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Chapter 10

FUTURE STRATEGY

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'The energy and drive of cancer research stems from the asking of questions. At all times the most significant advances have been made because the right question has been asked at the right time and in the right form.' (From the *Introduction* to the *42nd Annual Report of the British Empire Cancer Campaign*)

What is, and what should be, the nature of the fight against cancer? The primary objective, according to most people, is to be able to *cure* the disease completely. Other objectives, such as the alleviation of suffering, or the prolongation of life, are generally felt to fall so far short of complete cure that outstanding advances of these types are overlooked, and there is a widespread general impression that no progress has been made.

It is also a commonly held view that the main reason why no methods of curing cancer are known is that its cause remains a complete enigma. It should be obvious, however, that a knowledge of causation is more likely to lead directly to methods of prevention than to methods of cure. This is true of many other diseases and conditions. For example, knowledge of the more important causes of car accidents helps not at all in treating those injured in such accidents, but only in accident prevention. Similarly, until recently, the knowledge that smallpox was caused by a virus contributed nothing towards the effective treatment of those with the disease. In this case, its prevention was possible even before the precise cause was understood.

Cancer prevention

Our first approach to future strategy in Cancer Research is therefore, without doubt, to require that there be much greater emphasis on the possibilities of preventing the disease. Already we know enough about some of the causes of cancer to take active steps in this direction. Some of the chemical causes have been discussed in Chapter 8, and reviewed in

the *British Medical Bulletin* (1964)[1]. Research on tumour viruses is confidently expected to show that such agents are involved in the aetiology of human cancer (*see* Chapter 7). This may be followed by the development of methods of preventing virus-induced cancer.

It would, of course, be misleading to suggest that we know enough about the factors involved in the causation of human cancer to enable the prevention of more than a proportion of cases. Moreover, it is not always possible, or practicable, to avoid exposure to known carcinogenic agents.

Epidemiological investigations

Basic research has revealed an extensive range of factors involved in the causation of cancer. There is, however, a wide gap between this knowledge and a precise assessment of the importance of individual factors in causing human cancer. We must look to epidemiological studies of man to fill this gap. At present we are almost certainly only at the dawn of a golden age of epidemiology, in relation not only to cancer but to a variety of other diseases. The obvious success achieved by this method in demonstrating the strength of the association between smoking and lung cancer (DOLL and HILL (1964)[4]) is impressive, particularly the success of the prospective survey method. At the same time, however, one is also impressed by the surprising accuracy of the less precise, retrospective type enquiry (*see Report to Surgeon-General*, 1964)[9]. This is important, since retrospective surveys are much cheaper than prospective ones.

We envisage cancer research advancing by a combination of the experimental and epidemiological approaches; an experiment on laboratory animals reveals that cancer may be caused by a particular factor, so the epidemiologists endeavour to find out whether exposure of man to this factor increases his chances of developing cancer. Alternatively, an epidemiological study may reveal an unexpected correlation between exposure to a particular factor in the environment, and the development of cancer, so the experimentalists test the suspect factor for carcinogenicity in laboratory animals.

Experience so far indicates that, in the cases of many types of cancer, multiple aetiological factors are involved, some of the factors being more important than others. Thus, in the case of lung cancer, clearly, smoking is far and away the most important aetiological agent, although exposure to air pollutants, nickel, chromium, arsenic or beryllium may also induce the disease. A few types of cancer are apparently due solely to one factor. Thus the dominant gene, familial polyposis gene, determines the occurrence of cancer of the colon or rectum; and asbestos may be the sole cause of the rare tumour, mesothelioma. Once a strong association between exposure to a particular environmental factor and cancer has become evident, no further study of other, probably less major, factors is likely to

be of value, unless the survey takes into account the factor previously identified. Thus, no future study of the factors involved in the causation of cancer of the lung is likely to be of value unless smoking habits are taken into account, and controlled.

In the past, epidemiological surveys have tended to be too narrow in approach. As pointed out in the quotation at the beginning of this chapter, it is vitally important to ask the right questions. The epidemiologist is rarely in a position to know what the right questions are. Therefore, he should always err on the side of too many rather than too few enquiries.

Until recent years epidemiological studies have been limited to relatively small geographical areas of the world. It cannot be hoped, in such surveys, to pick up evidence of the effect of factors which involve the whole of the area surveyed. Internationally organized surveys are now in progress. In these, it is possible to include groups of persons with widely differing environments and, perhaps, widely different risks of developing particular types of cancer. The potentialities of international broad-based surveys are enormous, but they involve special difficulties. Thus, the diagnostic criteria for cancer are not all internationally agreed, and even if they were agreed, the standard of medical practice differs widely from place to place. In surveys where death from a particular form of cancer is the object of comparison between different exposure groups, far greater accuracy is obtainable if all diagnosis of cancer is based on autopsy findings. Autopsy rates (i.e. the percentage of persons dying who are examined post-mortem) differ widely in different countries. In the Middle East generally, amongst both Jews and Moslems, burial is supposed to take place within 24 hours of death. This leaves little time for autopsy, which, in any case, is unpopular for religious reasons. Even in Britain the autopsy rate is well below 50 per cent., which is much lower than in some other European countries. A general rise in autopsy rates and in the standard of diagnosis throughout the world are basic requirements if the full value of the epidemiological method is to be realized.

In this connection religious leaders should re-examine the codes of practice which they require of their followers. Many so-called religious irtes, or practices, are, in reality, no more than hygienic measures. As such, they were proposed long before the microscope had revealed the existence of micro-organisms. Science has now, in these ways at least, caught up with, and overtaken, religion. Therefore the hygienic measures ordained by various religions and sects can be considered rationally. Thus the Moslem should consider the advantages of circumcision in infancy by a qualified surgeon over the more hazardous and somewhat barbarous ceremony at the age of nine: and all peoples, irrespective of religion, should understand the advantages to be gained from high autopsy rates. At present, over wide areas of the globe, the true mortality rates from

various types of cancer cannot be calculated. In these areas the nature and extent of the cancer problem is quite unknown. It is hardly surprising, therefore, that the answers are slow to emerge.

An important aspect of the epidemiological investigation of cancer is the study of people who migrate from one place to another (HAENSZEL (1961)[5]; STASZEWSKI and HAENSZEL (1965)[10]; *British Medical Journal* (1966)[2]). STEINER (1954)[11] pointed out: 'Members of certain races have, however, unwittingly, performed aetiological experiments on a large scale by migration from one environment to another'. Thus, whilst the genetic characteristics of the migrant remain unchanged, some environmental factors such as climate, altitude, and air pollution, change immediately, and others, such as cultural and culinary practices, change more gradually after migration. Much could be learned from the study of migrants, again provided that the data for analysis are based on reliable clinical diagnosis and supported by information from autopsy examination in a high proportion of cases.

Tests for cancer

It is well established that genetic constitution may play a prominent part in determining susceptibility to cancer. For instance, white skin is far more susceptible than coloured skin to the induction of cancer through exposure to sunlight. Also, there is a significant, though weak, association between blood group and susceptibility to gastric cancer: persons with Group A blood being more susceptible than those with Group O (HOSKINS *et al.* (1965)[6]). There is, however, no single test, nor any battery of tests, which can either predict accurately that a particular person will develop cancer, or establish that he already has the disease. The search for such tests has in the past been intensive (*Public Health Monograph* (1953)[8]; *Journal* of the *National Cancer Institute* (1957)[7]). Few of the aspects of the biology of cancer considered in previous chapters encourage us to think that there is likely to be a single test, e.g. biochemical blood test or test for chromosomal abnormality, capable of distinguishing patients with all kinds of cancer from those without. Cancers invariably differ, biochemically, from the corresponding normal tissues, but the difference may be small and the nature of the difference is variable between cancers. In any case, the difference may well not be carried over into the bloodstream. If, in time, certain viruses are known to cause particular types of cancer in man, specific tests for antibodies to the virus or to characteristic tumour virus antigens, may become a practical possibility.

Cancer therapy

Certain views on this subject have been expressed at various points in the book. Nevertheless, there is some scope for bringing together and summar-

izing the views expressed. The limitations of surgery are obvious: it is not possible to remove every cancer cell when the disease involves vital organs or is disseminated throughout the body. The limitations of radiotherapy are also clear: the dose cannot be raised high enough to kill every cancer cell without doing unacceptable damage to surrounding normal, and perhaps vital, organs. The use of vaccines in the treatment of virus-induced cancers remains a possibility for the future, but it seems unlikely that they will be of value for more than a small proportion of cancers. We may be on the threshold of important discoveries in relation to the treatment of cancer by immunological methods. These may involve reinforcement of the host's immunological reaction against his own cancer, the provision of an abundance of immunologically competent cells, passive immunization with cells immunized against his cancerous tissue, or enhancement of antigenicity of the cancer so that the host reacts more strongly against it. It is at present too early to judge whether any of these methods will be of value in practice, or the proportion of cancers which can be successfully treated by any of these means.

For want of more encouragement in other approaches to therapy, we are bound to turn to chemotherapy, and to regard it as offering the most promise for the future.

Future approaches in chemotherapy

Of all forms of therapy, it is in relation to chemotherapy that the study of the biology of cancer has most to offer. Unfortunately, as basic sciences, chemistry, biochemistry and microbiology advanced earlier, faster and further than biology. The result, so far as cancer chemotherapy is concerned, has been that very large programmes of work have been undertaken in the absence of a sound biological basis, and even on a complete misconception of the probable biological nature of the disease. In the first place, cancer has been regarded as though it were a type of micro-biological infection—the cancer cells acting as parasites in the host. This approach entails the tacit assumption that the cancer cells are different from the host cells in a *constant and potentially exploitable way*. In the second place, it has been assumed that the special attribute of cancer cells is their rapid rate of multiplication. Thus, attention has been focused on producing drugs which interfere with growth mechanisms and cell-division. As pointed out by CONNORS and ROE (1964)[3] all the biological screening tests for cancer chemotherapeutic activity are, in effect, screens for anti-growth or antimitotic activity. It is not surprising, therefore, that most of the drugs so far available tend to be most effective against rapidly growing tumours and to have the drawback that they damage those tissues in the body which are normally the most mitotically active. In fact, the cell generation times in many cancers are longer than those in the gut mucosa

or bone marrow. In such cases, cytotoxic drugs may damage these tissues more than the cancer.

In future, as pointed out in Chapter 5, much more attention should be devoted to the invasiveness of cancer cells, for this is the property which, more than any other, makes cancer a lethal disease. A better understanding of the nature of invasiveness is needed, so that the possibility of developing drugs which inhibit the invasive powers of cells can be explored.

The possible role of viruses in the aetiology of human tumours is already stimulating the search for anti-viral agents of value in the treatment of cancer. In this endeavour success is more probable when specific causative viruses and their mode of spread have been recognized.

Homeostasis

One of our greatest needs is a much fuller understanding of homeostasis, which, in every case, the development of cancer infringes. The fact is that each body cell has a complete blue-print for the whole organism, but only expresses a small part of the information contained in that blueprint. By what mechanisms is the remainder of the information suppressed? Almost all body cells have the potentiality for behaving like cancer cells, i.e. growing, dividing, invading; why do they not behave so?

We know but little of the mechanisms involved. Circulating hormones are certainly involved in homeostasis of certain tissues, but much more localized mechanisms must be the basis of maintaining a fixed number of layers in the epidermis, and of controlling the turnover of cells in the gut mucosa. Doubtless, contact inhibition plays an important anti-invasive role. However, one is still left with the impression that homeostatic control systems built into individual cells during the development of the organisms from the fertilized ovum are most important in homeostasis. These are discussed in Chapter 3. To our mind, here lies the nux of the problems both of cancer causation and treatment. This is the most important growing-point in cancer research. In particular, we see the latent interval in carcinogenesis and tumour progression (see Chapter 1) as manifestations of a slow, progressive breakdown in a complicated system of homeostatic controls. A clearer understanding of these aspects of the biology of cancer should enable us to apply biochemical knowledge to much greater effect than at present. It is here that the advances in our knowledge of normal development are likely to play an increasing part in cancer research. The molecular mechanisms involved in embryonic induction, and the nature of the cellular changes which give the somatic cells their remarkably stable characteristics, still elude us. Advances in this field may lead eventually to methods of restoring the normal properties to malignant cells.

Research is disproof of hypothesis by measurement. The availability of methods and facilities too often dictates what shall be measured and,

therefore, the kind of hypothesis to be put forward. The authors of the present volume set out deliberately to challenge the existing pattern and emphasis of cancer research from the standpoint of biological knowledge and conjecture. More questions have been posed than answered, but if some of the new questions are closer to being the right ones than those upon which much current research endeavour is still based, a good purpose will have been served.

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