Surgical Section.

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Mr. GODLEE in the Chair.

The Growth of Malignant Disease in Man and the Lower Animals, with Special Reference to the Vascular System.

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ON two previous occasions I have had the honour of addressing meetings in London in connection with work referring to the relation of cancer to the vascular system. In coming before you to-day, I do not wish to travel over ground already known to you. It is my main intention to give you a short *résumé* of the whole extent of my work, and at the same time to draw your attention to methods of investigation which I am sure will prove beneficial to all willing to co-operate with me in the solution of a problem so intimately associated with the biology of malignant growths. My work has been conducted on human and animal material. I owe a debt of gratitude to Professor Ehrlich, of Frankfort, and to Dr. E. F. Bashford, of London, for valuable material derived from the mouse, such as carcinoma in its various forms, sarcoma, mixed tumours and chondroma. In the short time at my disposal I can only mention my general results. A detailed account of, and an exhaustive reference to, the literature of the subject will be found in a forthcoming treatise. The points of view from which I have approached my subject are the following: (1) How far is the vascular system responsible for the dissemination of malignant growths? (2) What are the general conditions of circulation in these growths? and (3) What purpose does the multiplication of blood-vessels in malignant growths serve—merely that of nutrition or also that of defence?

As to the dissemination of tumours along the vascular system, I may refer to a treatise of mine published several years ago in which I proved,

by means of an elective stain for elastic tissue, that both in the early stages of sarcoma, as well as carcinoma, an extensive invasion of tumour cells into the coats of blood-vessels occurs. It is a striking fact that this happens far more frequently in veins than in arteries, and again that the results of this invasion can only be traced locally, rarely exceeding the area of round-cell infiltration. Exactly similar results have been obtained in the case of carcinoma and sarcoma of the mouse. In examining mouse tumours, we must always bear in mind that we are dealing with vessels of comparatively small dimensions, whose elastic coat is hardly comparable with that of man. And yet careful investigation reveals in tumours of mice all the various stages of vascular degeneration common to man. I place such stress on these conditions as my extensive study of benignant growths, even of those verging upon the boundary of malignancy—for instance, goitre—has proved to me that tumour-cell infiltration into the walls of channels bounded by elastic tissue is a feature characteristic of malignant tumours only. I may add that, in those cases in which carcinoma of the mouse invades the lymphatic glands, the pathological condition of these glands is a counterpart to that found in man. The cells enter the marginal sinus and penetrate thence along the lymphatics into the medullary substance of the gland. It seemed to me of great interest to enquire into the conditions under which the tumour cells enter into the vascular coats. At a first glance it appeared most probable that they travel along the lymphatics. Yet all anatomists concur in declaring that the vascular coats contain no lymphatics, a statement confirmed by evidence gained from pathological experience, especially in cases of backward transportation of tumour cells along the lymphatic channels. In these cases the cells are almost exclusively confined to the perivascular spaces, and hardly ever penetrate the vascular walls. Hence we are bound to assume that the dissemination of tumour cells into the vascular coats is effected by blood-vessels. This seems all the more likely when we consider how different are the appearances of arterial and venous cancer, and how the distribution of tumour cells in arteries and veins coincides with that of the vasa vasorum. In arteries the tumour cells rarely proceed further than the outer coat, whereas in veins they are generally found beneath the intima. Thus arterial cancer appears as a form of periarteritis, venous cancer as one of endophlebitis carcinomatosa. Now it is accepted on all sides that the vasa vasorum in arteries remain within the limit of the outer coat, rarely branching into the superficial layer of the middle one, whereas in veins they extend beyond the middle coat into

the region of the intima. It is a remarkable fact that this question, which is of vast importance in the pathology of the vascular system, has met with such scanty attention in recent years.

In order to gain experience of my own, I made use of a series of injections performed on fœtuses, bodies of newly-born children, and on amputated limbs removed from individuals of various ages and for various reasons, such as injuries, tuberculous joint or bone disease, and senile gangrene. I applied a method which furnishes us with ideal preparations, and found that in fœtuses and newly-born children there is no material difference between arteries and veins as regards their nutrient vessels. The distinction previously mentioned is found in the first year after birth and prevails as long as the vessels remain intact. Hence arteries perform their important functions with a minimum supply of nutrient vessels. This explains the fact that we may dissect out an artery completely from its surroundings without affecting its nutrition, and again, that the artery retains its marvellous power of healing although cut off from its original base. The blood supply of the arterial wall explains another and almost more important fact, viz., that, as Virchow puts it, the arteries act as isolators of pathological processes. All this changes as soon as pathological conditions arise in the artery, from within or without. Then the connective tissue, and, above all, the vasa vasorum, begin to proliferate, and finally we find vein and artery alike permeated throughout their whole breadth by numerous vascular channels. Such conditions are most common in vessels within the area of malignant growth, and it stands to reason that such vessels are more likely to harbour the tumour cells than healthy ones.

We must next consider whether these degenerative conditions in the vascular system are the causes of secondary growth. I believe that our views as to metastasis have been much modified by recent experience, which goes to prove that, both in man and animals, tumour cells pass into the circulation even at an early stage of the malignant growth. Lubarsch, Borst and others are therefore right in declaring that we must clearly distinguish between embolism and metastasis in malignant growths, as so many of the tumour cells are destroyed within the circulation before they establish secondary tumours. The conditions under which these arise are most complicated, and probably depend upon a number of factors, partly of a chemical nature, hitherto quite unknown. The question which has given rise to much discussion is how these cells get into the vascular system. There can be no doubt that vascular degeneration, such as I have described, is

a predisposing factor, and yet Martin B. Schmidt has proved almost to a certainty that in his remarkable cases of abdominal cancer, in which diffuse embolism of the pulmonary arteries took place without the appearance of secondary lung tumours, the cells entered the blood-vessel through the thoracic duct. I am inclined to believe that we gain a more definite conception of the whole question of metastasis by paying due consideration to recent research work bearing on acute wound infection. Besides others I have, especially, Nötzel's work in mind; he has proved, in a series of experiments conducted on rabbits, that, after injection of bacteria into the knee-joints, these bacteria appear within a few minutes in the regional lymphatic glands and in the general circulation as well. The fact that these experiments were performed on healthy joints without any damage to them, and also without undue pressure of the injected material, allows of one conclusion only—that the absorption of the injected bacteria was effected by the lymphatic system. The rapid dissemination of the germs in these experiments appears to clash with the current theory of lymphatic circulation, inasmuch as the interposition of lymphatic glands has always been regarded as a retarding factor. Nötzel justly reminds us that, even in the lymphatic glands, anastomoses exist between afferent and efferent vessels, and that, according to the extensive investigations of Druner, such anastomoses are a most common occurrence among the larger lymphatic ducts. This again concurs with our surgical experience, which has shown that transverse ligature even of the thoracic duct has no ill effect upon the lymphatic circulation. On this basis we fully understand how germs travelling along the lymphatics enter the vascular system rapidly and without necessarily passing the lymphatic glands. We must, therefore, cease to regard the lymphatic glands as local centres of defence or as filters. All these facts have, in my belief, a most important bearing upon the problem of tumour metastasis.

As regards the relations between the lymphatic and vascular systems, I am inclined to assume that they are far more intimate than we have hitherto believed. It has struck me when injecting veins, such as the jugular, which are encompassed by lymphatic glands, that the injected fluid passes with the greatest ease into the glands, from which I infer that the vascular systems of gland and vein are closely associated. There must be relations of an intimate nature between the two systems.

I will not dwell upon the subject of hæmolymph glands, which are said to occur in man, but I wish to draw your attention to recent

embryological research. Serbin, of the Johns Hopkins University, has shown that in man and mammalia of a high order the whole of the lymphatic system is a derivative of the veins, not only of the jugular but also of the iliac veins. Numerous instances have been recorded by anatomists of the older school in which great lymphatic trunks have been found to enter into other than the jugular veins, such as the iliac, azygos and others. Unfortunately, Henle's refusal to accept these observations has debarred others from following up more closely the question whether such connections actually exist, or whether they are to be regarded as exceptional. Not until all these dubious points are perfectly cleared up can we hope to understand the question of metastasis in general, and of tumour metastasis in particular.

I now arrive at my second point: What are the general conditions of circulation in malignant growths? For information on this score we are obliged to go far back into the history of medical science, back to the writings of John Hunter, Schroeder van der Kolk, Broca and others. In recent years Ribbert has been the only one to deal with this question, which he does in a short paper in which he endeavours to prove that the deficiency of blood-vessels in carcinoma is the cause of cell necrosis. In order to elucidate this point more precisely, I have applied different methods for the human individual and the mouse. In cases of human cancer, I exposed the femoral artery and injected an emulsion of bismuth and oil into the blood-vessels. After tying the afferent and efferent vessels of the cancerous organ, I dissected them most carefully from their surroundings and exposed them to the X-rays. These specimens are incomplete from an anatomical point of view, yet they give us a general idea of the state of vascularisation in cancer. This is well demonstrated in my plates taken from cases of carcinoma of stomach, liver, and other organs (figs. 1 and 2).

On examining these plates, the first point that strikes us is that the regular distribution of blood-vessels is disturbed by the invading growth. We know from the splendid work which Mall and his pupils have done that the distribution of blood-vessels in the various organs is characteristic of them, and dependent chiefly upon their embryological development. As soon as a tumour develops in the liver, stomach, or any other organ, we see that their regular formation is replaced by chaotic irregularity. We find, also, in the growing tumour, an extensive new formation of blood-vessels. This is most apparent in the zone of proliferation, which in infiltrating tumours is at the periphery. As the cancerous growth increases in volume, its centre

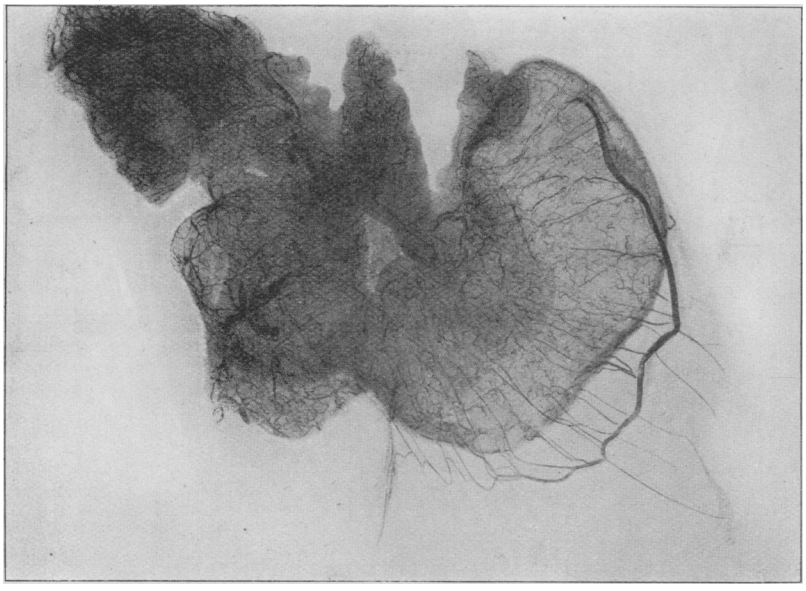

FIG. 1.
Carcinoma of Stomach.

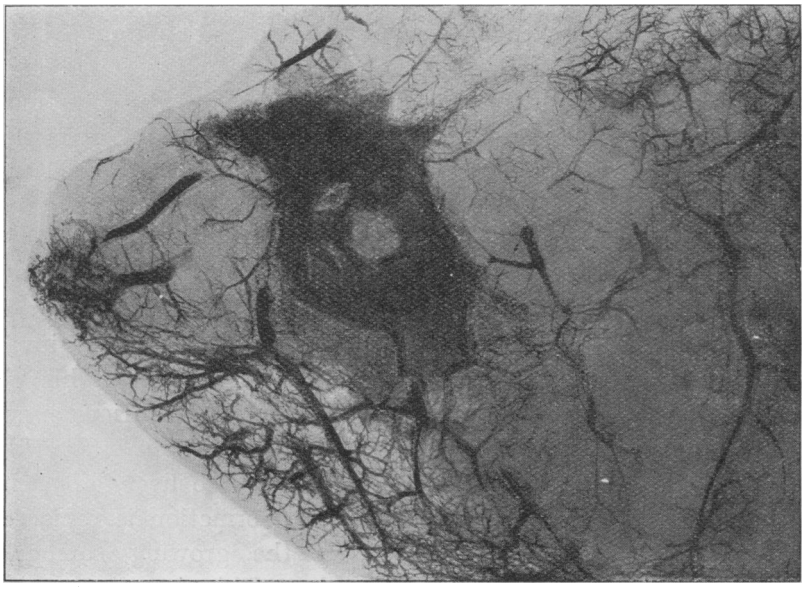

FIG. 2.
Carcinoma of Liver.

becomes necrosed and the newly-formed blood-vessels merely occupy the capsule. Ultimately the blood-vessels seem to disappear altogether, so that in this stage cancer is not rich in blood-vessels, but rather denuded of them. The mass of newly-formed vessels is of small calibre, and their branching is irregular to such an extent that big vessels split up into the smallest of their kind without intermediary types.

In order to amplify the results obtained in man, I have injected spontaneous and experimental growths occurring in mice by means of the following method. After exposing the heart of the anæsthetised animal I punctured the organ and injected Indian ink, avoiding excessive pressure. Indian ink, as the Johns Hopkins School of Anatomy has shown, is a medium which flows easily into the blood-vessels and mixes freely with the blood. By manometrical regulation of pressure we are enabled to modify the result of the injection according to the desired effect. After injection the specimens were fixed and hardened in alcohol. For microscopical purposes transverse and in some cases serial sections of the whole animal were made, which enabled us to gain an exact estimate of the relations existing between the transplanted growth and the surrounding organs. Such specimens likewise enable us to judge the origin of the newly-formed blood-vessels, their number, form and width, as compared with adjacent tissues or organs.

Another set of specimens was cleared after the Schultze method, by placing them first in alcohol, to which a few drops of potassium hydroxide solution were added, then removing them into glycerinated alcohol, and finally into pure glycerine. Marked differences in the whole arrangement and number of blood-vessels were discovered in the various malignant tumours examined. One common feature was observable in all of them. As soon as infiltrative growth of the transplanted cells sets in, a great commotion is produced in the surrounding system of blood-vessels. The degree of commotion is dependent upon the wealth of pre-existing vessels; hence, in strongly vascularised tissue, such as mammary gland or muscle, the vascular irritation is far more pronounced than in subcutaneous tissue which is poor in vessels. This irritation is seen most distinctly in the vessels in front of the growing tumour, and can easily be traced in regions to which the tumour has not yet advanced. The most striking feature of the irritation is the dilation of the affected vessel. It curls itself up into spiral coils and sends forth numerous capillary offshoots towards the invading growth. In carcinoma the newly-formed vessels arrange themselves almost entirely in the

peripheral area. As the volume of the growth increases the number of vessels decreases, and eventually, especially in cases of complete necrosis, the vessels totally disappear.

In sarcoma, again, the numerous vessels of new formation are evenly distributed throughout the whole growth, presenting themselves as a delicate, closely-woven network, even in the interior of the tumour. Nowhere are the differences as to vascular supply between carcinoma and sarcoma more apparent than in mixed experimental growths of the carcinoma sarcomatodes type. Even in cleared specimens it is easy to single out the cancerous and sarcomatous spaces by the varied degree of vascular injection.

Wholly different are the appearances in chondroma of the mouse. As Ehrlich has shown, this extraordinary growth presents a blood-red surface on dissection, from which he infers that its cells have distinctly angioblastic properties. I found its capsule rich in vessels, and likewise the derivatives of the capsules, the wide bands of connective tissue, which separate the islands of cartilage. Many of these vessels penetrate into the cartilaginous masses and open out into large vascular spaces, apparently losing all the characteristics of blood-vessels. These vascular spaces disintegrate the cartilage tissue. Numbers of cartilage cells are thus destroyed.

Since these various tumours are produced in the same species of animals by units of implanted cells, the results obtained bring two points into clear prominence. One that has been recently demonstrated by Bashford and others is that the stroma of experimental tumours owes its origin to the inoculated animal, and is not derived from the grafted cells. Another point of greater importance is the fact that the structural qualities of the stroma are determined by the tumour cell.

From what I have said regarding the vascular condition of carcinoma and sarcoma it might appear that there is a fundamental difference between them, inasmuch as the new formation of blood-vessels in sarcoma is so much richer than in carcinoma. This view has been advanced by many of our leading pathologists, who maintain that carcinoma and sarcoma, owing to their genetic affinity to the epithelial and connective tissue cells, react respectively upon the lymphatic and vascular system. Unfortunately, we know next to nothing as to what changes carcinoma induces in the number of lymphatic vessels. All we know is that proliferation of lymphatic glands sets in, in a manner first described by Bayer, and recently confirmed by Ritter, who goes so far as to affirm

that the swelling and new formation of lymphatic glands are a typical and early response on the part of the body to the invading cancer cells.

Against the theory of diminished vascular activity in cancer it may be stated that different forms of cancer vary in their wealth of blood-vessels. Bashford has acquainted us with the interesting fact that in his long series of experimental cancers he has observed complete and distinctive difference in the strains. A tumour poor in vessels and much necrosed was transformed into one of an exactly opposite nature. In this connection I may refer to Ehrlich's interesting observation on the transformation of carcinoma into sarcoma in the mouse. As you know, Schmorl was the first to record a similar case in man, one affecting the thyroid gland. Quite recently I had to treat a case of mammary cancer in which complete removal of the breast and the axillary glands on both sides failed to produce a satisfactory result. Numerous secondary growths formed in the front chest wall. After the patient had recovered from a bad attack of pneumonia and extensive suppuration spreading over the front chest wall, the metastatic tumours in the skin broke down and formed polypous, extremely vascular growths, which ultimately led to the patient's decease. On examining these tumours of the skin in their later stages, it was found that all traces of cancer had disappeared, and that fusiform-celled sarcoma had taken its place. On the strength of all this evidence I do not hesitate to declare that the difference in the vascular activity of carcinoma and sarcoma is a quantitative and not a qualitative one. A marked difference exists between the destructive powers of the carcinoma and sarcoma cells, since destruction of blood-vessels is so very much more apparent in cancer than in sarcoma.

I mentioned that the impetus which gives rise to the proliferation of blood-vessels emanates from the invading cell. On the other hand, the study of experimental tumours has proved that the new formation of blood-vessels itself is dependent upon the general powers of the individual to react, as well as upon the physiological condition of blood supply in the invaded tissues. It seems more than probable to me that, in a system weakened by age or pre-existent disease, the vascular reaction induced by the malignant growth is below the normal or fails to take place, thus giving rise to a condition first described by Thiersch as premature senescence of the connective tissue in cancer.

In any case, I regard vascular neoformation as a standard by which

we may test the body's power of reacting against malignant tumours. On the other hand, we can measure the virulence *(sit venia verbo)* of the tumour cell by the extent of necrosis found in the growth. I suppose most pathologists of the day are agreed that necrosis is not caused by accidental reasons, such as pressure, malnutrition, and others. Borst has rightly pointed out that in growths highly vascularised necrosis is a common occurrence. I may refer you to the case of chondroma in the mouse, a growth essentially vascular and yet permeated by cell necrosis. Necrosis, as Ritter has put it, is intimately connected with the primary cause of the disease in the same sense that it is in tuberculosis or other infectious diseases. I differ from Ritter in one essential point. He looks upon the border of healthy cancer cells surrounding the necrotic area as a reactive cell proliferation on the part of the body, and the area of necrosis as the tumour *sensu strictiori*. These cells on the necrotic border are, I believe, the militant survivors of the invading group, whereas the body's reaction is marked, as I have tried to show, by the newly-formed blood-vessels and connective tissue. The area of necrosis is, in my opinion, the battlefield on which assailant and defender both perish, for it is not only the tumour cell that is destroyed but the stroma as well.

I have now reached my last point, the consideration of what purpose is served by the new formation of blood-vessels. It would traverse our modern views concerning the functions of the blood to assume that only nutrient and not also defensive material is borne along the newly-created blood-channels. How can we account for the difference of vascularisation in healthy and in diseased blood-vessels on the basis of a nutritive theory? A healthy artery performing vital functions has a minimum of nutritive vessels confined to its outer coat. As soon as disturbance of any kind sets in, blood-vessels spring up and ramify throughout the whole breadth of the vessel's wall. Is it at all probable that the body would produce such a mass of vessels in order merely to feed a circumscribed thickening of the inner coat, frequently the only anatomical lesion definable? Does it not seem far more likely that the newly-formed vessels serve an intensified circulation in the arterial coat, thus guarding it against change from within or without? Here again, as in the case of Ehrlich's side-chains, is an instance of an arrangement in the body originally destined to safeguard one of its organs, but eventually developing into a cause of harm. In this connection I may recall observations of my own, recently confirmed by Schmidt, Lubarsch, and others. Tumour cells constituting a thrombus or embolism may

multiply within a blood-vessel and spread along its branches without forming adhesions to the vessel's coat. In case such adhesions form —*i.e.*, as soon as infiltrative growth occurs—the mass of cells is organised in the fashion of the ordinary blood-clot. In such cases it is quite the rule to observe that the cells degenerate, frequently to such an extent that the cancerous nature of the thrombus or embolism is completely obliterated. Only by means of serial sections can we determine the true genesis of the organised thrombus. My own experience has taught me that similar conditions frequently obtain in lymphatic glands, apparently the seat of secondary cancer. Clinically, all the symptoms of metastasis are evident, and yet histological sections of the gland merely reveal inflammatory hypertrophy. This accounts for the great difference of opinion amongst gynæcologists as to the advisability of removing lymphatic glands in cancer of the womb. I do not hesitate to declare that, as in the case of cancerous embolism, careful examination of the glands in serial sections would show that they contain isolated cancer cells, but that the bulk of these cells has undergone degeneration. All these facts prove that the body commands powers of combating cancer and healing it. An overwhelming amount of evidence on this score has been recently brought to light by Lomer. He refers to upwards of two hundred cases of cancer in which the clinical diagnosis was almost invariably confirmed by histological examination, and in which recovery ensued in some without surgical interference, in some after incomplete removal of the growth. In his first series of cases the cure was preceded by constitutional alterations of the blood induced by febrile infections of a general nature, by severe hæmorrhage, by extensive burns, and by blood-poisoning. In the second series the cut surface of the incompletely-removed growth was cauterised by heat or by chemical agents.

Are we justified in doubting the potential efficacy of X-rays and radium in cancer in the face of all that has been recorded in man and animal? If we analyse the anatomical basis of all those cases of cancer in which complete recovery or retarded growth has been achieved spontaneously or by means of mechanical, physical and chemical agents, we always discover the same reaction on the part of the body, namely, the formation of stroma. Of great interest, perhaps also of fundamental importance, is the fact that extensive local hæmorrhage serves as the precursor of this cell proliferation.

From these remarks it might appear that I regard the blood-vessels themselves as agents of defence. On the contrary, I staunchly uphold

Virchow's doctrine, so ably confirmed by Ehrlich's famous researches on the varied powers of oxidation in the body, that the cells are not fed by the blood-vessels, but that the cells feed themselves. Therefore I regard the network of newly-formed blood-vessels merely as useful in producing more active blood circulation. Intensified circulation itself, if I may so call it, is the effect of all those healing powers which I have just referred to, inclusive of inflammatory agents, such as have recently been recommended for the treatment of cancer by Bier and others. The efficacy of this intensified circulation is naturally dependent upon the presence of defensive factors in the blood. It will remain a subject for future research to discover what these defensive substances are, and above all, where they are manufactured. It seems to me that our present clinical and pathological knowledge already enables us to infer that the body's first line of defence is established on the boundary of the invading growth. From this point of view we understand cases like the following, which I believe have come within the notice of every surgeon. Patients suffering from cancer of slow growth and long duration are advised to have it removed instantaneously. The operation is successfully performed, and the healing process is normal. Yet the patient returns within a short time suffering from a recurrence which has grown rapidly and has assumed features of an alarming nature. It appears to me that in such cases the surgeon's knife has done harm. In removing the growth he has destroyed the barrier of defence which the body has carefully raised up during the long period of the tumour's existence. I know full well that many of my surgical colleagues will disagree with me. And yet I feel that the time has come for us to consider whether stereotyped surgical interference is the only remedy of the future for malignant growths. Should we not rather begin to individualise, as we do in every other disease which is brought to us for treatment? But how can we individualise if we pay no attention to the individual characters of the case we treat—if, above all things, we pay no heed to the efforts of the body to ward off the threatening danger? Can we wonder that such contradictory views still exist as to the rational and radical treatment of cancer? All of us know too well what a marked contrast there is concerning operative treatment and its ultimate results in mammary or uterine cancer as advocated by Bryant, Halsted, Wertheimer, Olshausen, and others. Nothing is more harmful to the progress of our science than doctrinary stagnation. We should not pause before the spectre of apparent retrogression. In our attempts to force the stronghold of cancer we fare no better than the engineer whose railroad winds

round and round the height he means to pass. And yet how comforting the knowledge that whenever we complete a circuit we have ascended to a higher level of truth.

If I have succeeded in proving to you that it is our duty not only to study the biological problem of the tumour cells, but to gain a deeper insight into the defensive agencies of the body as well, the purpose of this paper has been achieved.

I regard the following as the practical result of my work: A careful study of the vascular conditions prevailing in malignant growths affords an anatomical test of the reactive powers of the body. It will be necessary to collect more extensive evidence on these lines in order to bring it into closer relation with our clinical knowledge of the varied appearance and history displayed by the different forms of cancer affecting the same organ. In future, for example, in the case of the mamma it will not be sufficient for clinical and therapeutical purposes to distinguish between scirrhus, adenoma, &c., from a purely histological point of view as to the arrangement of the tumour cells, their different forms of degeneration, &c. It is equally important to discover their reactive powers on the body as tested by stroma formation. By this means we shall sooner realise my demand for treatment based upon a knowledge of the individual qualities of the growth.

On a future occasion I may be permitted to give you an account of my investigations into the causes of retarded metastases, and into the peculiar vascular conditions prevailing in localities predisposed to malignant growths. Above all things, I hope to be able to report on a first attempt to penetrate into the darkness of physiological conditions existing in malignant growths. I am engaged in research on the varied powers of oxidation and reduction characteristic of the various tumour cells.

I have purposely refrained from comparisons of any kind between malignant growths and infectious diseases, and yet it will hardly have escaped your notice that every point which I have discussed reveals most striking analogies between them. As far as syphilis and tuberculosis are concerned, I have dwelt upon these analogies exhaustively in a paper read before the International Cancer Congress at Heidelberg.