extends from the subserous lymphatic plexus to the deep fascial lymphatic plexus, and commences to spread centrifugally in the latter plexus. This invasion is followed by the appearance of a crop of subcutaneous nodules spreading centrifugally from the umbilicus. Such a case was recently under the care of my colleague, Dr. Essex Wynter, and on two occasions, the first a month before death, the second at the necropsy, I made careful drawings to show all the subcutaneous nodules present. I would add that the second drawing was made without any reference to the earlier one. The later drawing shows that the centrifugal spread of permeation in the fascial lymphatic plexus had made considerable progress. But this is not the point to which I would especially draw your attention.

In the earlier drawing (Fig. 1) the region immediately around the umbilicus is thickly sown with nodules. In the later drawing (Fig. 2) not a single nodule can be seen within a considerable distance of the point at which the fascial plexus was invaded. These sketches, therefore, afford a convincing and at present unique proof of the centrifugal spread of macroscopic repair as affecting, not single nodules, but groups of nodules.

#### CAUSES OF CENTRIFUGAL DEGENERATION IN CARCINOMA.

Why does a carcinoma cell ultimately degenerate and die? The phenomenon cannot be ascribed to the hostility of the phagocytes, for it is one of the most striking features of the histology of cancer that degeneration of its cells

precedes in point of time the access of wandering cells to the area of degeneration. Upon this point my observations have been confirmed by those of Bonney. Nor is the degeneration of the cancer cells due to the development of anticancerous properties in the fluids of the body, as Lomer is inclined to think. Beyond the area of degeneration the cells of the microscopic growing edge will be found actively spreading along the lymphatics and exhibiting a vigorous vitality, which sufficiently shows that no anticancerous bodies are present in the lymph. It would doubtless be true to say that failure of nutrition is the proximate cause of the degeneration which carcinoma exhibits.

We have seen that in any group of carcinoma cells the central cells—those furthest from the base of supply—are always the first to degenerate. But there is something special and peculiar about this failure of nutrition, for, as I have previously shown, immersion in the blood stream—the rich nutritive stock and common food supply of the body—is usually fatal to epithelial cells.

No doubt the excessive pressure produced by the active proliferation of the cancer cells is one cause of impaired vitality in the older deposits, and this pressure is increased by the contraction of the newly-formed cellular stroma in which the older foci of growth are embedded. There is, however, another factor to be taken into account, and one the importance of which I have only recently realized. If you look at this section of a permeated lymphatic, much distended and approaching the point of rupture,

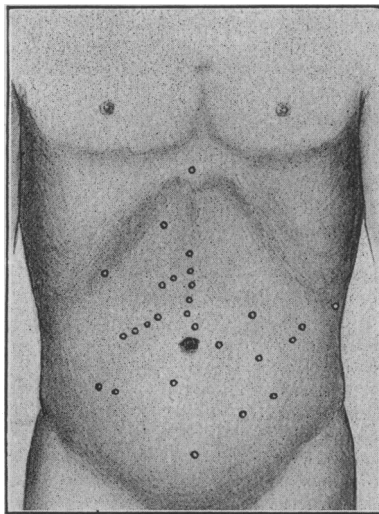


Fig. 1.—A chart of the subcutaneous nodules, spreading from a point just above the umbilicus, present in a case of stomach cancer one month before death.

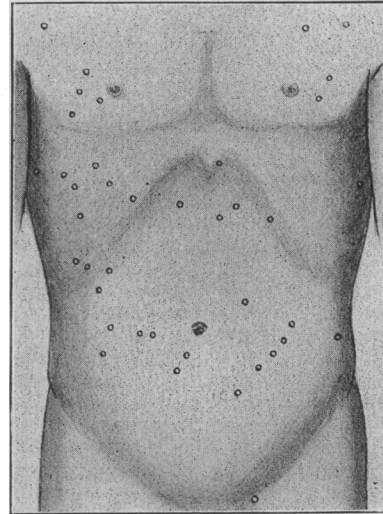


Fig. 2.—A chart showing the same case at the time of death. The nodules have continued to spread, but they have vanished from the region where they made their first appearance.



you will see that a single layer of cells at the periphery, although necessarily subject to the same pressure as the more degenerate central cells, still preserves the appearances of vigorous life. The chief point of difference in the environment of the peripheral healthy layer of cells is that they, as contrasted with the central degenerate cells, are in immediate contact with a layer of endothelial connective tissue cells. In this section of a stomach cancer which I show you, the dependence of epithelium for nutrition upon actual contact with connective tissue cells is even more strikingly shown. The cancerous epithelium forms everywhere a single layer lining the distended lymphatics of the permeated subserous lymphatic plexus, and all the central cells have entirely disappeared.

The solution of the problem of centrifugal degeneration in cancer appears to be suggested by the two sections I have just shown you.

*The Epithelial Cell an Obligate Parasite upon the Connective Tissue Cell.*

Certain of the cells of the body—the leucocytes, for example, and probably the haemal endothelium—are nourished directly from the blood plasma. Others, including most, if not all, of the cells of the connective tissue, are fed by the diluted blood plasma which is known as lymph. But the epithelial cells, in the course of their specialization, would appear to have lost this power of taking up nourishment directly from the body fluids. Epithelium appears to depend for its nourishment upon the products of the connective tissue cell conveyed to it, either by actual contact, or at least by close contiguity. The inability of epithelium to nourish itself from the fluids of the body is not a mere theory. I have shown in previous lectures that immersion in the blood stream is nearly always fatal to cancerous epithelium. Veit's work upon the deportation of chorionic villi shows that the same thing is true for the normal chorionic epithelium. Moreover the chorionic epithelium, although specially designed to hang into the blood stream, exhibits by the imperfect segmentation of its cells and the formation of syncytium, a process analogous to that by which the toxin of the tubercle bacillus leads to the formation of giant cells. And I would here remind you that the so-called syncytium is not, as is so often thought, a structure peculiar to the chorion; it may occur in any carcinoma when its cells come into intimate relation with the blood stream.

It would take too long to marshal the facts of normal histology which support this view that the epithelial cell is an obligate parasite upon the connective tissue cell. The many-layered epithelium of the skin which appears at first sight to contradict it, in reality forms one of the best proofs of its truth. The deeper layers of the skin epithelium are penetrated by a network of branching processes, easily visible in the negro because pigmented, derived from the underlying connective-tissue cells. The superficial layers of the epithelium, from which these nutritive processes are absent, are continually dying and being cast off.

In his recent Hunterian lectures,<sup>6</sup> my colleague, Professor Bonney, has established the new and very important fact that a local increase in the cellularity of the subepithelial connective tissues, accompanied also by a destruction of the elastic tissue, invariably precedes the appearance of a carcinoma.

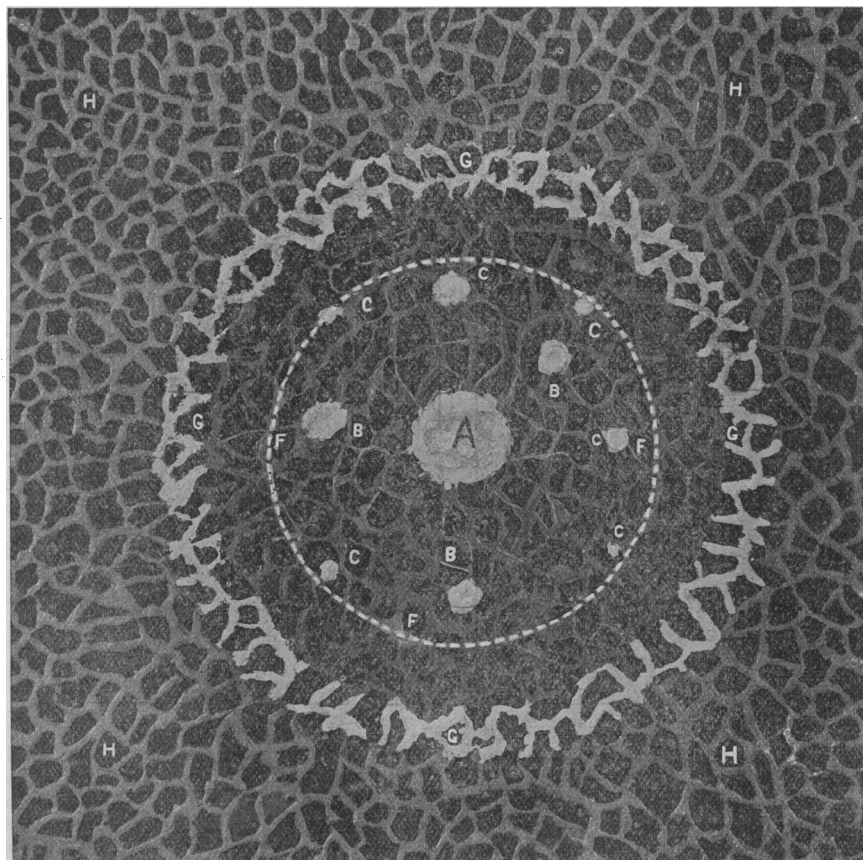
This increased cellularity is due to a precedent chronic inflammation. But if the chronic inflammation has progressed farther, and has reached the stage of fibrosis and diminished cellularity, he finds that there is little risk of a carcinoma originating in the fibrosed area. Dr. Bonney interprets the effect and mode of action of these changes as consisting essentially in the removal of various obstacles, to the process of infiltration. He says:

The tissue cell proliferation results in a rarefaction of the connective tissue in front of the advancing carcinoma cells, in the course of which mechanically resistant structures such as fibrous tissue and elastic fibres become softened and destroyed.

From my point of view,

the precarcinomatous increased cellularity of the subepithelial connective tissues, which Dr. Bonney has demonstrated, acquires additional significance. If the epithelial cell, normal or cancerous, can live only as a parasite on the connective-tissue cell, an abnormal aggregation of connective tissue cells beneath an area of epithelium will obviously tend to promote epithelial activity, and will provide a body of hosts or caterers who will supply the needs of any epithelial cells which penetrate into the rarefied precarcinomatous connective tissue.

Thus Dr. Bonney's observations would seem to offer strong support to my view of the parasitic nature of epithelium. But newly-formed connective tissue, such as is found in the scar of a wound, and in the stroma of a carcinoma, does not maintain its cellular character indefinitely. It becomes more and more fibroid, until



Figs. 3 and 4 are schematic representations of two stages in the life-history of a carcinoma. The lymphatic plexus, H H H, and the microscopic regions of the carcinoma, are represented as highly magnified, while the primary growth and its naked-eye secondary nodules are reduced in size.

Fig. 3.—A Carcinoma in the Evolutionary Stage. The active primary growth, A, is surrounded by secondary nodules, B B, and by smaller and younger secondary nodules, C C. The circle F F F is an imaginary line, separating the clinically appreciable region of the carcinoma from the outlying microscopic region, in which is found G G G, the microscopic growing edge of permeated lymphatics. Beyond G G G is the normal lymphatic plexus, H H H, while inside G G G the vessels of the lymphatic plexus, represented as thin white lines, have been destroyed and converted into fibrous threads.

only a few scattered cells, represented by mere nuclei, can be seen within it. According to Dr. Bonney, senescence of the stroma and degeneration of the cancer cells advance *pari passu*. And this is exactly what would be expected from the nutritional dependence of the epithelial cell upon the connective-tissue cell.

If it be granted that the cancerous epithelial cell depends for its adequate nourishment upon contact with a connective tissue cell, the centrifugal processes of repair in cancer become easy to understand. Considering first any small group of cancer cells, their continued proliferation must necessarily remove the more central cells from contact with the surrounding connective tissue, and must therefore lead to degeneration of the centre of the mass. In the second place, newly-formed connective tissue, such as composes the stroma of a cancer, rapidly and invariably becomes senile; that is to say, its cells disappear and are replaced by fibrous tissue, poor in cells, and therefore ill-adapted to nourish epithelium. Such appear to be the factors on which the natural cure of cancer depends.

It will be objected, and with some force, that certain carcinomata, neither at the time of the patient's death nor before, show any evidence of the centrifugal reparation which follows centrifugal spread.

It is certain, of course, that a carcinoma may cause death while it is yet in the infiltrative stage, and before there is any evidence of permeation; that is to say, the primary growth may be the only focus of the growth present in the body. But even in such cases,

ulceration, commencing at the centre, and spreading to the circumference of the growth, is a practically constant phenomenon, which testifies to the presence of commencing centrifugal repair. The evidence of centrifugal repair may be incomplete and partial simply because the life-cycle of the carcinoma, which probably varies extremely in length, may be still in one of its earlier stages at the time of the patient's death. At any period in this life-cycle, invasion of one or more of the serous cavities may take place, and may cut short the evolution of the growth by producing rapid visceral dissemination and death.

#### THE LIFE-CYCLE OF A TYPICAL CARCINOMA.

From the facts which I have laid before you I think it is possible to work out a scheme of the life-history of a typical carcinoma.

*Stage I.*—The growth is infiltrating the tissue interspaces around its point of origin, but has not yet obtained access to the lymphatic vessels which open out of them.

*Stage II.*—The growth obtains access to the small lymphatic vessels near its point of origin, and permeation

commences to spread centrifugally from this point. At this stage cancer cells obtain access to the trunk lymphatics, and embolic invasion of the lymphatic glands occurs as a minor and subsidiary process.

*Stage III.*—The permeative growing edge, spreading centrifugally, is cut off from the massive primary growth by fibrosis of the intervening permeated lymphatics. The symptoms dependent on contraction or puckering (retraction of nipple, flattening and shrinkage of the breast) consequently begin to show themselves, and the carcinoma becomes clinically recognizable.

*Stage IV.*—The massive primary growth continues to increase in size by infiltration. Around it, in the area of perilymphatic fibrosis, small macroscopic satellite nodules begin to manifest themselves. The permeative growing edge is now reaching such a diameter that the verge of operability may be approached (Fig. 3).

*Stage V.*—Although the growth continues to spread, centrifugal degeneration of the massive or macroscopic deposits is now beginning. It affects first the oldest portions of the cancer. The primary growth becomes degenerate and fibrotic at its centre, and consequently if the growth is on a surface, ulceration begins. The ulcer spreads centrifugally. The secondary nodules nearest to the primary growth degenerate from their centre outwards and disappear, while new ones spring up in the outlying area of lymphatic fibrosis left in the track of the still spreading microscopic growing edge.

*Stage VI.*—The proliferative energy of the massive or

macroscopic primary growth is exhausted. It ceases to spread, ulcerates to its margin, and finally heals over, leaving a scar from which cancer cells have disappeared. The secondary nodules have disappeared from the area immediately round it, also leaving scars. The centrifugal spread of the permeative growing edge may conceivably at this stage be arrested, but it usually continues to spread indefinitely, leaving in its track fresh secondary nodules (Fig. 4). This cycle of events may be interrupted at any point after Stage II by invasion of the serous cavities, or in rare cases by successful blood infection, and by consequent rapid visceral dissemination shortly terminating in death.

#### CANCER THERAPEUTICS: A CRITICISM.

The literature of cancer therapeutics does not contain the record of a single fact which cannot be paralleled among the histories of untreated cases. How, then, is the value of any particular method of treatment to be determined? It is futile to bring forward a few isolated cases in which the shrinkage or disappearance of primary or

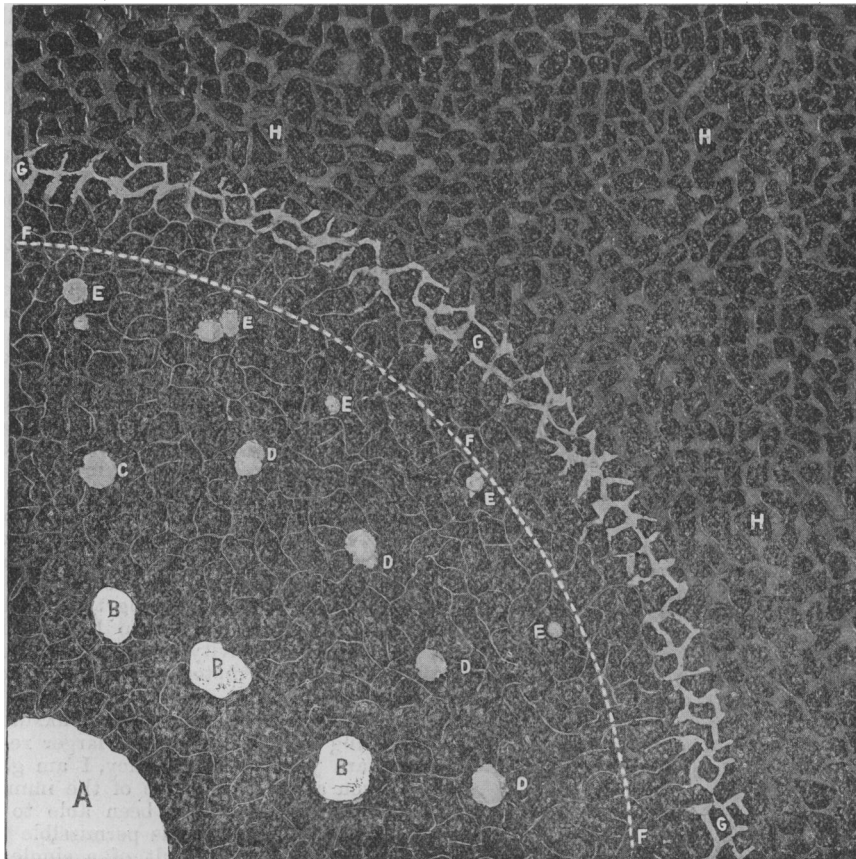


Fig. 4.—A Carcinoma in the Involutionary Stage. The primary growth, A, and the oldest secondary nodules, B B B, have now become completely fibrotic and inactive, and are represented by puckered scars. Fresh nodules, D D D, and others, E E E, still younger and more remote, have made their appearance in the rear of the microscopic growing edge, G G G, which, continuing to spread, has now attained a very large diameter, and is still advancing into hitherto intact regions of the lymphatic plexus, H H H. Within G G G all the lymphatic vessels have been converted into fibrous threads. Other letters as before.

secondary growths has been observed, for these phenomena, as we have seen, belong to the natural course of the disease. Their occurrence as testimony to the value of a remedy would only be significant when they frequently and immediately followed upon its employment in a number of consecutive cases. But in any case where centrifugal spread has been rapid and regular and accompanied by a crop of secondary deposits, and where upon the application of a remedy no further deposits appear, the remedy may be fairly presumed to have exerted an influence. In this connexion it may be pointed out that cases of stomach cancer, with invasion of the fascial plexus at the umbilicus, and with a crop of skin nodules spreading from this point, afford the conditions for crucial experiment in cancer therapeutics which are absent in almost all other cases. The observer sees the growth, as evidenced by skin nodules, spreading from a definite point in a definite plane. With the patient's consent, local measures, such as  $x$  rays, might be applied to one half of the body, while the other half remains untreated as a control. The effect of constitutional measures might be determined by their effect on the observed rate of spread of nodules from the umbilicus—a rate which can be determined from week to week, if not from day to day. More careful observation of these cases would give a precision to the study of the medicinal therapeutics of cancer which is at present conspicuously wanting.

It is not too much to say that a study of the processes of natural cure in cancer absolutely destroys the clinical evidence in favour of trypsin as set forth by Dr. Shaw-Mackenzie, the pioneer and introducer of this treatment. And the same thing is true of all other internal medicaments at present known, as judged by the published evidence, with the single exception of Coley's fluid in the treatment of sarcoma, a remedy which appears to possess distinct value. There would seem also to be no doubt of the effects of  $x$  rays in promoting the natural tendency to fibrosis in masses of malignant tissue which are directly accessible to the influence of the rays. But a very thin layer of normal tissue is sufficient to protect cancer cells from the action of the rays.

Fibrosis of the primary growth is often interfered with by the onset of sepsis, which necessarily produces increased local cellularity of the connective tissue. The beneficial effects of curettage and escharotics in advanced uterine cancer, perhaps also the temporary good effects of  $x$  rays and high frequency currents, are probably partly due to the antiseptic value of these measures. After their use the process of fibrosis of the primary growth is able to resume its normal course, and great local improvement occurs, without any arrest of the spread of the disease.

#### SECONDARY EFFECTS OF THE PROCESS OF NATURAL CURE.

One of the most striking facts brought out by my investigations is that the permeative spread of the cancer is followed by an almost coextensive destruction of the lymph-vascular system, and by contraction of the network of fibrous threads which replace the system of lymphatic vessels. The consequences are varied and important. They may be considered under the following three headings:

##### I.—*Contraction of the Tissues around a Carcinoma.*

The defensive process of perilymphatic fibrosis, and not the destructive processes of permeation and infiltration, is the cause of most of the symptoms by virtue of which an external cancer becomes clinically recognizable. In the case of the mamma, retraction of the nipple, flattening and shrinkage of the breast, adhesion to skin and fascia, all these symptoms are evidences of perilymphatic fibrosis, that is to say, of attempts at natural cure of the disease. Their absence is of no value in any given case as evidence against malignancy.

The tendency of a carcinoma to drag in towards itself a wide area of the surrounding apparently healthy tissues, a tendency which has never received a clear or adequate explanation, is an inevitable sequel of the process of perilymphatic fibrosis. If over a wide area round the growth the normal network of lymphatic vessels is replaced by a network of newly-formed, and, therefore, contractile, fibrous tissue, a general puckering and shrinkage of the affected zone is bound to follow.

##### II.—*Cancer en Cuirasse.*

The leathery thickening of the skin of the chest which is sometimes seen in breast cancer is not in its earlier stages accompanied by any cancerous infiltration of the integument. I have shown that the thin skin of the female breast may in these cases attain a thickness of 6 mm. before any sign of cancerous infiltration is manifest. The condition is primarily a pachydermia or lymphatic oedema of the skin, due to destruction of the fascial lymphatic plexus, and to consequent lymph-stasis. Only in the later stages is the skin actually invaded by cancer cells.

##### III.—*The Brawny Arm of Breast Cancer.*

According to Mr. Sheild, the brawny arm of breast cancer is due to the pressure of a mass of growth upon the axillary vein. But excision of part of the axillary veins is not, as a rule, followed by swelling of the arm, which, moreover, is frequently seen in cases where no palpable axillary growth is present. My senior colleague, Mr. T. W. Nunn,<sup>7</sup> has pointed out that the axillary veins may be completely enveloped in a cancerous mass, and yet the arm may not be swollen. He believes that the oedematous arm is due to obstruction of the main lymphatics by growth within them, and, no doubt, this is a part of the truth. But ablation of all the axillary glands, which must involve complete interruption of the trunk lymphatics, is not, as a rule, followed by oedema of the arm, doubtless because a collateral lymphatic circulation is established. Some other factor besides obstruction of the axillary trunk lymphatics is evidently necessary.

The permeation theory of dissemination appears for the first time to explain fully the condition. Perilymphatic fibrosis, the sequel of permeation, destroys the affected lymphatics utterly, leaving only fibrous cords to represent the original vessels. The process is not restricted to the lymphatic trunks, but affects also the smaller lymphatics. As soon as lymphatic fibrosis has extended some little way down the arm the lymphatic connexions of the whole limb are entirely severed, and the lymph can only return partially and imperfectly by percolating through the tissue interspaces. A condition of lymphatic oedema results, which in time produces the brawny arm of breast cancer.

The brawny arm may be found fully developed in cases where no evidence of active cancerous growth remains. It is a pachydermia affecting the arm in consequence of lymphatic fibrosis, and is to be regarded rather as an evidence of the activity of the natural curative processes than as a direct symptom of cancerous growth.

##### THE OPERATION OF LYMPHANGIOPLASTY.

Pending the achievement of larger results by methods which are yet in their infancy, I am glad to be able to show you a minor instance of the immediate fruition of cancer research. I have been able to devise a simple operation by which, if it is permissible to judge from the strikingly successful result of a single recent case, the brawny arm of breast cancer may in future be prevented or cured with restoration of the usefulness of the limb.\* The problem to be solved was this: How to provide a new set of lymphatic vessels for a limb in which the normal lymphatics have been destroyed.

Without going into detail I may say that the permanent introduction into the subcutaneous tissues of a number of buried silk threads running from the wrist upwards to terminate in the loose areolar tissue over the scapula appears to have solved the difficulty. In the case where I performed this operation the excess of fluid was rapidly drained away from the arm by capillary attraction, and the oedema subsided in a few days, although the condition was of nearly three years' standing. The pain was completely relieved. The operation is, so far as I know, an entirely novel one, and it appears to deserve a distinctive name, for it is probably applicable in pachydermia of every kind, whether due to the filaria, to cancer, or to septic lymphangitis.

I would suggest for it the name "lymphangioplasty," and I confidently hope that its usefulness will not be restricted to cancer, but that it will remove elephantiasis from the list of incurable diseases.<sup>8</sup>

This operation was the direct outcome of pathological

\* The results of a number of other cases have since confirmed this expectation. See *Archives of the Middlesex Hospital*, vol. xii, p. 28.

investigations, which showed that the brawny arm of breast cancer indicates arrest rather than great activity of the cancer process, and is produced by lymphatic obliteration. Its success confirms the pathological conclusions upon which it was based, and shows that the more recent methods of pathological histology are full of unexhausted possibilities.

#### MEANS OF PROMOTING THE NATURAL CURE OF CANCER.

We have seen that the natural local cure of cancer is brought about by fibrotic processes which cut off the cancerous epithelium from that contact with connective tissue cells which is necessary to maintain its vitality. Superficially, at any rate, this process presents some analogy with the natural cure of tubercle, which also takes place by a process of fibrosis. And certain cases in which I have seen great apparent benefit to cancer patients as the result of a change of residence from town to country, or from a sea voyage, lead me to suggest that the open-air treatment, which has proved so successful in tubercle, may be worthy of trial in the more chronic cases of inoperable cancer. The treatment as applied to tubercle would require modification for cancer; the carcinoma patient, for instance, as contrasted with the tuberculous patient, would probably require less food and more exercise; but there would appear to be no very strong objection to the tentative treatment of cases of inoperable cancer side by side with cases of tubercle in sanatoriums. Under no circumstances whatever should the treatment be recommended as a substitute for operation, if operation is possible.

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## THE TREATMENT OF CANCER BY THE USE OF POTASSIUM BICHROMATE.

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#### [A PRELIMINARY COMMUNICATION.]

THROUGH the courtesy and indulgence of the Editor of the *BRITISH MEDICAL JOURNAL*, I am permitted to lay before the profession, of which I have the honour to be a member, a number of cases of cancer successfully treated by the use of injections of bichromate of potassium into the substance of the tumour. The dose used is from 7 to 10 minims of a sublimate solution; in some cases 15 minims are injected. In 1906 I submitted a paper on the treatment of rodent ulcer, which perhaps at that time was not of sufficient importance to claim publicity. Since then, however, about 25 cases of cancer treated by my method, with notes, were presented to the Académie de Médecine, Paris (November 29th, 1908). It is these cases, with notes, I herewith present for the unbiased and charitable criticism of my professional brethren.



Fig. 1.—Case II. Cancer of breast beginning to slough.

she consulted me, having first consulted Dr. Jackson of Nelson, who informed her that the cancer had returned. There was a lump about the size of a hen's egg in the line of the cicatrix. I commenced treatment in January, and it was quite well in March, 1908. The result of the treatment is that there has been no further recurrence. She has lost the cancerous cachexia, and is looking quite well and feeling strong. This was a case of secondary scirrhus.

#### CASE II.

Miss N., of Nelson, aged 42. She came to me on May 21st, 1907, with a lump in the breast. This the Clinical Research Association, London, reported on as follows (May 30th, 1908): "This is evidently a malignant growth of a carcinomatous type. But the specimen is too small to say whence it has originated." She was not well until June, 1908, on account of my having been ill with rheumatic fever, and the treatment having been suspended. The photographs show the case when it began to slough, and when (on November 3rd) it was quite well.

#### CASE III.

Mrs. B., of Bristol, aged about 54. She came to me in June, 1906, with large growth in breast. The doctor in Bristol advised her to have breast taken off for cancer. On examination I found a large growth which had fastened itself upon the ribs just over the heart. She was under treatment about four months. When the slough came away a large portion of one rib came away also. Dr. Laurent, Professor of Operative Surgery at the University of Brussels, saw this case at my house. His opinion was that there had first been some tuberculous condition preceding the cancerous growth. I had a report from her on October 28th, 1908. She is quite well, with the exception of some peripheral neuritis. Her own doctor in Bristol is of opinion that the general neuritis is due to an exposed intercostal nerve—a nerve exposed by the portion of rib sloughing away. She put on 20 lb. in weight after treatment. She looks well and has lost the cancerous cachexia which previous to treatment was well marked. Dr. Dymoke and Dr. Reynolds, of Bristol, both say it was a case of cancer.

#### CASE IV.

Mrs. K., of Blackburn, aged 82. She came to me in 1906 with a large tumour in the posterior triangle of the neck. The Clinical Research Association report, November 3rd, 1906, was: "This specimen is a portion of the integument. Its deep surface is invaded by a new growth, which appears to be an epithelioma. There are no cell nests, but the central cells in the processes have undergone granular degeneration. The lesion is evidently a secondary formation." The photographs (see p. 590) show the growth previous to treatment and the condition afterwards. This patient died about December, 1907, from some intercurrent disease; I think it was bronchitis.

#### CASE V.

T. S., of Accrington, aged 77. He had a rodent ulcer on right right side of nose as large as a franc. He went to Dr. Frankish, who told him it was a cancer, and refused to attempt anything for him. He came to me on November 5th, 1907, and was well in seven weeks. I applied bichromate upon cotton-wool to the place, the cotton-wool remaining *in situ* until the following day. He had four applications. Slough followed, which separated in about three weeks, leaving a clean granulating sore, which healed up in a week.

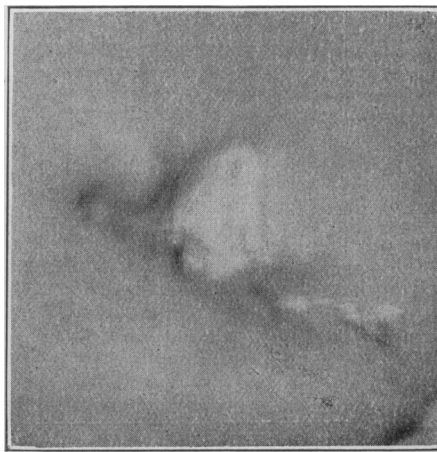


Fig. 2.—Case II. Cancer of breast. After treatment.

#### CASE VI.

Mrs. McL., aged 52. First went to Dr. Reid of Preston, then came to me in February, 1908. The Clinical Research Association report, February 14th, 1908, was: "This piece of tissue is infiltrated by a carcinoma, which is spreading along the lymphatics in the cutis vera. The growth has the usual

characters of a scirrhus carcinoma." She was quite well on July 20th, 1908, as she was also at the last report on November 3rd. Accompanying are photographs (see p. 590).

#### CASE VII.

Mrs. P., aged 53. She saw Dr. Cran Duthie of Blackburn and Dr. Rawlins of Manchester—a cancer specialist—in May, 1907. Both advised her to have the breast off. She came to me the same month, and was quite well by October 20th, 1907. She

#### CASE I.

L. A. R., aged 47. She had her breast taken off at the Victoria Hospital, Burnley, in August, 1907. In January, 1908,