The bearing of comparative and experimental investigation on the association of some forms of cancer with chronic irritation / by E.F. Bashford.

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Publication/Creation

[Place of publication not identified] : [publisher not identified], [1914?]

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[Excerpt from Vol. XXXV., No. 5 (1914) of the Journal of The Royal Sanitary Institute.]

The Bearing of comparative and experimental investigation on the association of some forms of cancer with chronic irritation,

by E. F. Bashford, M.D., Director of the Imperial Cancer Research Fund.

Being Abstract of Lecture to Institute, delivered on Wednesday, April 29th, 1914. (Illustrated by Lantern Slides.)

TEN years ago I wrote a paper* for the Congress of this Institute, held in Glasgow, in which the possible value of the comparative study of cancer was urged. This fact determined me in choosing a title for what I have to say this afternoon, and which, although not now new, will enable you to see the progress made since I last addressed you. The comparative and experimental study of cancer during the past ten years has had very far reaching effects on our knowledge of the disease. By comparative investigation I mean the study of cancer in all the races of mankind inhabiting the British Empire, living under very different conditions as regards climate, soil, and diet, and of cancer throughout the vertebrates, whether living in a state of nature or under domestication, and also the experimental study of the disease in a large number of different species, especially of the mammalia. In the laboratories of the Imperial Cancer Research Fund, true new growths have been transplanted in the dog, in the rabbit, in the guinea pig, in the rat, and in the mouse. In addition, growths of doubtful nature have been studied in the dog and in the fowl. For reasons of convenience, by far the greater proportion of experimental observations has been made on the mouse. The life of this animal is very short, the animal is prolific, it is cheap, and many thousands can be conveniently housed. Hence the extension of experimental observations to such animals as the dog, rabbit, guinea pig, and rat has, up to the present, had its chief value in demonstrating that the results are not restricted to the mouse, but, since they apply to the dog, they will in all probability apply also to man.

Observation of the disease in different races of mankind has brought into prominence a number of instances in which its anatomical distribution as known in Europe was singularly altered by the practice of native customs. For example, cancer of the skin of the abdomen was found to occur with great frequency in India, and cancer of the mouth was found to be as frequent in women as in men, both of these circumstances being quite different from what is known in Europe. Many other instances can be stated, but perhaps even more instructive are similar observations on

* The comparative study of cancer, Vol. XXV., 1904, of the Journal of the Sanitary Institute.

animals, such as the occurrence of cancer at the root of the right horn of draught cattle, but never at the root of the left horn. These observations apply to what are really unintentional experiments, and as such are of the greatest value, in the light they throw upon the association of some forms of cancer with chronic irritation.

These preliminary remarks may suffice to indicate that in concentrating laboratory experiments mainly upon the tumours of the mouse, a reasonable restriction has been made, because the essential results will almost certainly be applicable to man without the necessity of repeating them on the same enormous scale in other animals such as the dog, or the horse, or the cow, which could not be kept conveniently in the many thousands which are necessary. The mouse shares with the human female a great liability to cancer of the mamma, and all other forms of cancer found in man occur in the mouse.

I propose to illustrate my following remarks by a series of lantern slides showing salient examples of chronic irritation contributing to the production of cancer in man, in the cow, and in the mouse, and illustrating how experiment has thrown light upon this connection. I would guard myself by pointing out that chronic irritation has determined the site at which cancer developed in the instances illustrated. Following under the microscope the processes occurring at these sites, and ultimately leading to cancer, has not cleared up its nature. The observation of the forms of cells does not afford a sufficient clue to the nature of cancerous transformation. In all of the examples illustrated a long period of cell proliferation intervenes before cancer develops, and the production of this prolonged state of chronic proliferation is the only feature which the irritants have in common. Later on I shall refer to experiments designed to find some explanation of what leads to the formation of cancer during exposure to chronic irritation.

As is well known, cancer can be transferred from one animal to another of the same species. The process is not a process of infection, but is an actual transplantation, in the same way that plants are transplanted in the garden, but in cancer the living animal is necessary to provide a soil for the cancer cells to grow in. The first point to consider in regard to the great frequency in cancer is to determine whether it is communicated naturally from one animal to another. During the past twelve years healthy mice, young and old, have been housed with mice naturally suffering from cancer and mice inoculated with it. The housing of animals in this way, where they have been exposed both to possible natural and experimental infection,

has in no case led to a higher frequency of cancer than has occurred in mice not so exposed. This has a most important bearing on the occurrence of so-called cancer-houses in mankind. I am frequently asked whether an ancient family mansion should not be burned down because of the occurrence of cancer in successive members of the family, and I am frequently consulted regarding the anxieties of persons who wish to occupy a house in which a patient has died of cancer. I have been asked whether it were not necessary to deprive a grandmother of the society of her granddaughter, the only companion of her old age. My reply invariably is that I should have no objection to occupying a so-called cancer-house myself, and give my reasons, but to go into them would be to depart from the subject of this lecture. Let me call to your mind how difficult it is to obtain accurate information regarding the causes of death of a number of persons living in a single house over a prolonged period of years, and also point out that cancer is so frequent a cause of death that ultimately one woman out of seven, and one man out of about ten above the age of thirty-five dies of it. Therefore aggregations of cases of cancer are bound to occur frequently in the same place, whether it be a large area, a house, or even a single room. To enumerate a hundred so-called cancer-houses, or even ten thousand, is no evidence at all, either one way or the other, because the question to be solved is simply this: Is cancer more frequent in certain houses than it is in others? The data available for the human being, into which I have inquired, are valueless for settling this question in the form in which it is formulated. For man it is a question incapable of solution, and therefore wrongly formulated. On the other hand, experiments on the mouse have proved quite definitely that the disease is not communicated from one animal to another, either by infection or by transplantation. The fear of some such occurrence is the only *raison d'être* for raising the question of cancer-houses at all, and, this being the case, the subject is one unworthy of further serious discussion.

When, however, we come to consider the relationship of the cancer cell to the individual in which it is found naturally arising, the state of affairs is very different. Although it is extremely difficult to transfer a cancer cell from the mouse in which it arose, it is always possible to reinoculate the animal with its own cancer. Another question regarding the great frequency of the disease is that of heredity, which again has been found incapable of solution in man because of the length of life and the unreliability of the observations. From the commencement of our investigations we determined to study heredity in short-lived animals, and

Dr. Murray's experiments demonstrated that by in-breeding cancerous stock it has been possible almost to double the frequency of cancer in the case of mice whose mothers and grandmothers have suffered from cancer of the breast. Other experimental methods have shown that this increase is not due to a constitutional modification suitable for cancerous growth throughout the body as a whole, because mice with the hereditary taint do not offer a more suitable soil for the growth of tumours than the animals not so tainted. These experiments point to a localised tissue susceptability rather than to a constitutional liability to the disease. When chronic irritation has preceded the development of cancer the hereditary factor may predispose the tissue to cancerous change during the prolonged proliferation produced by the chronic irritation. One of the most striking facts is that the disease does not develop in all persons exposed to the same conditions. Therefore, for this and other reasons, the relation between chronic irritation and cancer is spoken of as "mediate."

I now pass to a different kind of experiment designed to throw indirect light upon the mediate relation between chronic irritation and cancer, by ascertaining whether the characters of a cancer remain constant or vary. This investigation has only been made possible by studying many different kinds of tumour during prolonged propagation by transplanting from one mouse to another over and over again. At each transplantation the tumour suffers a trauma and its structure is completely disintegrated. The ready-made tumour cells are maintained in a state similar to that obtaining under chronic irritation. These observations fall into two main groups, as regards structure, and as regards powers of growth, and other more subtle properties. Briefly, the diapositives demonstrate that the characteristics originally shown by a tumour are retained with great constancy; but, exceptionally, marked variations may occur, both in structure and in powers of growth. Characteristic structure may be entirely lost, and a wholly undifferentiated cell mass may result, and remain during many years of cultivation. Other powers, such as that which leads to the production of sarcoma, may be lost.

Before passing to the consideration of alterations in the powers of growth, it is necessary to explain the methods devised to study them by referring to what are known as the immunity reactions, but more correctly as the resistance which can be induced against the growth of the cancer cell. This resistance can only be induced by the tumours or tissues of the same species as that to which the cancer belongs. Normal tissues produce a higher degree of resistance and one which lasts longer than does tumour

tissue. This fact is of importance, and will be recalled later. The mechanism is not fully elucidated, because the responsible agent has not yet been separated from the living animal, *e.g.*, demonstrated in the blood or serum after bleeding. It is, however, distributed throughout the body and circulates in the blood. Its effect is to paralyse certain properties of the cancer cells, rendering them unable to obtain that specific scaffolding of connecting tissue and vessels, without which they cannot grow into a tumour. In the case of natural cancer complete healing is very rare, occurring not as often as once in a hundred mouse tumours; but there also some change in the tumour cell is of prime importance, so that the connective tissues no longer subserve the needs of the cancer cells, but obtain the upper hand.

I pass now to the study of changes in the powers of growth, which have been specially elucidated by Dr. Russell. The powers of progressive growth possessed by the cancer cells are their most striking property. It is the property which requires explanation, and it is the one which we must control if we are ever to find a cure for cancer. On the whole the powers of growth remain constant, but there are occasionally exceptions, where a tumour which originally grew slowly and badly acquires maximum powers of growth. After transplantation normal tissue grows only for a short time, and it is to be observed that some tumours behave in a similar manner. Other tumour strains grow very rapidly and always progressively, spreading throughout the body. Experiments show that the growth of normal tissue, after transplantation, is terminated by the production of resistance to its own growth. When a tumour originally endowed with only limited powers of growth, because it produced resistance against itself, becomes transformed into a tumour with progressive growth, the change is due to the cells having *lost* the power to produce resistance. You will be aware that in the past, and even to-day, attempts are made to explain cancer by assuming that a stimulus to growth is necessary. Indeed, this assumption lies at the base of the idea that cancer is due to some parasite, or is due to some chemical product in the body *stimulating* growth.

The only experimental data yet obtained show that exactly the opposite can occur. The power of continuous growth becomes possible because of the loss of a hindrance to growth, and then a transplantable tumour comes to behave in normal animals just as a spontaneous tumour does in its natural host. This is the main result which has come out of all these elaborate experiments which I have briefly outlined and illustrated. It has been ascertained by prolonged propagation, and often repeated injury

of a very large number of different kinds of tumours, during more than twelve years. It is during this process that from tumour cells capable of only limited growth, there have been obtained tumour cells capable of progressive growth, and of maximum danger to the organism. The inference may be justified, that what the cancer cells do during propagation, they are also capable of doing in the host in which they arose, and that by some similar process during the prolonged proliferation, attending on chronic irritation, the normal cell presents also variations, some of which are capable of progressive growth. Towards promoting this particular variation the hereditary factor acts in some not clearly defined way. The whole problem focusses itself into the question of the study of growth, and of the forces which correlate it and control it in the human body. We know very little of normal growth, and the facts I have been relating to you are the first insight we have been able to obtain into how growth may be stopped and powers of growth acquired. Of interest is the frequency with which it is necessary to refer to alterations in the relations obtaining between the cancer cells and the connective tissues, providing them with a scaffolding.

Comparative and experimental investigations have had an important practical bearing upon the statistics of cancer in man. They showed how the organs of predilection varied for different species of the mammalia; they demonstrated that age was associated with the development, but was not necessary for the continued growth of cancer, and the importance of considering the age incidence for separate organs. Applied to man these observations meant that cancer in mankind must be similarly studied if useful statistical information was to continue to be obtained. The experimental work, especially its bearings on the association of cancer with some forms of chronic irritation, also has given courage to those who desired to have this additional statistical information in regard to cancer in man. Formerly all cases of cancer were lumped together, and questions of expense stood in the way of having any analysis of the occurrence of cancer in different parts of the body made. For some years past it has been possible to have occurrences of cancer in different parts of the body analysed, and thus two very interesting facts came out. It is certain that an increase of cancer is not taking place in some parts of the body, for example, the skin, uterus, and the liver and gall bladder. For other parts of the body, especially the stomach and intestines for both sexes, a large increase is recorded, and how far some at any rate of this increase is due to improved diagnosis and certification is yet to be determined. The male sex suffers more than the female from cancer of the upper half of the alimen-

tary canal, and this greater liability has been associated with the greater irritation of this part of the canal in the male who smokes, drinks, and gulps down his food. Whether the abandonment of these habits would lead the male to have less of these forms of cancer than the female I am not prepared to say. In the case of the uterus it is possible that owing to early and correct diagnosis a near approximation has been made to the absolute incidence, and that therefore to-day we are observing the beneficent results of surgical treatment.

The other interesting result of analysing the different sites of cancer has been to show that the age of onset and maximum incidence varies, so that there are two main forms of curve. One in which the disease increases up to the end of life, as in the case of the face, lips, and breasts, and the other in which, after attaining a maximum, there is a falling off to the end of life. Thus, it is necessary to consider cancer in each part of the body separately. This necessity applies not only to the mere liability of different organs at different ages, but also if we are to determine whether or not cancer is more frequent in certain occupations, or more frequent in, say, one part of the country than in another. We should expect certain forms of cancer to vary in their frequency, rather than that the frequency of the disease as a whole will show great fluctuations. The data upon these subjects have been accumulating in the Registrar General's office since 1911, and will be published in due course. At the present moment I only mention them in order to show how comparative, experimental, and statistical methods are being combined in order to elucidate the problem of cancer.