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THE INFECTIVITY OF CANCER: A RETROSPECT AND A FORECAST.¹

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BILLROTH, in a remarkable lecture on the interaction of living vegetable and animal cells, reads us an emphatic lesson which it behoves all scientific workers to lay to heart. "Now-a-days," he says, "everything is too hurried. We suffer from an insatiable craving for new, or apparently new, facts in the hope of obtaining a possible sensational success. No time is allowed us for an occasional rest to reflect upon or to reconsider the onward course of scientific inquiry. Where are we? What have we left behind? What is ahead? Is it worth while to go farther in this direction or in that? Has detailed work given us a profitable knowledge of or an insight into the whole subject? No one now finds time to answer such questions."

Surely if the words of the master are true of pathology generally they are still more true of that small department of the science dealing with the causation of cancer. The feverish energy of modern pathologists is nowhere better seen than in the endeavour to discover the origin of this disease. Observation has been piled upon observation with such rapidity that it has hardly been possible to keep pace with the daily additions to our knowledge made within the last four or five years. There is, however, an uneasy feeling in the minds of many clinical surgeons that all is not right, and that the foundations upon which this huge superstructure rest are insecure, for they are founded upon a hypothesis. There can be no doubt that such unbelief is not wholly wrong, for too many workers have assumed for a fact what they should only have held as a theory.

The working hypothesis of the infective nature of cancer is that cancer depends upon the presence of a specific organism which is a protozoon rather than a protophyte, and that it requires a special soil, which we call predisposition, for its successful cultivation. This hypothesis is based partly upon evidence to be appreciated by the trained pathologist, and partly upon evidence of a popular character which appeals to the unscientific mind in much the same manner as do the tenets of religion and of politics.

¹ Read at a meeting of the Oxford and District Branch of the British Medical Association.

I propose in this paper to shortly review these two chains of evidence; and as it raises several points in which practitioners in the Thames Valley can help me, I asked your secretary and my friend, Mr. Lewis Morgan, if I might read my paper in the Oxford district.

The scientific evidence is mainly experimental, partly derived from the histological examination of cancerous and other tissues, and partly from the results of the inoculation or grafting of cancer upon men and animals. Much of the evidence based upon the interpretation of minute histological appearances is to my mind invalidated by the fact that the majority of observers have confined their attention to the examination of cancerous tissues, and have not taken the trouble to compare the results thus obtained with those seen in similar tissues only slightly removed from the normal.

This method of examination has been carried so far that in some cases the examination of a single tumour has been thought to afford sufficient evidence upon which to base an entire theory. Unusual appearances, due either to faulty methods of preparation or to changes in the cells themselves, have been said to be protozoa without any attempt to prove that they were so, whilst the bare statement of one observer has been accepted by another who has employed it to elaborate and father a theory of his own. There is, however, a single redeeming feature in this mass of crude hypothesis, for each observer has drawn to the best of his ability what he has seen, and we thus possess a large and often splendidly-executed series of plates to illustrate the minute appearances in the epithelial cells of cancer. Nothing is perhaps more remarkable than the manner in which each investigator has felt his inability to describe in words these appearances; in no branch of pathology has the skill of the lithographer, the photographer, and the engraver been called in with such signal success as in this inquiry into the cause of cancer. We shall owe the solution of the riddle in all probability to these pictures and to those which are yet to be published, for there is no likelihood of a speedy conclusion to our labours.

The appearances are for the most part as varied as the nationality of the observers. A few only can be traced, even in their broadest outlines, through the whole series, and many of those which appear to be common to all varieties of cancer are also met with in epithelial cells which have not been obtained from carcinomatous tissues. The appearances common to the largest number of observers are, as might have been expected, the simplest. They are tiny circular bodies, varying in size, but many times smaller than red blood corpuscles, found either singly or in groups, sometimes inside the cells and sometimes lying between them.

The explanation of these bodies has yet to be obtained, but I here show you photographs of them. You will see that some of them are intracellular whilst others lie between the cells, and you will also notice that they vary in size. It may be that such bodies are the result of some cellular change of which we are ignorant; it may be that they are peculiar to the epithelial cell endowed with those characters which render it cancerous. We have as yet no evidence that they are protozoa, we have still less reason to say that they are a cause of cancer. We can only state for the present that

they are fairly constant appearances in those epithelial cells connected with cancer either directly as a part of its growth or indirectly as a result of grafting cancer upon epithelial tissues. Attention should therefore be concentrated upon these bodies, and an endeavour should be made to trace out their life-history.

The second part of the experimental evidence adduced in favour of the infective nature of carcinoma is that derived from the grafting of cancer upon human beings and upon animals. The grafting of cancer upon human beings appears to me to be an indefensible and unscientific proceeding. If it be grafted upon persons who already have cancer, as has been done in Germany and in France, any seemingly successful result is open to the unanswerable objection that the body was already infected, and that the growth claimed to be produced artificially was merely a result of dissemination. It seems unreasonable to expect a successful graft upon healthy persons because, so far as we know, there must be a predisposition to the disease, and we have every reason to suppose, from the clinical experience gained in cancer hospitals and in the daily practice of surgeons, that cancer cannot be transmitted directly from person to person. Dr. Budd's cases in which five surgeons to the North Devon Infirmary at Barnstaple died of cancer within a short time I believe to be purely accidental, whilst if cancer of the uterus in a wife is productive of cancer of the penis in the husband, it should surely be more frequent in India than in Europe. Sexual intercourse has become a fine art in the East, where the *Imsac* or *prolongatio veneris* is so common, that Europeans who have married Hindu women are contemptuously compared by their wives to village cocks. The Hindu women, says Burton,² "cannot be satisfied (such is their natural coldness, increased doubtless by the vegetable diet and unuse of stimulants) with less than twenty minutes," yet it does not appear that cancer of the generative organs in husband and wife is at all more common among the Hindus and Moslems than it is amongst ourselves. The frequency of cancer in India is as yet unknown, but the various female doctors attached to the Zenana missions could afford us much help if they would obtain reliable statistics upon this important point.

There appears to be some evidence that cancer can be grafted upon animals. The disease is not common in wild animals, but it is not rare in highly-bred varieties and in those farthest removed from the original type, for it is met with in white rats, long silky-haired rabbits, spaniels, and Pomeranian dogs, sometimes in horses and in special breeds of cows. It occurs in these animals under the same clinical conditions as in man—that is to say, when they get old and when their epithelial cells become decadent, especially if they have been subjected to long-continued irritation. We have then in animals the same predisposing causes to cancer as in man, and as we can vary these causes at will and for several generations, we possess all the materials for an experimental investigation into the cause of cancer. If carcinoma be infective, therefore, we should be able to produce it by grafting cancer upon those animals which have been placed as nearly as possible under the conditions which are believed to be the most likely to allow of its growth. Many experiments have been made by thus grafting cancer upon

² *Alf Laylah wa Laylah*, v. 76.

animals, the source of the cancer being either human or animal, the animal carcinomata being derived from the same or other species. The experiments have failed with very few exceptions. Hanau's experiments at Zurich are well known. He grafted a squamous-celled epithelioma from one rat into the tunica vaginalis of another, and the second rat died within three months with cancer of the peritoneum. This experiment appears to have been more free from fallacy than many other successful cases which have been reported, but it has not proved itself capable of repetition until quite recently, when Dr. Morau claims to have grafted a cylindrical epithelioma from the axilla of a white mouse into other mice, who thereupon developed small hard tumours of a similar structure to that grafted. He concludes from his experiments that heredity plays a considerable part in the development of cylindrical epitheliomata by affording a suitable soil for their development. He also thinks that new growths vary in their virulence, and became less inoculable from one generation to another. Gestation seems to hasten their evolution. They grow less inoculable and less virulent as they pass through fresh organisms. These conclusions are of great importance, but they need confirmation, and although cancers are tolerably common in animals, yet they are not of every-day occurrence. I should therefore esteem it a very great favour if any of you who come across such animals would send them to me at the laboratories of the Royal Colleges of Physicians and Surgeons in London. They will be immediately and painlessly destroyed, but I shall utilise the growth from which they are suffering.

These experiments of grafting upon animals cancer derived from human beings has not been attended by any satisfactory results. I believe that the nearest approach to a satisfactory positive result were certain appearances which I obtained after grafting human epithelioma and scirrhus into the irritated vaginæ of rabbits. In these experiments, as you will see from the photographs some of you hold in your hands, the small circular bodies found in carcinomata were observed within and between the rabbits' epithelial cells at the point where the carcinoma had been grafted. I have not yet satisfied myself, however, that these bodies cannot be explained in other ways than by assuming them to be parasites which have crept into the epithelium from an external source. All experiments tend to show that carcinoma cannot be grafted experimentally from men to animals, for the animal cells appear to have the power of destroying human cancerous tissues. It appears, therefore, that experiments in this direction should be made with diseased tissues derived from animals of the same species and not with pieces of carcinoma.

Evidence obtained from analogy is always weak, and the explanation of *ignotum per ignotius* is proverbially bad, at any rate in its naked simplicity, and in science, though it often serves its turn sufficiently well in displays of rhetoric. It is sufficient, therefore, to allude to the singular similarity existing between the appearances met with in cancer cells and those occurring in the blood of patients suffering from malaria. In both cancer and ague the appearances are identical in form and in attributes. It might be that the "ague parasite" and the "cancer parasite" are members of the same family, the one acting upon the blood corpuscles

and the other upon epithelial cells. It might be, on the other hand, that both are the result of cell alteration. If the malaria parasite can be made to prove its existence as a cause of the disease—and I think that Marchiafava and others have gone far to prove it—there would be comparatively little difficulty in tracing its congener along the same lines of inquiry. The results derived from a study of the malarial parasite are therefore a matter of the greatest interest to those pathologists who are engaged in working out the causation of cancer.

Statistical evidence is nearly as misleading as that derived from analogy, but it appeals more to the unscientific than to the trained mind. It has been worked out for cancer in one direction by Mr. Haviland, who has come to the conclusion that cancer occurs most frequently in those who live in water-logged soils—a conclusion which is in complete accord with that held by those medical men in England and France who practise near rivers liable to flood. This conclusion would be of very great value if it could be corroborated by other than statistical evidence, for it would strengthen our hypothesis that cancer is infective, and it would at the same time suggest that the infective agent passed some part of its existence outside its host's body, and probably in the soil itself. General practitioners in alluvial districts liable to periodical floods might render great service by recording and publishing from time to time an accurate account of all the cases of cancer which they treat, noting the exact locality of each, its pathological variety, as well as the seat of its first manifestation, and when it occurs in women the influence, if any, of pregnancy either in regard to its commencement or any modifying effect which this condition may produce.

The popular belief in the infective nature of cancer is founded even upon weaker evidence than the scientific. There is a widespread belief that cancer is hereditary, yet out of 1,719 cases recorded by Lebert, Paget, Sibley, Siegrist and Snow, the disease only showed itself in the relatives of the affected person in 235 instances, or about 13 per cent. of the total number. Valuable information would probably be obtained upon this point by any general practitioner who would take the trouble to ascertain how often cancer had been hereditary in the patients who come under his own observation, and how often the blood relations of such persons had been affected with other and non-malignant forms of new growth. We might ascertain by these means whether a soil or a receptive condition was in reality necessary or usual in cancer. The older statistics are vague on this point of heredity. The diagnosis of cancer was often difficult, and was therefore overlooked, or other forms of tumour, themselves innocent, were incorrectly assumed to be malignant. Better education and an advance in all methods of clinical and pathological research have set aside these fallacies, and there is at present little difficulty in obtaining a correct diagnosis. Statistics of the hereditary nature of cancer, however, can only be amassed slowly, for they must rest on the personal observation of skilled observers and not upon the unsupported testimony of the patient to whom every cancer is a tumour and in whose mind "tumour" is synonymous with cancer.

Sir James Paget has raised another point of very great interest when he urges upon us the necessity of studying the

characters of mixed disease. In an address to which I had the pleasure of listening this day fortnight, he says, "We are familiar enough with the inheritance of various diseases such as cancer, tuberculosis, gout, rheumatic arthritis, neurosis, and a great many more. All these we recognise as being diseases derived by inheritance, or at least derived under such conditions by inheritance as may make persons more prone to this or that disease." He says: "It has never been studied carefully what may be the result when one patient has one transmissible disease and another has another; what comes if one parent is a member of a cancerous family, and another a member of a tuberculous family? Do these two diseases in any respect disturb one another? Are they mutually exclusive, or do they mingle together? We know that acute tuberculosis and acute cancer never make rapid progress together; they seem, in so far as that, to be antagonistic. But what comes of it when they are mingled together by inheritance? Of that, I think, we certainly know nothing." Mr. Roger Williams has recently devoted attention to this point, but we still want to know more about it.

Much interest is periodically excited by the occurrence of cancer in several members of a family who, though living together, are not related by blood. Thus Bernard Peyrilhe, in his *Dissertatio de Cancro*, issued in 1774, relates the case of a man who had cancer of the jaw after nursing his wife with cancer of the breast; and Tulpus, who lived a century earlier (1594-1674) notes that a servant died of cancer after tending her mistress affected with the same disease. A large series of observations, culminating in those of Guelliot of Reims, have been collected gradually; they show that such cases do occasionally occur. It does not, however, seem more reasonable to adduce them in favour of the infectivity of cancer than it would be to say that insanity was infectious because the superintendent of an asylum became mad, and his wife and friends living with him in the house suffered from brain fag, or were eccentric.

The local epidemics of cancer are of greater interest than the concomitant cases above mentioned. These local outbreaks have been very carefully considered by Arnaudet, Fabre, Fiessinger, Guelliot, and others. They are usually at first sporadic—carry off certain individuals and then disappear. Animals, as well as human beings, are liable to them, and it appears as if visceral cancer were rather more frequent in such cases than the external forms. There are obviously two explanations of these epidemics if they really occur, for Arnaudet's observations in Normandy have recently been called in question by practitioners residing in the district, but the reports of other epidemics have been allowed to pass unchallenged. If they exist there are obviously two explanations of them—the one that they are mere coincidences, as was thought to be the case in similar outbreaks of pulmonary phthisis before the discovery of the tubercle bacillus; the other that they are due to an infective organism finding by chance in a given locality several persons of proper receptive capacity coincidentally with a satisfactory means of distribution. Time alone will show which is the correct explanation, but such cases should be borne in mind, and every detail noted as it occurs. The cases are sometimes met with in a single house, sometimes in a group of neighbouring houses, sometimes in a part of a town or village, whilst sometimes an entire dis-

trict may be temporarily affected. The greatest pains should be taken to ascertain whether in such outbreaks there is a single factor or a group of factors common to the whole of the persons attacked, and the outbreak should be examined on exactly the same lines as have yielded such good results in cases of typhoid, diphtheria, and other epidemic diseases. The diploma in public health is now so frequently obtained that in every district there are medical men competent to undertake the task.

Chaotic as are our present ideas in regard to the origin of cancer, we have good reason to hope that they may shortly be reduced to order. Feeble as is the evidence upon which the working hypothesis of the infectivity of the disease is based, it is daily being strengthened by observations,—clinical, pathological, and statistical. A few years since we were ignorant of the life-history of nearly all the parasitic worms. The labours of Cobbold and of Leuckart, of Rolleston and Thomas, of Manson and of Lewis, have now made all clear to us. There is no reason why the steady work done upon the origin of cancer should not be rewarded in the future with the same meed of success as in the past has attended that bestowed upon the larger animal parasites, for the study of bacteriology has given us new methods, and has enabled us to deal with much more minute objects than was formerly possible.

It appears in the light of our present knowledge that if an organism be the cause of cancer, it should be amœboid and spore-producing, spending a part of its life in damp earth and a part in epithelial cells. It should be extremely tenacious of life, and must have a long resting period though its spore-bearing time may be very short. Its effect upon epithelial cells would be rather to stimulate them and cause their amitotic division than to lead to their destruction, and this irritation of the cells might perhaps serve the secondary purpose of providing the complex proteid foods necessary for the growth of the organism.

I have brought this paper before you, gentlemen, in the hope that it may direct your attention to those points in connection with the cause of cancer, in which you are able to afford very material assistance at the expense of a very small amount of trouble.

The numerous communications which I receive every year from practitioners in all parts of the country show how keen is the interest they take in the solution of this difficult problem, and how willing they are to afford every possible assistance to those who, like myself, are trying to work it out from a scientific standpoint. Clinical research, however, must go hand in hand with scientific investigations if the best results are to be obtained. Hospital notes are of service, but they are as nothing compared with the facts and figures to be gathered by those who, like yourselves, spend years in the same locality, and have opportunities of watching the various manifestations of disease in successive generations of many families. With each of you who attain to old age there dies a wealth of knowledge which is absolutely wasted, knowledge which, as locomotion becomes more easy and families are earlier scattered, can never be regained.

I will therefore recapitulate the chief points in which you can render service by careful and accurate observation. The influence of heredity should be ascertained in every case of

cancer, the inquiries being made in reference to the collateral as well as to the lineal descent. A vague statement that such and such a relative died of cancer is insufficient; the exact variety of cancer should be ascertained, the duration of the disease, and if possible the seat of the primary growth and of the secondary deposits; in women, too, it should be noted whether pregnancy has any bearing upon its commencement or upon its progress. The family diathesis on the parents' side is easily noted in a single word. The occurrence of such innocent tumours as wens, warts, and fibromata in other members of the family is also ascertained without difficulty, and when they occur, the ages at which they grew and the position which they occupied should also be recorded. It is still an open question whether gout, rheumatism, and other manifestations of an arthritic diathesis are in any way associated with cancer, and there are some who maintain that in a community where flesh is sparingly consumed the largest meat eaters are the most likely to be affected with cancer. It would therefore be well to consider these points. Those who reside in districts where cancer is especially frequent should bear in mind the work done by Haviland, and should ascertain in each house where cancer has occurred whether the soil is water-logged either generally as a result of floods, or locally from damp and wet cellars. All local outbreaks of cancer should be examined as to their cause in the manner usually adopted to ascertain the source of any of the more common epidemic diseases, and an endeavour should be made to ascertain what factor in the life or surroundings is common to each of the persons affected. It might be well also for those who are interested in the subject to tabulate the domestic remedies recommended and used for the cure of cancer, as their number is undoubtedly very numerous. An infusion of the common dead nettle taken to the extent of half a pint a day, and also used as an enema, has been recently and strongly recommended to me as an infallible cure for encephaloid cancer of the rectum, and its good results have been pointed out in an individual case. It is interesting as a piece of folk-lore, but it is otherwise useless. Lastly, we require more information as to the frequency with which cancer occurs in those countries where women are secluded, and this can readily be obtained for us by those newly admitted members of our Association who are privileged to enter the zenanas and harems of the world.