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THE PREVENTION OF CANCER

EDITORS

Clinical Aspects

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Experimental Aspects

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CHAPTER 1

THE PRINCIPLES OF CANCER PREVENTION

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INTRODUCTION

Cancer prevention encompasses all that is known concerning the causation of neoplastic diseases and the avoidance of exposure to causative factors. It includes the recognition and treatment, where possible, of pre-cancerous states, but it stops short of early diagnosis of the established disease.

The public image of cancer is of a single disease the causation of which is veiled in mystery. In practice, cancer is best regarded as many different diseases caused by many factors. More, in fact, is known about the causative mechanisms involved in the induction of some types of cancer than is known about many non-neoplastic diseases, even some which have already been brought under preventive or therapeutic control. In other words, an exact or full knowledge of causative mechanisms is not necessarily a prerequisite of cancer prevention or control. The general state of knowledge of cancer is manifestly incomplete, so that attempts to prevent the disease must be based on the fullest information available. Moreover, such attempts should be kept constantly under review so that new knowledge is exploited with the least delay. It is proper, therefore, that the present book is based on a resumé of present knowledge of cancer causation gleaned from experimental, clinical and epidemiological studies.

It is important to interpret experimental studies on laboratory animals correctly in terms of the human situation, and space is therefore devoted to this topic at the end of this chapter.

Inevitably, in all fields of scientific endeavour there is some delay before laboratory discoveries find practical application. This stems partly from a poverty of communication between basic and applied scientists and partly from the fact that application may require not only the basic knowledge but also the development of special methods or apparatus. One of the purposes of this book is to facilitate communication, both by bringing knowledge from the laboratory to those who can apply it, and by confronting the experimentalist and epidemiologist with problems as they appear in the clinic.

Laboratory and epidemiological findings relevant to cancer prevention are discussed in this chapter, whilst the needs of the future, particularly that for increasing epidemiological studies in relation to cancer aetiology are considered in the final chapter. We state there, and wish to emphasize the point by stating here also, that in the future, general practitioners and hospital consultants concerned with the management of cancer patients must take a more active and willing part in epidemiological research. A serious attempt to throw light on causation should be routine in the investigation of every case of cancer. In the future such an attempt may, as

indicated in a later Chapter, involve an elaborate series of tests. But at present, in most cases, it cannot usefully involve more than a careful and thorough examination of the present and past environment of the patient. From the results of the interrogation of numerous patients with similar types of cancer, it is to be hoped that information on causative factors and mechanisms will emerge.

THE NATURE OF CANCER: GENERAL CONSIDERATIONS

The nature of cancer as a disease process is likely to be well known to most readers and therefore it will only be briefly considered here. Cancer usually begins with the proliferation of abnormal cells (derived apparently from normal body cells) at a particular site anywhere in the body. Sooner or later, depending on the degree of malignancy, metastases appear as a result of the dissemination of cancer cells from the original site through the blood or lymphatic system, or by direct spread or transference across tissue spaces such as the pleural or peritoneal cavities. Proliferation is a feature of the cells which constitute all cancers, but the rate of proliferation may not be unduly high. In the adult state, body weight remains more or less constant so that in normal tissues the rate of formation of new cells must be equal to the rate of destruction of existing cells. A visible tumour results if the rate of cellular formation exceeds the rate of cell destruction. Provided that this disparity exists, a rapid rate of cell proliferation is not essential for tumour formation. In fact, the rate of proliferation of cells in many cancers is slower than that for some normal tissues in the same host. Thus, few tumours contain cells which multiply as fast as those in the normal intestinal mucosa or bone marrow.

Perhaps the most distinguishing feature of cancer cells is not their rate of proliferation but their ability to invade other tissues. In the normal state, cells of one organ are not found in other organs. An impressive wave of cellular proliferation accompanies the healing of wounds, but in the end, all the tissues involved are found in their respective places. Invasiveness is the feature which best distinguishes a benign tumour from a malignant one, for the reason why a benign tumour does not give rise to metastases is presumably that it cannot invade surrounding blood or lymph vessels or tissue spaces. Nevertheless, a definition of cancer could not depend solely on its invasive ability, because in some types of neoplastic disease, namely the leukaemias and lymphomas, the cells concerned are derived from body cells which, in the normal state, have the ability to invade other tissues. It is possible that the more chronic forms, for example, chronic myeloid and chronic lymphatic leukaemia, are comparable to benign tumours of other organs, and that the dissemination of the cells involved is not a part of the malignant process.

Laboratory studies (Ambrose, 1966; Easty, 1966) have shown that cancer cells, in parallel with their ability to invade, show changes in their surfaces. Thus, the surface negative charge is higher, cells show less tendency to stick together, and, in tissue culture anyway, this lack of intercellular adherence is accompanied by great cellular motility.

There are arguments concerning the origin of cancers: are they derived from a single altered cell, or do they result from a field change in a whole

tissue? In the laboratory it has sometimes been possible to start a lethal neoplastic process in an animal by the introduction of a single tumour cell from a genetically similar animal of the same species. Other evidence in favour of the single altered cell hypothesis is the demonstration of the same chromosomal abnormality in every cell examined from a particular tumour. On the other hand, it is common knowledge that field changes are often present in the vicinity of early cancers. Thus, an invasive carcinoma of the uterine cervix may be surrounded by a wide zone of carcinoma *in situ*, and skin cancer following exposure to arsenic or ionizing radiation is invariably accompanied by widespread epithelial hyperplasia and hyperkeratosis. Obviously, under circumstances where a whole tissue or organ is exposed to a carcinogenic stimulus, the question whether the cancers which arise do so from a single cell is difficult to answer and, indeed, academic. On the other hand, if the field change out of which a cancer arises is of the nature of a pre-cancerous lesion, it is possible that the neoplastic process began with the formation of the pre-cancerous lesion and that this, in turn, arose from a single cell.

For the purposes of cancer prevention two features of cancer deserve special mention: the latent interval, and tumour progression.

In the laboratory the interval between exposure to a carcinogenic agent and the appearance of a tumour may be almost as long as the life-span of the species concerned. Thus, a small dose of a chemical carcinogen injected subcutaneously into a mouse on the day of its birth may cause tumours of various organs to develop in it at any time thereafter. As a rule the first tumours are not seen until 10 weeks. This may be regarded as the minimum induction period in relation to the particular carcinogenic exposure. So far there is no evidence that animals so treated at birth ever revert to normal in their likelihood of developing cancers. Almost up to the end of their life they have a higher risk of developing tumours than mice untreated at birth (Walters, 1966). It is not possible, therefore, to calculate an absolute mean induction period, for any average calculated will depend on when animals which did not die from cancer expired from other causes. Not infrequently, one reads statements such as 'it takes 20 or 30 years to get lung cancer from smoking'. Such statements imply that 20–30 years is the mean induction period, whereas, in all probability the extra risk of lung cancer from having smoked at any time during life probably persists, at least to some extent, throughout the remainder of life. On the other hand, the risk of developing lung cancer late in life is less in persons who stop smoking if only for the reason that they receive a lower dose of the chemical carcinogens in smoke. Further reference will be made to this subject in relation to co-carcinogens in tobacco smoke.

Another feature of the latent interval is that continued exposure to the carcinogenic agent is not required, though not necessarily without effect. Thus, in the experiments of Walters (1966), mice which were injected once with a chemical carcinogen when newborn, still developed tumours late in life even though no other carcinogenic treatment was given during life. If the mice had been given repeated injections of carcinogens, cancers would have appeared in them all at an early date (and in this case a realistic mean induction period, or latent interval, could have been calculated). It is

interesting that even when massive or repeated doses of a carcinogenic agent are given the induction time cannot be reduced below a certain minimum.

Of all the features of cancer there is none more important, or more neglected than the phenomenon known as tumour progression. This refers to the process whereby the histological appearances, invasiveness and growth rate of a neoplasm gradually change in the direction of greater malignancy. There are numerous examples of this; for instance, in many organs it is advisable to remove benign tumours because of the risk of progression to malignancy. In the case of the uterine cervix the risk that intra-epithelial carcinoma (that is, carcinoma *in situ*) will progress to invasive cancer provides the rationale for radical treatment; chronic forms of leukaemia commonly progress to acute forms.

Elsewhere (Roe, 1966) it has been suggested that the process of progression is not limited to the change from benign or less malignant to more malignant tumour, but extends from the moment when cells are first exposed to a carcinogenic stimulus. Thus, progression is taking place during the latent interval, indeed the need for progression from an incomplete stage of neoplasia to a stage of complete neoplasia may be the reason why the latent interval exists.

It is easy to overlook the fact that in many cases of chemical carcinogenesis, both in experimental animals and man, the cells which form a malignant tumour are not those which were exposed at any time to the relevant carcinogenic stimulus. On the contrary, the two are separated by many generations of cells. Roe (1966) postulated that one of the effects of a carcinogen on a cell is to lead to irregularities in the way it divides and in the way subsequent generations of cells derived from the exposed cell divide. As a result there arises a mixed population of cells. Natural selection operates on this mixed population so that as one generation succeeds another increasingly vigorous cell lines take up the running. Vigour implies an ability to secure nutrients and divide again after only a brief interval. It also involves an ability to withstand homoeostatic mechanisms which control the growth of normal tissues.

This concept of carcinogenesis has the advantage that it provides a plausible explanation of the latent interval and explains why the exposure of similar cells to the same carcinogenic stimulus leads to the induction of tumours of widely different histological types and after greatly varying intervals. It also explains pleomorphism and the occurrence of irregular mitotic figures within tumours. Finally, it may explain how drug resistance arises during cancer chemotherapy: drug-resistant cell lines quickly come to the fore when the process of natural selection is artificially boosted by the administration of a drug which poisons the drug-sensitive majority.

One of the weaknesses of the concept is that it presupposes a knowledge of normal homoeostatic mechanisms. Unfortunately our knowledge of these is very limited. Several hormone systems are recognized, many negative feed-back mechanisms have been postulated, but we know very little of the forces which regulate the development of the adult from the embryo, how the proliferation process which accompanies tissue repair is brought to an end, or why any tissue cell, despite what appears to be a full complement of chromosomes, fails to express all but a small part of its genetic information.

THE NATURE OF CANCER IN MAN

Superficially there are differences between cancer in laboratory animals and in man, but they are more apparent than real. It must be remembered that the laboratory mouse has been deliberately developed from the wild species as a tool for research. Its advantages include its small size, its short life-span and the fact that by brother-sister mating for 20 or more generations genetically pure strains may be produced. One result of these advantages is that we know a considerable amount about the role of genetic factors in the susceptibility of mice to various types of cancer. Also, it has been possible to produce strains in which 100 per cent of the individuals develop a particular type of cancer. Further research has shown that in some such cases vertically transmitted viruses (*see* Chapter 9) rather than genes are the primary causative factors. These findings could hardly have been anticipated 60 years ago before the mouse was developed as a laboratory tool. In human cancer research we are very little further forward than we were in the case of the mouse 60 years ago. The difficulties are admittedly great. The study of uni-ovular twins is the nearest equivalent in man to the study of inbred strains of mice. Careful multigeneration epidemiological studies and various indirect methods have to be substituted for direct methods in the search for genetic factors and vertically transmitted oncogenic viruses. Above all, the relatively long induction period in man makes cause and effect relationships more difficult to identify.

Notwithstanding these differences and difficulties there is no reason to believe that man is not prey to the same wide variety of carcinogenic factors as all members of the animal kingdom so far studied.

CURRENT KNOWLEDGE OF CAUSATIVE FACTORS

The known causes of cancer include physical, chemical, genetic and viral factors. Of the physical causes, ultra-violet and ionizing radiation are the most important. The role of trauma and other types of physical irritation is less obvious. As far as man is concerned exposure to actinic radiation is a major hazard, and by far the most important cause of skin cancer. Radiotherapy of non-cancerous conditions, the accidental exposure of radiotherapists, and the exposure of miners and factory workers to radioactive chemicals have claimed many victims. Diagnostic radiation is not a major cause of cancer (*see* Chapter 8).

A wide variety of chemical agents are known to cause cancer in both laboratory animals and man. Historically, chemical carcinogenesis was first observed in man by Percival Pott in 1775, with his observation of scrotal cancer in chimney sweepers. One hundred and forty years later the first tumours were induced experimentally with coal tar in animals. The late Sir Ernest Kennaway and his colleagues at the Royal Cancer Hospital were the first to prepare carcinogenic compounds in pure chemical form. These were aromatic polycyclic hydrocarbons of the type thought to be responsible for the carcinogenicity of coal tar and of various mineral oils. Since the late 1930s many different types of chemical carcinogens have come to light. These include the aromatic amines and aminostilbenes, urethane, many different biological alkylating agents, various metals, such as nickel, iron, beryllium,

chromium and arsenic, and minerals such as asbestos and numerous azo dyes. Recently several new classes of carcinogen have been discovered, such as a whole range of different nitrosamines and lactones. These discoveries are important because such compounds are more likely to occur in nature than some of the previously recognized purely synthetic carcinogens.

Today, man encounters potentially carcinogenic chemical agents in every part of his environment. Agricultural chemicals such as herbicides, insecticides and fertilizers reach his food as contaminants, whilst numerous chemicals such as emulsifiers, anti-oxidants, stabilizers, and colourants are added to it for purposes of preservation or product appeal (*see* Chapter 3). During the roasting or frying of food the carcinogen, 3,4-benzpyrene, is formed. The same carcinogen is present in smoked food. In his home he inhales numerous dusts and sprays in course of household maintenance or in toilet preparations and cosmetics (*see* Chapter 4). Some of the drugs and pharmaceutical preparations in his medicine chest are potentially carcinogenic (*see* Chapter 5). The creosote with which he preserves his garden fences is strongly carcinogenic for mice.

It is widely held that people not exposed to food additives and contaminants in the same way as in the modern West experience a lower incidence of cancer. Although there are certainly differences in the incidence of certain types of cancer between civilized and primitive communities it is difficult to pinpoint any cancers, except those of lung and bladder, which can be attributed to the Western way of life. On the other hand, there are good reasons to suspect that particular types of cancer prevalent in certain primitive communities are directly attributable to their dietary habits. As pointed out by Roe and Lancaster (1964) there exist in nature several very potent carcinogens such as the aflatoxins produced by the fungus *Aspergillus flavus* which affects groundnuts and many cereal crops if stored under hot, damp conditions.

Perhaps the most dramatic demonstration of carcinogenesis in man is in connection with occupational exposure to chemical agents. Reference will be made in subsequent chapters to many examples of this; a full survey of the subject is provided by Hueper and Conway (1964).

The role of hormone status is very clear in the case of the induction of some tumours in laboratory animals. In man there are no clear-cut examples of this. Similarly, despite an abundance of examples of viral carcinogens in many species of animal, no human cancer virus has yet been found (*see* Chapter 9). In both cases, certainly in the second, the lack of examples in man is likely to be due much more to ignorance than to any fundamental difference between man and other animal species.

As pointed out above, genes play an important role in carcinogenesis in laboratory animals. In some cases, genetic constitution appears to determine absolutely whether or not a particular type of cancer appears under ordinary environmental conditions. In other cases genes determine more the susceptibility of the animal to exogenous carcinogenic stimuli. As a rule these two manifestations of gene activity run parallel, so that a strain which is genetically disposed to develop a particular type of cancer spontaneously is also more susceptible to the induction of the same type of cancer in response to exposure to a carcinogen.

In man, several examples of genetically determined cancer are known. One of the best known is familial polyposis of the colon and rectum. In this case, as far as we know, cancer is likely to arise without the additional exposure to a carcinogenic agent. In zeroderma pigmentosum, on the other hand, the genetic peculiarity seems to be an abnormal sensitivity to the carcinogenic effects of ultra-violet radiation.

MECHANISMS OF CARCINOGENESIS

In the past there has been much speculation as to the essential change in carcinogenesis. As an increasing number of causative factors have appeared the concept has arisen of a 'final common pathway' linking genetic, viral, chemical and physical carcinogenesis. The existence of such a pathway is entirely academic with regard to the contents of this book. Here we are concerned at a more practical level with cause and effect, and steps toward cancer prevention can begin without detailed knowledge of fundamental mechanisms. There are, however, two aspects of carcinogenesis which deserve special mention. These are indirect carcinogenesis and co-carcinogenesis.

Not all carcinogens act directly on the first tissue with which they come into contact. Special sensitivity of a tissue may be necessary, or metabolism of a non-carcinogenic precursor to the active proximal carcinogen may only take place in certain tissues. Thus, certain aromatic amines, whether they are inhaled, ingested or enter the body through the skin, give rise selectively to bladder cancer. Another type of indirect carcinogenesis seen in the laboratory is through the effect of a substance on the hormonal status. Thus reserpine increases the incidence of liver tumours in mice indirectly through an effect on the hypothalamus (Theret, 1962).

The subject of co-carcinogenesis has been reviewed by Salaman and Roe (1964). For practical purposes co-carcinogenesis refers to the enhancement of the carcinogenic activity of one agent by another. Under possibly artificial conditions in the laboratory the process of carcinogenesis has been split into two stages: tumour initiation and tumour promotion. Tumour initiators, like complete carcinogens, alter tissues permanently in the direction of tumour formation but do not lead to actual tumour formation by themselves. Tumour promotion takes initiated tissues, but not normal tissues, forward to the stage of tumour formation. A long interval may separate initiation and promotion, but tumours still arise in response to promoting treatment. Unlike tumour initiation, tumour promotion is a partly reversible process. The type of agent which acts as a tumour promoter also acts as a co-carcinogen when applied at the same time as a weak carcinogenic stimulus.

It is at present difficult to know how important a role co-carcinogens play in the genesis of human cancer. Roe and colleagues (1959) suggested that the carcinogenic effect of cigarette smoke was the result of the combined action of carcinogens and co-carcinogens in the smoke. This now seems more likely in so far as epidemiological data suggest that stopping smoking has a more beneficial effect on the subsequent incidence of lung cancer than one would have expected if all the carcinogenic activity were due to complete carcinogens whose effect is irreversible (Doll and Hill, 1964).

EXTRAPOLATION OF RESULTS OF ANIMAL EXPERIMENTS TO MAN

Species differ widely in their susceptibility to different carcinogens. However, the most potent carcinogens readily cross species barriers. There is no species of laboratory animal which acts as the perfect model for man. It is difficult to carry out meaningful large scale experiments on higher primates, especially in the search for weak carcinogens. In general, a positive result in a laboratory carcinogenicity test is most likely to have significance for man if the dose administered is small or realistic, if the route of administration is similar to that in man and if it can be confirmed in the same and in other species. Roe (1965) reviewed the problem of extrapolating from the laboratory to man in detail.

FUTURE RESEARCH NEEDS

Clearly rational cancer prevention stems from knowledge of causative mechanisms. Our knowledge of causation in relation to human cancer is limited, but certainly not negligible. In the case of some types of cancer, and in the case of cancer due to some types of exposure to carcinogenic stimuli, it is possible to apply preventive measures without delay. In other cases it is difficult to apply knowledge of how to prevent the disease.

Where we have no knowledge of aetiology, it is urgent that we strive, through the intelligent use of both epidemiological and experimental methods, in combination where possible, to discover causative agents.

It is essential that, where it is proposed to add new chemical agents to the environment, they are fully tested on laboratory animals first. For the main part legislation exists to see that this is done. But such research will not necessarily throw light on existing causes of cancer. Many substances which are naturally present in food, or which have been added to food for decades, or even centuries, have never been tested for carcinogenicity on the grounds that substances traditionally present in the diet may be regarded as safe. Until recently, numerous pharmaceutical products had not been submitted to adequate screening for carcinogenicity. The full testing of such substances represents a prodigious amount of laboratory work. Nevertheless, it is urgent that it is undertaken for it may reveal causes of cancer so far overlooked.

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