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IN

ONCOLOGY

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PART TWO: CLINICAL PROGRESS

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12 Preventing Cancer in the Community

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INTRODUCTION

Everybody knows that chimney sweeps and men who work with tar or pitch are especially liable to develop cancer of the skin, but is that layer of soot that falls out of the polluted atmosphere, to collect on the office window-sill a cancer hazard? We know that smoking is associated with increased risk of development of cancers of the lungs, larynx, pharynx and, possibly, bladder, but we know all too little of why smokers smoke or of the hazards associated with other forms of self-indulgence which might fill the void for persons who stop smoking. We know that workers exposed to asbestos dust to such an extent that their lungs become choked and scarred by it are in grave danger of developing cancer of the lung and of the pleural membrane that covers it, but do the little bits of asbestos fibre that become suspended in the air around asbestos mines and factories, or as a result of the wear and tear of car brake linings in big cities, contribute to the lung cancer burden of the population at large?

There are chemicals that cause cancer of the bladder, and it is known that in the past, virtually 100 per cent of groups of men exposed to these substances in chemical works have developed bladder cancer. But is exposure to traces of these chemicals, because of pollution of the environment with them, dangerous? The x-ray martyrs died as a direct result of cancers caused by heavy exposure to ionizing radiation. Is the increased background level of radiation attributable to the explosion of nuclear devices in the atmosphere a real cause for concern in relation to

cancer? Do the liver tumours that many pesticides, such as DDT, seem to cause in laboratory animals (Innes *et al.*, 1969; IARC, 1970), herald a future pandemic of liver cancer in man? And if the answers to any of these questions is 'Yes', is the social order, even in the so-called advanced countries, such that preventative measures can be and would be implemented? Is man still in command of his long-range destiny or are the pressures of over-population and the creed of the 'quick buck' going to be allowed to determine the future of the world? Is man's environment getting better or worse in respect of cancer hazards?

SOME BASIC INFORMATION ABOUT CANCER

Cancer is not a single disease, but very much a mixed bag of conditions with some similarities and many differences. The essential feature of the cancerous process is that it is a manifestation of internal strife between living cells – a breakdown of order within the body – and not, as with bacterial diseases, the result of attack by living agents from outside the body. The cells of which cancers consist, which proliferate to form lumps, which invade and destroy surrounding normal tissues and which migrate to distant sites in the body, are derived from seemingly normal body cells. There has been much debate recently as to whether cancers develop because the cells that consitute them are abnormal, or because there is a failure in the defence mechanisms by which abnormal cells are destroyed or restrained from exhibiting their cancerous potentiality. Undoubtedly both explanations are partly true: in the case of some cancers, the cellular abnormality is seemingly the sole determinant; in others, damage to the body's defences is apparently the more important contributory cause.

A wide variety of cells makes up the human body, each having special structural and functional features. The body's proper functioning is dependent on an elaborate system of communications and controls between its constituent cells. The ability of individual cells to receive messages and to act on them is vital to the welfare of the body as a whole.

The remarkable thing is that, despite its complexity, the adult body is derived from but a single cell – the fertilized ovum. That cell has, coded within its nucleic acids, all the information necessary for producing all the varieties of cells found in the adult body, and all the information necessary for the staged development of the adult from the single cell stage through prenatal life, babyhood, and childhood. Perhaps even more remarkable is the fact that every cell in the adult organism, despite its specialized structure and function, appears to have a complete copy of the body blue-print present in the nucleus of the

fertilized ovum. In other words, each cell probably has all the information necessary to produce the whole organism. Experiments involving the transfer of nuclei from cells derived from adult animals into denucleated fertilized ova indicate that this really is the case. The mechanisms by which the bulk of information which ordinary body cells do not express is suppressed constitute a subject of much current research.

With so much complex information contained within the nucleus of each body cell, it is easy to see the need to keep the blue-print firmly locked up so that it remains intact and a faithful copy of the original. The inappropriate expression of normally suppressed information could give rise to abnormalities of structure and/or function – even in tumour formation. But what if the blue-print has been damaged or altered in some way? What would happen if a cell could express part of a damaged master-plan and multiply and produce other cells with abnormal blue-prints like itself? Is this the mechanism that underlies the formation of cancers? And if so, how does the blue-print get damaged? Is this a frequent event? Can we prevent it? Has the body any defence against it? Is there a mechanism for the repair of damage to blue-prints? Or can normal body cells recognize cells with damaged blue-prints and destroy them? These, in simplified terms, are the sort of questions that scientists, concerned with fundamental cancer research, are asking today. It is generally accepted that the blue-print can be damaged by a process akin to mutation, and that errors in the suppression of information can occur. It is also recognized that cells may acquire extraneous information as a result of infection by viruses and that the expression of this new information may be associated with cancerous behaviour.

For the purposes of the present chapter, which is concerned with preventing cancer in the community, there is need to consider only two questions: 'To what extent is industrialized twentieth century man contributing to his own cancer burden by increasing the risk of damage to the blue-prints within living cells?' and 'To what extent are the changes he is introducing into the environment affecting the body's defences against such damage or the effects of it?'.

CANCER IN MAN

Many of us go happily through most of our lives in the fond belief that cancer is a disease that affects 'other people'. We might even go as far as assuming that it is in some way a person's own fault if he gets the disease. The latter prejudice runs deep and is a part of the fundamental behavioural reaction of 'kicking the weakling out of the nest'. The truth

is less palatable. On average, approximately 1 in 4 of us is likely to develop a cancer before we die and 1 in 5 of us may well die from the disease. In the majority of cases there are no good grounds for suggesting that the sufferer is in any way responsible for his or her developing the disease.

The chances of dying from one or other form of cancer as compared with the chances of dying from a non-cancerous cause have increased since 1900; but the main reason for this is that the chances of dying from infectious diseases, such as tuberculosis and diphtheria, or from metabolic diseases such as diabetes, have fallen. Until a few years ago, the average number of years that males in England and Wales were expected to survive has been steadily increasing. In women, the expectation of life is still increasing. Increased average length of life means that, nowadays, more men and women live to ages at which cancers are most apt to arise, so that cancers and deaths from cancer appear to be more frequent than was once the case. But this apparent increase in frequency does not tell us that the environment is more dangerous from the point of view of cancer than it used to be. In order to be knowledgeable on this point we need information about the risk of developing, or dying from, different forms of cancer for people of different ages. For example, we need to be able to calculate the risk of man or woman developing or dying from, for example, cancer of the stomach during the year between his 60th and 61st birthdays, and to compare the risk for a man who was aged 60 in, say, 1920 with that for a man aged 60 in 1970. In practice it is impossible to make accurate calculations of this kind, because records of cases cured of cancers are not available, deaths from cancers are not always accurately recorded especially if post-mortem examinations are not carried out, and criteria for diagnosis are liable to change. Nevertheless, it seems fairly clear that the risks of developing many forms of cancer have been falling during this century. The age-standardized risks of dying from cancers of the stomach, oesophagus and liver, for example, have decreased in both sexes and those from cancers of the breast and uterus have fallen in women. On the other hand there has been a sharp rise in risk of dying from cancer of the lung in both sexes, but especially in men. A recent rise in the age-specific death rate from leukaemia (i.e., cancer of blood-forming tissue) seems now to have levelled out.

In the light of this information, it is reasonable to conclude that, except in the cases of cancers of the lungs, bladder, kidneys, adrenal glands and blood-forming tissues, changes in the environment in Britain during the present century have, if anything, been associated with a reduction in exposure to agents that favour the development of cancers

(carcinogens). However, there is no room for complacency, in view of the increasing risk of death from lung cancer. We have little idea how a large number of recently introduced changes in the environment may affect cancer death rates in the future; and moreover, we have no right to assume that the present levels of exposure to carcinogens are close to the minimum levels achievable.

We know that cancer is not simply a disease of civilization or of industrilization, but we do not know the extent to which industrialization, during the eighteenth and nineteenth centuries, increased the risk of development of different kinds of cancer, nor how the age-standardized risks that prevail today compare with those extant before the industrial revolution.

THE IMPORTANCE OF ENVIRONMENT IN THE CAUSATION OF CANCERS

Theoretically, either genetic or environmental influences may be responsible for the very wide geographical differences in incidence of different types of cancer. Recent studies of change in risk of development of particular forms of cancer in people who migrate from one country to another point to environmental influences as being more important than genetic ones. In Japan (Haenszel, 1961; Haenszel and Kurihara, 1968) the risk of dying from cancer of the stomach is approximately five times higher than that in Caucasians in the United States of America. By migrating to the environment of the United States of America, Japanese people dramatically reduce the risk that they or their children will develop cancer of the stomach. On the other hand, cancers of the colon and lung which are not common in Japan become a more serious threat to Japanese who migrate to the United States of America, where the risks of these forms of cancer in Caucasians are much higher.

The importance of environmental factors in causing cancers in man is also indicated by the growing list of known occupational cancer hazards (Hueper, 1966). Skin cancers may arise following exposure to soot, coal tar, creosote, mineral oils, arsenic, sunlight (e.g., in outdoor occupations), and x-rays. An increased risk of cancer of the lung is associated with uranium mining, an old process of refining nickel, the manufacture of bichromates from chromite ore, the manufacture of coal gas, and exposure to dusts containing arsenic or asbestos. Woodworkers (Acheson *et al.*, 1968) and nickel refiners (using a now obsolete process) (Doll, 1958, 1970; Morgan, 1958) are (or were) at increased risk of developing cancers of the nose or nasal sinuses and men exposed to certain substances of the chemical class known as aromatic amines

are at grave risk of developing cancer of the urinary bladder. Certain other dusts, aerosols, and chemicals to which people are exposed at work are under suspicion of being associated with increased risk of cancer development, but the difficulties of pinpointing cancer hazards are increasing. New chemicals and new industrial processes are being introduced faster than it is possible to evaluate their safety; and the long latent interval that separates first exposure to a carcinogen and the development of cancer makes it difficult to recognize causative associations, especially where men move from job to job or are exposed to more than one suspect chemical. It is reasonable, therefore, to assume that there are many as yet unrecognized occupational cancer hazards. Even if none of them are serious, the fact that they are unrecognized, makes it impossible to be sure that carcinogens of industrial origin are not escaping from the factory environment into the general environment, to raise the level of carcinogenic hazard to which we are all exposed.

It would be wrong, however, to be an alarmist about this possibility. As explained earlier, the age-standardized risk of death from many forms of cancer seems to be declining. Epidemiologists associated with industries or working in university departments and Government-financed cancer registries are keeping an ever more watchful eye on the incidence of cancers in occupational groups; and occupational hygiene standards are improving. Where a carcinogen is also an 'irritant' and produces acute effects as well as the delayed effect of increasing the risk of cancer development, workers are likely to be, at least to some extent, protected from exposure to it anyway. The biggest danger relates to insidious hazards from non-irritant carcinogens.

THE ROLE OF STUDIES ON LABORATORY ANIMALS IN DETECTING CARCINOGENIC HAZARD

Most countries now require that chemicals be shown to be non-carcinogenic in laboratory animals before they can be added to food for any purpose, (WHO, 1961). Most new drugs also have to be shown to be carcinogenically harmless before their use is permitted (Berenblum, 1969). In some ways, the danger of misinterpretation of the results of laboratory tests, rather than the likelihood that carcinogens will find their way through the safety net, is the bigger problem at the present time! An experienced toxicologist, if he sets his mind to it, can show that virtually any substance – including, for example, distilled water or glucose – is 'carcinogenic' according to definitions currently accepted in some quarters. There is, therefore, a danger that the tag 'carcinogen' will become attached to so many chemicals, including all sorts of

natural food constituents, that the taking of precautions against exposure to any of them will seem pointless. It is no longer enough to divide chemicals into carcinogens and non-carcinogens: it is essential at least to try to distinguish between potent carcinogens likely to be hazardous for man, and weak carcinogens that may only be active under artificial laboratory conditions. It is equally important to try to distinguish between agents that cause cancer directly and agents that non-specifically increase the risk of its occurrence.

Theoretically, it is possible that a substance which gives entirely negative results in tests on laboratory animals, will produce cancer in man. However, there is at present only one example of a human carcinogen, arsenic, which has not been shown to induce cancer in animals of any other species.

THE PRESENT SITUATION AND THE FUTURE

In Britain we know something about the factors which contribute to about 50 per cent of cancer deaths in men but only 15 per cent of cancer deaths in women (Roe, 1971). There is an association between smoking and risk of death from cancers of the mouth, pharynx, larynx and, possibly, urinary bladder. These associations have been apparent for many years and have been given wide publicity. Nevertheless, a majority of males smoke. Giving up smoking has been more common in social classes I and II than in social classes IV and V (*see* Table 20a in Todd, 1969). This suggests that affluence alone does not determine whether and how much men smoke, and we really do not know at present whether social classes I and II contain more ex-smokers because they are more aware of the association between smoking and risk of disease or because their status in society offers them more alternatives to smoking than are open to people in lower social classes. Clearly the social aspects of smoking and smoking-related disease deserve more attention than at present.

A few deaths, certainly less than 10 per cent of all cancers, are due to cancers of the skin, lung, nasal sinuses and bladder associated with occupational exposure to dust and chemicals. A few skin cancers are directly attributable to exposure to sunlight and a few cases of cancer of various sites and of leukaemia are due to exposure to x-rays used in medical diagnosis or treatment. Uncircumcised men who develop cancer of the penis might not do so had they been circumcised. Regular dental care might protect a proportion of men who develop cancer of the mouth.

In women, the most preventable form of cancer appears to be that of the uterine cervix. Choice of a circumcised marital partner and

restriction of marital intercourse to one partner is likely to reduce their risk of developing and dying from cancer of the neck of the womb. We know little or nothing as yet about the causation of some 50 per cent of cancer deaths in men and 85 per cent of cancer deaths in women. In particular, we know very little about the likely causes of cancers of the stomach and large intestine which are relatively common in both the sexes, and next to nothing about the causation of breast cancer. Recent reports suggest that cancer of the pancreas is not only more common among diabetics but also among professional chemists.

Studies on migrants suggest that the causes we seek should be sought in the environment and that genetic factors are likely to be less important (Haenszel, 1961; Haenszel and Kurihara, 1968). It is fashionable, if nothing else, to point accusingly at man-made chemicals and at pollution as being the likely cause of all human ills. In relation to food, however, unknown, naturally-occurring carcinogens are as likely to be causing cancers as unnatural substances that are added to food, or that contaminate it. The situation with regard to the safety testing of drugs is not yet satisfactory and examples of pharmaceutical preparations that have given rise to cancer in man can be cited. Nobody yet knows whether 'the pill' predisposes to the development of cancers or protects against it. In any case, by helping to restrict population size, it may be doing more to preserve the quality of the environment than any harm it does in favouring the development of any form of cancer.

THE PROBLEM OF THE FUTURE

The overriding problem for the future and the one that is in some ways increasing faster than the will or the means to solve it relates to what may broadly be called 'pollution', particularly non-reversible pollution.

We already know that the easily detectable carcinogen, 3,4-benzopyrene, which is formed during the incomplete combustion of any fuel and which is a seemingly inevitable by-product of the industrialized society, pollutes not only the air we breathe, but also the water we drink and the crops we harvest from our fields (Food and Cosmetics Toxicology, 1965). It is present only in trace amounts in water and crops, but its presence there tells us that factory effluents, vehicle exhausts and domestic chimney smoke contaminate the whole of our environment. Clean Air Acts have had a remarkably beneficial effect in reducing the smoke and sulphur dioxide content of London air during the past decade, and are beginning to have the same effect in other cities, but on the international scale, and in relation to pollution in the broadest sense, the problems are increasing in size and complexity (Martin and Wilkins, 1962; Lawther, 1965, 1971; Waller, 1971).

It is not possible today to point to any pollution problem, even the rising level of background ionizing radiation from atom bomb tests, and predict dire consequences in the near future in terms of increased cancer risk. However, sooner or later somebody somewhere may see fit to release a potent carcinogen into the general environment in such a way that it causes an epidemic of cancer.

In the meantime, we would do well not only to go on searching for specific carcinogens in the general environment, but also to seek answers to the two questions posed earlier in this chapter, and now made slightly more explicit.

Is the risk that individual body cells will be changed from the normal state to the cancerous state (by damage to the blue-print or other mechanism) increasing as a result of pollution of the environment by traces or more than traces of a myriad of new carcinogens?

Does exposure to any of these new substances, alone or in combination, serve to weaken body defences which normally prevent the development of cancers from previously damaged cells?

An even more serious question is: Is there a steady build-up of either of these types of activity such that we are already condemning future generations to an intolerable burden of cancer risk?

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