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ON THE ORIGIN OF CANCER*

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Why does a patient get cancer? That is a question which summarizes the problem of cancer and which must have often occurred to you when a patient presents himself or herself, apparently in good health except for some obscure and not necessarily painful symptoms, and on examination a malignant growth is found, sometimes in an early stage but possibly already in an advanced stage, although the patient may have presented himself as soon as he noticed that something was wrong. It is this insidious onset of cancer—striking a patient like a bolt from the blue—which has given the disease the air of a grim mystery.

Interpretation of Age Incidence

If I were asked in what respect the experimental investigation of cancer of the last fifteen years has most profoundly altered our outlook on the cancer problem, I would say it lies in the correct interpretation of the age incidence. The frequency of cancer increases with increasing rapidity as age advances. This can be readily seen from the following table, which gives the mortality rate per million people from cancer of all sites in decennial age groups in England and Wales:

Age Groups:	0–	15–	25–	35–	45–	55–	65–	75–
Cancer Mortality Rate . .	52	41	140	596	1,893	4,390	8,711	12,707

The death rate from cancer increases in almost geometrical progression. I know of no other disease which exhibits a similar phenomenon. This remarkable feature of the disease must therefore have a fundamental significance.

Formerly the insidious onset of cancer—the bolt from the blue—led us to believe that the origin of cancer begins with the first appearance of a malignant cell. This, as will be discussed presently, is due to an intracellular change by which a normal cell becomes transformed into a malignant one, and our attention was riveted to the investigation of this change as the one and only problem concerned in the aetiology of cancer. The fact that cancer occurs much more frequently in old people than in young or even middle-aged people was explained formerly by the assumption that the senility of the tissue is the predisposing factor in the origin of cancer. It was believed that in such senile tissue cancer arises suddenly. But the experimental investigation of cancer has shown clearly that it can be induced in a young or middle-aged

organism as readily as, if not more readily than, in an old one; and, further, that when cancer has arisen the malignant cells soon grow in a young organism as readily as, if not more readily than, in an old one. This rules out senility as a direct aetiological factor in cancer.

Carcinogenic Agencies

When it became possible to induce cancer experimentally it was found that there are a great many different agencies capable of inducing cancer in such a tissue as the skin: chemical substances, such as tar or the pure organic substances synthesized by Kennaway and Cook; physical agencies, such as light, x rays and radium rays, heat, and even gross parasites.

All carcinogenic agents have this in common: that they induce cancer only after a lapse of time occupying a considerable fraction of the normal span of life characteristic for each species; and, furthermore, that this period of induction is much more prolonged with a weak carcinogenic agent than with a very active one. We have learned, further, that during the prolonged action of these carcinogenic agents the tissue on which they act undergoes pathological changes, and that cancer arises within this altered tissue. Now in man the bulk of cancer patients belong to the last half—even the last third—of the normal span of life. We can therefore conclude that *in man cancer arises as the result of carcinogenic stimuli acting over a prolonged period occupying a considerable fraction of the span of life; and if this is so it follows, further, that cancer does not appear as a bolt from the blue in a healthy tissue, but that as a result of this prolonged action of a carcinogenic agent the tissue or organ on which it acts undergoes pathological changes before cancer develops.* That the preceding existence of such precancerous conditions was not generally—and still is not generally—recognized is due partly to the fact that they need not be sufficiently severe to manifest themselves as a definite disease, especially when they develop in tissues or organs which are not readily accessible to clinical examination. They have, however, long been recognized in the skin, where the whole course of carcinogenesis is visible. The term “precancerous condition” was, in fact, coined forty years ago by dermatologists as the empirical result of clinical observations.

Two Phases of Development

We see, then, that the development of cancer, whether it arises spontaneously or whether it is induced experimentally, presents two phases. The first phase is a long

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preliminary one which we may call "*the origin of cancer.*" This extends over a long period of years amounting to a considerable fraction of the span of life—hence the characteristic age incidence of cancer—and it culminates in the sudden transformation of a few normal cells into malignant ones. During that phase in a more or less extensive though localized area of tissue a pathological condition develops, characterized by increased cellular proliferation in which subsequently cancer arises in a single cell or a small group of cells. The development of this precancerous condition depends upon the action from without on the cells of a given tissue of agencies of the most diverse nature—agencies which are called carcinogenic agencies. Carcinogenic agents may be substances foreign to the body acting locally where they are applied; they may be abnormal metabolites acting locally; or they may be formed in the body as normal metabolites—for example, oestrone, a hormone formed by the ovary but which produces its carcinogenic effect not on the cells where it is formed but on the cells of another organ remote from its origin—the mamma. But I emphasize the statement that during this preliminary phase the cells are being subjected to agencies acting on them from without.

Now the scene changes from the environment of the cell to its interior. When a cell within a precancerous area undergoes the transformation into a malignant cell a new race of cells arises. A change occurs *within* the cell which confers upon it the biological behaviour by which we recognize malignant cells and by which malignant cells kill the organism in which they have arisen. This biological behaviour characteristic of a malignant cell is its autonomous growth.

We pass now to the *second phase* of our problem—the *growth of cancer*; and I wish to emphasize that there is an essential and fundamental distinction underlying the mental concept of these two phases as two distinct and separate problems. The problem now is: What is the nature of the difference between the normal cell and the cancer cell? This difference does not consist, as is sometimes stated, in the acquisition of the property of growth. For the normal cells of the epithelium of the skin or of the intestine, of the lymphatic tissues, of the blood-forming tissues, and particularly of the cells of the embryo, all have this power to grow—that is, to form new cells. But this normal growth is subject to inhibitory and stimulating influences which regulate it in such a way as to ensure the well-being of the whole organism. The cancer cells are no longer subject to these stimulations and inhibitions. They are a new race of cells. They grow—that is, they multiply—sometimes rapidly, but sometimes very slowly, but always without any regard to the physiological needs of the tissue in which they have arisen and without regard to the physiological boundaries imposed after the growth of normal cells. By their destructive autonomous growth in a vital organ they kill the organism in which they have arisen. When a malignant tumour has appeared, either spontaneously or by experimental procedures, the cells of this tumour will continue to grow and form new tumours when placed into other perfectly normal animals. They can be kept growing *ad infinitum* by successive transplantations into normal animals in a perfectly normal environment and without any further application of the carcinogenic substances which have brought about their appearance.

Summarizing these experimental facts once more: we can transform a normal cell into a malignant cell by acting on it from *without* the cell; this phase represents

the *origin of cancer*. But when this transformation has once occurred the malignant cell pursues its course in the absence of any agent acting on it from without. We are faced now with the problem of the *growth of cancer*. Whatever it is that drives the cancer cell on in its autonomous growth must reside within that cell, and that intracellular change is irreversible. The investigation of this second phase of the cancer problem is clearly much more difficult than that of the first phase. For our concern is now with subtle problems of cellular pathology, where even a rudimentary knowledge of cellular physiology is lacking. Essentially our task in investigating the growth of cancer is to search for differences between normal and malignant cells.

But it is not sufficient to discover differences, for these might be not the cause but the effect of the abnormal behaviour of malignant cells. It is necessary to establish differences which can account for the characteristic biological behaviour of malignant cells.

Growth of Cancer : Two Conceptions

Numerous attempts have been made to explain the growth of cancer by highly speculative conceptions. I shall content myself with mentioning very briefly two conceptions which are founded on a basis of experimentally established facts—namely:

1. That the intracellular change is represented by an alteration in the metabolism of the cell in such a way that it enables the cancer cell to obtain the energy necessary to maintain its life by a process of fermentation—that is, a process which does not require the abundant supply of oxygen required for the maintenance of life of the normal cell.
2. That the intracellular change is due to the presence of virus.

These two conceptions must not be regarded as mutually exclusive theories, but as working hypotheses having as their object to elucidate from different angles the autonomous growth of the malignant cell. Thus it is by no means unlikely that the presence of a virus within a cell might alter the metabolism of a cell, and it has in fact been found by Crabtree that in certain virus diseases, such as fowl-pox and vaccinia, in which there is a temporary cellular proliferation, the metabolism is similar to that characteristic of malignant growths. As this lecture is concerned with the origin of cancer, I must refrain from a discussion of these two conceptions. A detailed exposition of the conception of a virus being responsible for the growth of malignant cells has been given in recent years in papers by Peyton Rous and by W. E. Gye. Both the conceptions which I mentioned are working hypotheses, and if they are to be judged, as working hypotheses should be judged, by their results, they have been most fruitful.

What interests us from the point of view of the origin of cancer is the question how these conceptions are to be reconciled with the long preliminary phase necessary for the development of malignancy. That a fundamental and permanent change in the metabolism of a cell requires a long period of adaptation to abnormal conditions can be expected *a priori*. Less obvious is the explanation why a long preliminary period is necessary to enable a virus to enter a cell and transform it into a malignant one.

The Virus Hypothesis

The conception of a virus being responsible for the autonomous growth of cancer has met in the past with a strong opposition. This is due mainly to the fact that

most of the viruses with which we are familiar are the causes of highly contagious diseases, such as small-pox, measles, and foot-and-mouth disease. But it is not an essential feature of a virus infection to be contagious, any more than it is an essential feature of a bacterial infection. A virus is by definition a particulate pathogenic agent, capable of multiplying, foreign to the organism, and of a uniform size which is below the limit of microscopic vision but above that of the largest organic molecule known to exist in the normal cell.

It is clear that the conception of a virus in the cancer cell cannot alter the clinical features of the disease, but must adapt itself to them. Cancer is not a contagious disease. Even the fowl tumours in which a virus can be demonstrated are not contagious. Assuming then for the sake of argument that the growth of all malignant cells is due to a virus, how could we correlate this with the established facts concerning the aetiology of cancer, such as the existence of a long preliminary phase or the characteristic age incidence which is the statistical expression of this preliminary phase?

If we produce a tumour in the skin of a mouse by dibenzanthracene, or in the mamma of a mouse by painting the skin with a chloroform solution of oestrin, we clearly do not introduce thereby a virus. The virus must, therefore, have been pre-existent in the animal in a non-pathogenic condition. And since such tumours can be induced in a high percentage of animals, these viruses must be frequently present in a non-pathogenic condition. The treatment with dibenzanthracene or oestrone respectively would then appear to play the part of so altering the cells that the virus becomes pathogenic for them. This is by no means an extravagant assumption to make, for even with bacterial diseases there are well-known examples where either bacteria or their spores remain non-pathogenic, but become pathogenic when the tissues are subjected to abnormal conditions. The point I wish to make here is that even if the growth of malignant cells were due to a virus the prolonged preliminary phase in which the tissue undergoes a pathological alteration—the precancerous condition—would still remain a determining factor in the aetiology of cancer.

Quite recently Dr. Peyton Rous has published an account of experiments which illustrate this relationship in a very striking manner. There exists in rabbits an infective papilloma of the skin—which is due to a virus—the so-called Shope papilloma. This papilloma can be transmitted to other rabbits by introducing cell-free material obtained from such a papilloma into the scarified skin of a normal rabbit. After two weeks a papilloma begins to appear which may grow for several weeks and eventually regress; or it may continue to grow and form large masses. After an interval of many months a malignant tumour sometimes develops underneath such a papilloma, but no virus can be obtained from such a malignant growth, although it is present in the papilloma. Rous subjected the ears of rabbits to tarring lasting over periods varying from two to four months. As a result a number of warts appeared on the skin. If tarring is now discontinued the warts as a rule disappear gradually, and in order to produce a carcinoma in a rabbit tarring has to be carried on for eighteen months or more. But when Rous, after two to four months' tarring, introduced into the tarred rabbits the virus from the Shope papilloma by intravenous injection, the tar warts, after an interval of three weeks—the incubation period of the virus—began to grow with explosive rapidity, as if the virus had become localised in them, and after one or two months true carcinomata of the skin developed in the tarred ears.

A similar experiment, but with a different virus—the fibroma virus of Shope—has been carried out by Andrewes, Ahlström, Foulds, and Gye. The fibroma virus ordinarily

produces fibroma-like connective-tissue swellings on subcutaneous injection into rabbits. These swellings eventually undergo spontaneous regression. But when this fibroma virus was injected intravenously into rabbits which had received previously an intramuscular injection of tar, connective-tissue swellings appeared at the site of the injected tar, and these swellings did not regress but grew progressively like true fibromata, and in two cases growths arose which had the characters of true malignant new growths of the connective tissue.

Experiments such as these demonstrate very clearly the existence of the two phases in the aetiology of cancer: the preparatory action of the carcinogenic substance (tar), followed by the effect of the virus on the cells which had been prepared for its reception and in which the virus becomes localized.

The Factor of Susceptibility

From the account which I have given so far it would appear that a malignant tumour develops whenever a carcinogenic agent is applied. But fortunately that is not so. I say *fortunately* because if my account was correct the incidence of cancer in man, especially in people of 60 years and more, would be much heavier than it actually is. The carcinogenic agents or stimuli are so numerous and various that it is difficult to see how one could avoid being exposed to them, and cancer would then appear as a normal concomitant of old age, like the greying of hair or any of the other signs of old age. Fortunately the effect of carcinogenic agents is heavily conditioned by factors which reside within the organism and which we may group together under the term "*susceptibility*." Ten years ago I drew attention to the significance of this factor by the following experimental observations:

If the skin of a large number of mice is subjected to a prolonged treatment with a weak carcinogenic agent, some mice will develop a skin carcinoma after about four months, others after six months, eight months, or even a year, and some individuals will remain completely free from cancer. Since these differences are found while the animals are kept under identical conditions, they must be due to a factor or factors of susceptibility intrinsic to the animals.

The importance of this factor has since been demonstrated experimentally by another technique. In mice it is possible, by prolonged inbreeding obtained by brother and sister mating, to produce strains of mice in which the genetic constitution of the individuals belonging to a particular strain is very nearly the same. If one breeds such a strain from a cancerous ancestry, it is possible sometimes to obtain a strain of mice with a very high incidence of spontaneous cancer in one particular organ—most commonly the mamma. In such a strain only the females develop mammary cancer after they have passed a certain age. In this way strains have been obtained in which 70, 80, and even 90 per cent. of all the females develop spontaneously cancer of the mamma. Conversely, it is possible to breed strains of mice in which the incidence of spontaneous cancer of the mamma in the females is very low, and may even be zero. If now the males of such strain are subjected to treatment with oestrogenic hormones, it is possible to induce mammary cancer even in males; but the readiness with which they respond to this hormone varies greatly in the different strains. In the males from a high mammary cancer strain, mammary cancer appears in 100 per cent. in from four to eight months; in males from a low mammary cancer strain in from eight to twelve months; and in males from strains in which the females never develop mammary cancer spontaneously the oestrogenic hormones may be completely unable to induce cancer, although given over a much longer period and therefore in larger amounts. Here again the origin of cancer is bound up with the existence of an intrinsic factor of susceptibility which is transmitted from parent to offspring.

Susceptibility is a deliberately vague term because our knowledge concerning it is as yet very incomplete. It comprises all those factors which condition the effect of the various carcinogenic agents. It may be concerned with the facility with which these agents induce the precancerous condition, or again it may be concerned with the facility with which the malignant transformation sets in within such precancerous conditions. Dr. E. Horning and I have shown recently, for a strain of mice with a very high incidence of mammary cancer, that the susceptibility to cancer of the mamma in this strain is due to an endocrine imbalance, particularly an imbalance between the oestrogenic hormone from the ovary and one or more hormones of the anterior lobe of the pituitary. Another important point is that an organism highly susceptible to the development of cancer in one particular tissue—the mamma—is not necessarily very susceptible to the development of cancer in a different tissue—the skin, for instance. In animals highly susceptible to mammary cancer the skin may, in fact, be resistant, and sometimes highly resistant, to the action of substances carcinogenic for the skin.

The conclusion we should draw from this line of work is that what is inherited is not cancer as a disease but a susceptibility to the development of cancer—that is to say, a tendency to respond with the development of cancer to carcinogenic influences which may be so weak as to be ineffective to the average normal organism—and, further, that this susceptibility is not a susceptibility to cancer generally, but is limited to one or at the most very few organs or tissues.

Remote and Proximate "Causes"

We have now completed our rapid survey of the origin and the growth of cancer.

It has been said by a distinguished physicist that problems are often found to be insoluble because they have been wrongly formulated. This is certainly true of the search for the *cause* of cancer. If I have been able to make myself clear to you, you will agree that the question, "What is the cause of cancer?" is meaningless. Does it refer to what I have called "the origin of cancer"—that is to say, the prolonged preliminary phase without which in the majority of cases cancer would not arise? Or does it refer to the growth of cancer—the sudden intracellular change which confers upon the malignant cell its power of autonomous growth and of metastasizing? They represent, as I have said before, two entirely distinct problems. If we wish to adhere to the use of the term "cause," we may distinguish them by calling the one the *remote causes*—that is, the origin of cancer (and these comprise not only the carcinogenic agencies but also the factor of susceptibility), and the other the *proximate cause*—that is, the growth of cancer. If we take as an example the skin, where the aetiology of cancer can be studied most readily, we know that cancer of the skin can be "caused" by, *inter alia*, light, x rays and radium rays, contact with tar, with certain organic hydrocarbons, and with certain lubricating oils. Here there are six different remote causes of skin cancer. They all lead up to the intracellular change, which we may assume is the same whatever the remote cause may have been, since malignant tumours produced by one carcinogenic agency, though differing *inter se*, do not essentially differ from malignant tumours produced by any of the other carcinogenic agencies. We may assume, then, that the *growth* of cancer of the skin is the same, no matter what the *origin* may have been; and, further, that the growth of cancer is the same for *all* organs and tissues, no matter what

the origin may have been. But we should always bear in mind the mental reservation that this unity of the proximate cause is an assumption which we can only accept so long as there is no evidence to the contrary.

We see, then, that cancer from the point of view of the proximate cause—that is, its growth—may be regarded as a single disease. But from the point of view of the remote causes—that is, its origin—cancer is a multiplicity of diseases. From this second point of view each tissue has its own specific aetiology, different from that of other tissues; and we must even go further and admit that there may be different remote causes for each tissue. I have just given an example by referring to a number of remote causes of skin cancer. My colleague, Dr. Horning, and I have been able recently to bring evidence to show that cancer of the mamma can be due to—or, as I should say, has for its remote cause—an endocrine imbalance between the ovary, the pituitary gland, and possibly, also, the adrenal gland. But it does not follow that this applies to all cases of mammary cancer.

We should therefore discontinue the search for the cause of cancer, which is based on a naïve and crude simplification of the problem, and substitute for it the exploration of the causation of cancer, bearing in mind always that this comprises the two separate and distinct conceptions of the origin and of the growth of cancer.

Experimental Analysis of Carcinogenesis

In the experimental analysis of carcinogenesis we have now reached a point where the two factors—carcinogenic stimulus and susceptibility—can be introduced into the experiment in almost quantitative doses. Their relationship can be expressed, though somewhat crudely, by a simple equation applying to two known and measurable variables, A and B, and a constant, C, where A is the carcinogenic stimulus and B the susceptibility, while the constant C represents cancer. The equation is $A \times B = C$.

In that equation an increase in A involves a diminution in B, and vice versa—that is to say, the aetiological importance of the factor of susceptibility increases as the strength of the carcinogenic agent or stimulus diminishes. A weak carcinogenic agent which will elicit cancer readily in a highly susceptible individual will remain ineffective in an individual with a lower susceptibility, and where the susceptibility is very low even a strong carcinogenic stimulus may be ineffective. Moreover, when cancer develops in response to a carcinogenic stimulus applied to individuals of different levels of susceptibility it will develop more rapidly in those with a low susceptibility than in those with a high susceptibility.

Under experimental conditions we can therefore predict whether an animal will or will not get cancer of the mamma by controlling the two factors—carcinogenic stimulus and susceptibility. The carcinogenic stimulus is a pure chemical substance—oestrone—which can be given in accurately measured doses, while susceptibility can be varied by using different inbred strains of mice with a known incidence of spontaneous cancer of one particular organ.

Applications to Cancer in Man

When we try now to answer the question with which I opened this lecture—"Why does a patient get cancer?" by transferring these findings and conclusions to man, we meet at once with the difficulty that the two factors susceptibility and carcinogenic stimulus, which under experimental conditions were variable and known, now are variable but unknown. The equation reads now $X \times Y = C$.

We know that the patient has cancer and our task now is to search for shreds and patches of evidence concerning the part played by susceptibility and concerning the nature of the carcinogenic stimulus. This is clearly a difficult task. But it has to be faced if the advance in our knowledge of cancer obtained by the experimental study in animals is to lead to a control of the disease in man. That it is not an impossible task is shown by the knowledge obtained in recent years.

The part played by the factor of *susceptibility* has been made evident by the recent statistical investigations of Wassink in Holland and of Waaler in Norway on the familial incidence of cancer. I have reviewed the evidence in some detail in two recent papers, and I need only summarize it here. There are certain organs—the mamma, the uterus, and the prostate—in which there is a very high familial incidence which is restricted to one particular organ. The immediate female relatives of a woman with breast cancer show a remarkably high incidence of breast cancer, but not of cancer in other organs, nor do their male relatives show an abnormally high familial incidence. Similarly, the female relatives of a woman with uterine cancer show a high incidence of uterine cancer. In such tissues as the skin or the lip there is no very clear evidence of a high familial incidence, while some organs, such as the stomach, show a definite increase, though it is much less marked than for the mamma, uterus, and prostate. The extraordinary degree to which the incidence of mammary cancer is influenced by the family history is well illustrated in the accompanying diagram, which represents the proportion of cancer of the mamma in the total incidence of cancer in two populations—one the general female population, and the other the population of female relatives of patients with mammary cancer.

Diagram showing the comparative total cancer incidence in men and women, and the share of breast cancer in the total cancer incidence, in (A) the general population (Holland) and (B) the relatives of patients with breast cancer.

It is necessary to mention that even for those organs where the familial incidence is high only a proportion of the relatives—about 25 to 30 per cent.—develop cancer. Even so, these findings have a very important practical bearing on the early diagnosis of cancer, particularly in such organs as the mamma, uterus, and prostate. Thus the existence of a history of mammary cancer in the relatives of a middle-aged patient who presents herself with symptoms suggesting the possibility of a malignant growth in the mamma would, in my opinion, justify an immediate operation, even if the diagnosis of a malignant growth has not been established beyond a doubt.

A Preventable Disease

The search for the stimuli and agents responsible for the incidence of cancer in man is a most difficult task. We know that stimuli and agents carcinogenic for one tissue are not necessarily carcinogenic for other organs, and that even if we restrict ourselves to one organ the agents capable of eliciting cancer in that organ are numerous and diverse. Perhaps the greatest difficulty in this search is due to the conditioning influence of suscepti-

bility. As a result of this, when two individuals are exposed to the same carcinogenic stimulus one may develop cancer while the other remains free from it. In spite of these difficulties we are now beginning to acquire a knowledge of the *origin of cancer* in man which will make cancer a *preventable disease*.

The recognition of cancer in man as essentially a preventable disease is, in my opinion, one of the most important results of scientific cancer research. It is based on the correct interpretation of the well-known characteristic age incidence of cancer in the light of the knowledge obtained by the experimental study of carcinogenesis to which I have referred earlier in this lecture—namely, that the onset of cancer is not a sudden one but is always preceded by a long period of induction, occupying a considerable fraction of the span of life of the species, during which the tissue in which the phenomena of malignancy eventually develop undergoes definite pathological changes. I correlated these two phenomena in a B.M.A. lecture in 1925; and a further study of this relationship emphasized its importance, for it meant that cancer was in principle a preventable disease. What is necessary now is an application of this knowledge to the study of cancer in man. We can now search for the origin of cancer by identifying the pathological conditions which precede the onset of cancer and their causes.

In certain tissues such as the skin, the tongue, and the vulva—that is to say, tissues which are readily accessible to inspection—the existence of precancerous conditions has long been recognized by clinicians, although the validity of such a conception was questioned by many pathologists. In any case, it was not recognized that these conditions represent special examples of a general phenomenon which is applicable to the vast bulk of the cases of cancer occurring in all organs. It is only in quite recent years, when our knowledge of the origin of cancer has made rapid advances, that an attempt has been made to correlate the incidence of cancer in organs not accessible to inspection with preceding disorders and diseases.

Clinical Correlations

A very striking example of such a relationship has been demonstrated recently. At the International Cancer Congress in Brussels in 1936 two physicians (Dr. Ahlbohm from the Cancer Centre in Stockholm, and Dr. Wassink from the Cancer Centre in Amsterdam) read two papers with the identical conclusion—namely, that cancer of the mouth, pharynx, and oesophagus in women is preceded with surprising frequency by a type of anaemia known as simple achlorhydric anaemia, which is associated sometimes with dysphagia and is then known as “the Plummer-Vinson syndrome.” This type of anaemia occurs usually in women from an early age to middle age onward. It is characterized by achlorhydria and an early loss of teeth. The nails are frequently soft and spoon-shaped. In this condition the mucous membrane of the mouth, tongue, and hypopharynx is pale, dry, and atrophic, and there are often fissures around the mouth. The facial type is stated to be readily recognizable.

In Ahlbohm's figures, of 153 women with cancer of the buccal cavity and oesophagus, ninety-nine (65 per cent.) had suffered from simple achlorhydric anaemia with or without dysphagia. Here, then, is a disease, recognized as a separate entity more than twenty-five years ago and readily recognizable, which, after many years, is followed very frequently by the development of cancer in certain definite sites. There is at first sight no obvious connexion between the two diseases. This and the failure to recog-

nize that the origin of cancer has to be sought for almost always in some pathological condition pre-existing for many years are the reasons why the association between the two diseases has not been recognized until recently. This type of anaemia is readily curable by iron and hydrochloric acid, and since such treatment restores also the atrophic condition of the epithelium to the normal it is practically certain that the effective treatment of this type of anaemia will prevent the subsequent development of cancer which would otherwise occur in certain sites in two-thirds of the patients suffering from this type of anaemia. Although this relationship affects a number of women which is numerically small it is of fundamental importance, for it demonstrates clearly the possibility of elucidating by clinical investigations the origin of one particular form of cancer, from which its prevention logically follows.

I am convinced that a similar aetiological relationship can be found for the occurrence of cancer in many other organs. Thus Hurst has presented evidence that carcinoma of the stomach is frequently preceded by organic and functional changes—namely, a gastritis associated with either a hypochlorhydria or a hyperchlorhydria. Here, however, the relation between these disorders and the subsequent development of cancer is not so simple as in the example which I have just given. These preliminary disorders may, according to Hurst, give rise to a variety of gastric diseases. They tend to malignant disease of the stomach only in those constitutionally disposed to gastric cancer. The causes of gastritis are widespread and trivial, and consist largely of mechanical, thermal, or chemical insults to the gastric mucous membrane, resulting from such conditions as imperfect mastication, septic infections in the buccal cavity, dietetic irregularities—in a word, from imperfect alimentary hygiene. They can therefore be avoided.

Statistical investigations have given valuable information pointing to the same conclusion. The late Dr. Stevenson showed, fifteen years ago, that when the male population of England is divided into five social classes the incidence of cancer of all sites exposed to injury increases rapidly as we descend the social scale, but is approximately equal for the sites not exposed to injury. The exposed sites consist of the skin and the upper alimentary canal, including the stomach. By making a similar analysis for a Continental country (Bavaria) where suitable statistical material is available I could confirm Stevenson's observation. The incidence of gastric cancer shows, then, that the external agencies responsible for the development of cancer in the stomach can be avoided, and are avoided more successfully by the upper social classes than by the lower ones. Here, again, there is evidence that cancer of the stomach is to a large extent preventable.

I have already referred to the recent findings of Horning and myself that cancer of the mamma in a certain strain of mice is due to an endocrine imbalance between the ovarian hormone oestrin and an anterior pituitary hormone which is the physiological antagonist of oestrone. The imbalance can be restored experimentally by the injection of an anterior pituitary hormone—and mammary cancer can thus be prevented. We must, therefore, search for endocrine factors in the aetiology of mammary cancer in women. Here, again, one must not assume that all cases of mammary cancer have the same aetiology. The endocrine type is most likely to be found among women with a marked familial incidence of mammary cancer. Perhaps the statistically established fact that breast cancer is more frequent in unmarried women than in married

women—and that, moreover, in women equally exposed to the risk of pregnancy it is more frequent in those women who are less fertile—may find an explanation in such an endocrine imbalance.

Need for a "Follow-down" System

The task of establishing in man such aetiological relationships is not an easy one. It is rendered more difficult by the lack of a suitable organization. We have to-day in many hospitals a "follow-up" system for cancer patients. This has as its object to trace the results of treatment. What we need now is a "follow-down" system for cancer patients in which the development of the disease is traced down to its origin. Such a system requires the careful clinical examination by a trained physician of a large number of cancer cases with special regard to their previous history. The relation between a certain type of anaemia and the subsequent development of cancer in certain sites was established by two clinicians working in two cancer centres. It would seem necessary, therefore, to establish in a few hospitals a separate department, under the control of a physician, through which all patients admitted to the hospital suffering from cancer of the internal organs, especially those which are numerically important, such as the breast, uterus, and digestive tract, must pass for an investigation into their previous medical histories.

But perhaps the greatest difficulty is the unjustifiable pessimism which pervades the medical profession concerning cancer. We are still being told by distinguished clinicians that cancer is a mystery, that we know nothing about cancer, and that we must wait until the cause of cancer is found—whatever that may mean—when the cure for cancer will automatically follow, which is by no means true.

Cancer is, unfortunately, a sensational disease; but the prevention of cancer is unsensational work. The physicians who prevent a hundred cases of cancer have less evidence to establish their success than the surgeons or radiologists who cure five, nor will they get for their achievement any credit or financial reward. The results of prophylactic work will become evident only after many years by a careful analysis of the national mortality statistics.

We often hear of proposals for an educational propaganda among the public for an earlier diagnosis of cancer; what is much more needed is an educational propaganda among the medical profession to establish in their minds the conviction that cancer is largely preventable and that every effort should be made to prevent it.

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