MODERN VIEWS ON THE CANCER PROBLEM *

BY

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One might define the cancer problem as the attempt to discover what causes cancer and how it can be cured, but this is much too vague a definition for the present day, and I would suggest that the questions we are attempting to answer are: what are the processes involved when a tumour arises in apparently normal tissue cells, what initiates this change, and how can it be prevented or arrested?

When we desire to solve a problem there are several ways in which we may proceed, but that which most appeals to me, and I believe to most of us, is first to assemble all the facts that can be relied upon and then to attempt to draw logical conclusions from these facts. The conclusions so reached can then be tested against the facts to see if they all fit properly into place. If they do, we can seek further confirmation by noting what other facts we can deduce from the conclusions, and if we are then able to find such further facts we can fairly safely infer that we are on the right track, and have gone a long way towards finding the correct solution of our problem. This is the method of solving problems so dear to the authors of detective stories, and it has much sound reasoning behind it. Now I propose to deal with the problems of the cause of tumours, and more particularly of cancer, much in this manner—that is to say, I propose to marshal those facts which are undisputed with regard to the problem of tumours, and then to draw conclusions and show how they fit, or do not fit, the facts.

What may be called "the cancer problem" will, I believe, always rank as one of the most remarkable that human intelligence has ever been asked to solve. For at least thirty years it has been the subject of very intensive study by a large number of eminent persons, and considerable sums of public money have been expended in attempts to solve it. Since the inception of the British Empire Cancer Campaign some twelve years ago this effort has been very materially accelerated. More scientists have been attracted to the search, both in England and all over the world, and I do not think I am exaggerating when I say that no scientific problem has previously attracted so much intensive investigation as this one. Many, very many, of the investigations have had negative results, but facts may be either positive or negative, and negative facts are nearly, if not quite, as important as positive ones. The facts that have now been established, both negative and positive, I shall attempt to enumerate.

Established Facts Concerning Tumours

1. Tumours, both innocent and malignant, are found in all mammals, in birds, and in fish, but so far have not been found in the invertebrates.

2. The incidence of tumours—that is, the number of individuals suffering from tumours per 1,000 living, corrected for age—seems to be about the same all over the world. The actual incidence in the animal kingdom is not ascertainable, but there does not appear any sound reason to suppose that with the proper corrections it would differ very much from that of human beings. Tumours certainly occur in wild animals and birds.

3. Though the incidence of tumours is approximately the same, the site incidence—that is, the particular part or organ affected—varies very widely. For instance, while the cancer incidence per 1,000 in England and Japan is almost identical, there is a very great difference in the site incidence. Also certain animals seem much more liable to have tumours in particular situations than others: birds in the genito-urinary tract; mice in the mamma; cattle and horses in the intestines.

4. A tumour cell is specific to its original form, wherever it may be. Thus a rectal tumour which recurs in the liver, brain, or in the bones still retains its character as a rectal tumour, and a tumour which starts in the ducts of the mammary gland still retains this character if it recurs in the spine or in the lung.

5. A tumour results from the overgrowth of one cell (possibly of a small group of cells), and all those composing the tumour are derived from this one cell. The surrounding cells are not converted into tumour cells, or in any sense absorbed into the tumour.

6. The tumour cells are normal cells dividing at an excessive rate. When a normal tissue cell divides, one cell remains as a replacement cell, and the other proceeds to differentiate, but all tumour cells are active dividing ones and very little differentiation takes place. In every tissue, whether it be skin, epithelium, gland, or connective tissue, the renewal of damaged or worn-out cells is confined to a single layer of cells, which we may call the replacement cells. These are the cells nearest the connective tissue or basement membrane, and are usually called "basal cells." These alone divide, and the remaining cells in the tissue are differentiated cells which have lost their ability to divide. A better term for them would be basal cells, but this might cause confusion, since we have such expressions as basal-celled carcinoma, as distinct from epithelioma; although as a matter of fact all tumours are primarily due to basal cells—that is, reproducing somatic cells. A true tumour cannot occur in a highly differentiated cell, such as one of the cells of the hair or nails, and is very rare in the brain.

7. The differences that have been demonstrated between tumour cells and normal cells, such as increased oxygen consumption and increased power of breaking down sugar, may be construed as the result of their greater activity as compared with the normal cells.

8. Tumour cells are species-specific. Thus human tumour cells will not grow in any other animal; mouse tumour cells will not grow in rats; avian tumour cells will not grow in rabbits, and so on. The specific character of tumour cells is very exact. It is extremely difficult to transfer human cancer from one individual human to another human; it has often been tried, but only in one or two instances has it succeeded.

9. Tumours are a disease of growth. Normal growth goes on in the human body through life in order to make up for wear and to replace damaged tissues. Tumours are due to local excessive growth—that is, growth in excess of the general requirements of the body to replace wear and repair loss.

10. In certain families, both of humans and of animals, it has been observed that tumours very rarely, or never, occur, while in others the incidence of tumours is very high. The tendency to tumour production is an hereditary character which by artificial breeding can be either increased or decreased. The proof of this is that tumours in human beings are much commoner in certain families than in others. In certain interbred mice cancer of the mammary gland occurs in 90 per cent. of the females, while in other similarly interbred mice—those which have been bred brother to sister for a number of generations—cancer does not occur at all. The best

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proof of this fact is that in homologous twins or uniovular twins, when a tumour occurs in one twin it is always found to be present also in the other in the same organ, at the same time, and of the same character. McFarland and Meade have collected twenty cases of uniovular twins having the same kind of tumour in the same situation at the same age. Moreover, they were quite unable to find a single instance of a homologous twin with a tumour whose fellow twin had not the same tumour, in the same place, at the same time.

11. Tumour formation may occur at any age, but the vast majority of tumours occur in the later stages of life—that is, when the individual is becoming old.

12. In the last few years a great deal of research has been devoted to a study of carcinogenic agents. The most potent of all is a chemical agent produced synthetically from simple chemical substances, called 1:2:5:6-dibenzanthracene. This substance, if painted on to the skin of a mouse, will almost inevitably produce an epithelioma. If injected into the peritoneal cavity of rats it will cause extensive sarcomatous formations. It is not an irritant in any sense, but no other known substance will give rise to cancer with such certainty. Other cancer-producing agents are tar, α rays, and radium. It has been claimed that these agents are irritants, and produce cancer owing to the chronic irritation that they arouse. But with the exception of tar they are not irritants. Formalin, which is a potent irritant to human tissues, cannot be made to cause tumours, and mustard gas, which is a most violent irritant, not only does not cause tumour formation but inhibits it. It has been proved that if tar or 1:2:5:6-dibenzanthracene is applied to mice alternately with mustard gas, such mice will not develop cancer, while the control mice, which have been painted with tar or 1:2:5:6-dibenzanthracene and not with mustard gas, do. It must be noted that all the proved carcinogenic agents are substances which are not apparently present in a natural or normal environment.

Phenomenon of Excessive Reproduction of a Cell

Now let us consider what conclusions we may logically deduce from these facts. A tumour, whether simple or malignant, is the result of a tissue replacement cell, a somatic cell, reproducing itself at an excessive rate as compared with the normal rate for the tissue of which it forms part, and as an inevitable consequence in course of time a tumour develops. Thus if one of the basal cells of the skin suddenly begins to divide once every two days instead of once in fourteen days, it is obvious that in time a swelling or tumour will form as the result of the excessive reproductive activity of this one cell: and as each descendant of that cell, having inherited this property of excessive rate of division, will continue the process the tumour will get larger and larger.

This, in simple terms, is the way in which a tumour forms; but how are we to explain why it occurs? I think few people will disagree with this explanation of the way in which a tumour develops, but there is still great disagreement as to the cause of this phenomenon. Many theories have been suggested to explain why a normal tissue cell suddenly begins to reproduce itself at an excessive rate. The two chief theories at the present time are: (1) That the change is caused by an infective agent—a living parasite—that has found a means of access to the cell nucleus and caused the change in its behaviour: the infective theory. (2) That the change is due to a mutation of the genes in the nucleus of a somatic cell resulting in an excessive rate of reproduction: the genetic theory. It may be noted that the first theory tries to explain why a tumour starts, while the second

attempts to explain the method of tumour formation. They are not, therefore, necessarily antagonistic.

The Infective Theory

This theory assumes that an infective agent, a parasite of some kind, obtains entrance to the somatic cells and so acts upon them that they proliferate at an excessive rate and cause a tumour. This theory is very pleasing because, if true, it would seem possible to find a poison which would kill the parasite without damaging the patient, or a vaccine which would protect him from infection.

The following are the objections to such a theory. If tumours are due to infection by a parasite then the incidence of tumours among civilized communities should be decreasing, since owing to modern methods of hygiene most of the known infective diseases—such as typhoid, cholera, and small-pox—due to bacteria and viruses are becoming less frequent; the incidence of tumours, however, is increasing. Again, our knowledge of diseases due to infective agents (parasites) is considerable, and there is no single example of a disease due to such causes showing the extraordinary specific characters that are seen in tumours. While there are some infective diseases which are peculiar to one species of animal, such as small-pox and varicella in humans, and distemper in dogs, and foot-and-mouth disease in cattle, they are not so specific as cancer. Other animals besides dogs can have distemper, and foot-and-mouth disease attacks horses, deer, and even man occasionally. The extremely specific character of tumours has no counterpart among the known infective diseases of animals or man.

The most convincing argument against tumours being due to an infective agent or parasite is the fact that is afforded by the incidence of tumours in homologous twins. If tumours are due to an accidental infection by an infective agent, we can hardly believe that both the twins became infected by the same agent at the same time, and that it infected the same organ; also there is no instance of one twin being infected and not the other. Coincidence might account for this occurrence in two, or possibly three, instances, but could not account for twenty.

Genetic Theory of Tumours

This theory explains the causation of tumours as the result of a genetic change in one or more of the somatic cells. We know that when the nucleus of a living cell divides in order to form two cells, the process called mitosis, a change or mutation occasionally occurs which results in an alteration of the arrangement of the genes upon the chromosomes, or even an alteration in the genes themselves. It is by these chance mutations in germ cells that new varieties and species of organism have been produced in the course of evolution. Such mutations may, however, occur in the nuclei of somatic cells as well as germ cells, and there is evidence that they do. Now when a gene mutation occurs in a cell nucleus, every succeeding division of that cell will result in the change being passed on, so that the mutation or change is permanent in the descendant of that cell. A mutation in a somatic cell can, however, produce no appreciable result, since it will only be present in one single cell, as somatic cells do not increase in numbers. Should, however, the change or mutation be for an increased rate of mitosis then it is obvious that in time there will be a colony of mutated cells produced by this single cell. The cells in the mutated colony will be normal cells, except that their rate of reproduction will be faster than normal. *This is exactly what a simple adenoma or papilloma is found to be.*

This theory explains why a tumour remains specific to the tissue in which it started, even though it occurs as a metastasis in the bones or the brain; also why tumours are specific to one species of animal. After all, we should hardly expect that cells from one kind of animal would grow in another of a different kind. It explains why the same tumour is sometimes found in both homologous twins. Since the genetic susceptibility of the twins is identical, if there is a hereditary weakness of certain somatic cells which renders them liable to mutation in one twin, it will also be present in the other to exactly the same extent.

It attempts to explain why certain carcinogenic agents cause tumours, since we know from recent experimental investigation that x rays and radium are capable of causing gene mutation of germ cells and somatic cells. The curious fact that a mouse tumour can be transplanted from one mouse into another again and again is explained by his theory. Some of the mouse tumours have been transplanted sixty times—that is, they have passed through sixty generations of mice—and yet have retained their original character. It is obvious that if the tumour cells are the progeny of the original mutated cell they will retain the characters imposed upon them by that parent cell.

Innocent and Malignant Tumours and the Genetic Theory

There are no known facts about tumours which are not explainable by this theory, but if it is correct, how are we to explain the difference between an innocent tumour, which does not metastasize, and a malignant one that does? We have still to find an explanation, but a paper recently published by J. C. Mottram on the rate of growth of tar warts in mice seems possibly to afford a satisfactory solution. He postulates that the growth rate of the tumour cells decides whether the tumour will be benign or malignant. If the growth rate is slow the connective tissue is able to develop so as to maintain the normal relation between itself and the tumour cells, but if the growth rate is fast the connective tissue is sometimes unable to maintain this relation and the tumour cells invade the connective tissues, and a malignant tumour results. It seems quite possible that this simple explanation may be the correct one. There is still a great deal of work and much hard thinking to be done before the question of the aetiology of tumours can be finally settled, but it is obvious that considerable progress is now being made.

Modern Developments in Treatment

Not so very long ago cases of malignant tumours were looked upon as hopeless, even by our profession; but those days have passed, and surgeons are now able to cure a proportion of cases. It is true that we can do very little for the advanced cases that still form far too high a proportion of the whole, but in cases where the diagnosis is made reasonably early good results are obtained. To-day a number of hospitals have what we call "follow-up systems" for cancer cases, and the figures show that if we leave out the very advanced ones the percentage of cures for cancer of the uterus and rectum is over 50 on a five-year basis, and for cancer of the breast the figure is still better. Rodent ulcer is curable if taken in time, and the same is true of epithelioma. A fairly high percentage of cures is also being secured for cancer of the tongue and pharynx. These results are being obtained partly by operation, partly by radium, and partly by a combination of both.

It may be said that our present methods of treatment in some situations are effective, if only the cases can be diagnosed at a sufficiently early stage.

POISONOUS SUBSTANCES TO DESTROY TUMOUR CELLS

A number of such substances have been experimented with, but only a few found suitable for use in human beings. Of these certain compounds of lead and selenium have been used successfully, and in a few cases destruction of the tumour without producing fatal results to the individual has been achieved. Unfortunately such substances have proved to be very poisonous, and their use is attended with considerable danger. Cobra venom has also been tried, but with no definite results.

At the present moment several investigations are being carried out with new forms of x -ray plant. Some of the plants with very high voltages give off rays which closely resemble the rays of radium. Another plant, which has been produced in Germany and works with low voltages, seems to promise better results than the high-voltage ones; it can be applied locally to the tumour in the operating theatre, if necessary, and may prove a distinct advance in the treatment of certain cases.

It has been shown that it is possible to obtain a homologous serum from rats which kills tumour cells in culture *in vitro* but has no harmful effects upon normal cells. In other words, by injecting tumour emulsion into resistant animals the serum from these animals causes the destruction of tumour cells. By the use of such sera it has proved possible to cause regression of spontaneous tumours in both mice and rats. Considerable further work is required before similar sera can be used for the treatment of human tumours, but these very important research investigations are being pushed on, by grants from the British Empire Cancer Campaign, as energetically as possible. There seems at least a hope that the active substance in such sera will be successfully separated and made available for the treatment of human beings, but the work is extremely difficult, and it may take some time before success is achieved. A number of other sera and extracts of placental tissue have been proposed for the treatment of cancer, but there is no reason that I know of to believe that they have any influence at all upon tumours.

The cancer problem is a very difficult subject to discuss in a short lecture and at the same time to make oneself reasonably intelligible. The subject of human genetics is a very new branch of biology, and at present most imperfectly understood, but it has thrown an entirely new light already upon the whole subject of tumours, and in my own opinion makes it possible at last to understand their aetiology. Investigation into both the origin of tumours and their treatment in human beings is being intensively pursued all over the world to-day, and a complete solution of the problem should not be much longer delayed.

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The Royal Italian University for Foreigners, which has its seat at Perugia, was founded some ten years ago to disseminate knowledge of past and present Italy, and arranges courses of instruction from July to December. In 1936 the University will open in April. Beginning next July, there will be lectures on Dante (*Il Paradiso*); the eighteenth century in Italian literature, art, history, politics, and science; and modern and contemporary Italy. The programme of the courses in advanced culture, which will be held in October, November, and December, will be published in August. Information concerning enrolment, fees, diplomas, and reductions in the cost of travel and accommodation can be obtained from the Rector, Regia Università Italiana per Stranieri, Perugia, Italy.