CHAPTER 59

A LOOK TO THE FUTURE

FRANCIS J. C. ROE AND RONALD W. RAVEN

During the last century the pattern of disease prevalence and the spectrum of causes of death have changed out of all recognition. Infectious diseases have in great measure been conquered, in some cases by purely preventive measures such as isolation or immunization, and in other cases by the use of effective chemotherapeutic agents. The importance of the contribution of preventive measures is easily overlooked, perhaps because there is no drama attached to the fact that a person does *not* develop a particular disease, whereas the cure of a critically ill patient by the administration of a drug may be very dramatic.

A reduction in the mortality from infectious diseases is bound to be matched by an increased risk of dying from other causes such as cancer. Thus, one effect of the conquest of infectious diseases is that more people survive to ages at which cancer is more likely to develop. For this reason the proportion of deaths attributable to cancer has been steadily rising and, today, approximately 1 in 5 deaths are from this cause. We hasten to point out that this does not mean that the risk of developing cancer at any particular age is, in general, increasing. In fact, for most sites in the body the risk of dying from cancer at a specified age has been slightly receding, partly as a direct result of the deliberate introduction of preventive measures in industry, and partly, it is thought, as a result of a general improvement in living standards and personal hygiene.

Only for a few sites has the risk of dying from cancer at a specified age increased. The most important of these is cancer of the lung in men. In this case the increase is so big that it has reversed the trend towards increased longevity which started at the beginning of the present century. The table summarizes these considerations by showing a comparison of mortalities from cancers of different sites in men and women between two cohorts (*see* Case, 1956) born around 1871 and 1901, thus indicating that the prominence given to the association between smoking and lung cancer is not misplaced.

Recently, there has been welcome evidence that the apparent rise in mortality from leukaemia in childhood has ceased (Case, 1965). The fact that mortality from bladder cancer is still rising should certainly be regarded as a challenge by industries such as the rubber and cable industries, where there undoubtedly has been, and possibly still is, a bladder cancer hazard (Case, 1964; Davies, 1965).

TREATMENT AND EARLY DIAGNOSIS

It is generally accepted that the scope for improving cure rates by the traditional methods of treatment, surgery, radiotherapy and chemotherapy,

is limited. There is room for hope that instruction of the general public in the early symptoms and signs of cancer, and that the streamlining of the passage of patients from the time and place of first suspicion or positive diagnosis of the disease to instigation of effective treatment, will lead to an improvement in cure rates. However, there are definite limits to what may reasonably be hoped from this approach, since many internal forms of cancer are silent and symptomless until they have reached an advanced stage.

TABLE

Age-specific Death Rates per 1,000 Living per Year, for Men and Women aged 60–65 years for Cancer of Different Sites

Cause of death (cancer site)	*Cohort born around 1871*		*Cohort born around 1901*	
	♂	♀	♂	♀
Stomach	1·35	0·85	1·27	0·54
Intestines and rectum	1·31	0·91	0·89	0·71
Liver and gall bladder	0·30	0·29	0·16	0·13
Tongue, oral cavity and pharynx	0·51	0·05	0·14	0·06
Larynx	0·23	0·04	0·12	0·02
Oesophagus	0·46	0·11	0·19	0·09
Skin	0·08	0·04	0·05	0·03
Breast	0·01	0·99	0·01	0·87
Uterus	—	0·64	—	0·49
Testes	0·01	—	0·01	—
Prostate	0·28	—	0·25	—
Lungs	0·36	0·12	**2·48**	**0·29**
Bladder	0·18	0·06	**0·27**	**0·06**
Kidneys and adrenals	0·07	0·05	**0·11**	**0·05**
Leukaemia	0·04	0·04	**0·13**	**0·10**
Ovaries	—	0·21	—	0·29
All neoplasms	6·15	5·10	**6·98**	4·37
All causes	28·78	21·07	28·54	15·02

After Case (1956). Bold figures indicate sites at which the incidence of cancer had increased in cohorts.

In the case of cancer of the bladder it is by no means certain that early diagnosis by the cytological examination of urine samples alters the ultimate prognosis. It is true that this method of screening detects cases with bladder neoplasms which are still small or non-invasive and which can be wholly removed by local treatment, but where such lesions occur in persons who have been exposed to potent bladder carcinogens, the whole of the bladder epithelium may be in a pre-cancerous state. The lesions which appear earliest may not be the ones which will eventually kill the patient. Indeed, as pointed out by Wallace (*see* page 252), local treatment of the early lesions may hasten the onset of the malignant change.

The recognition of pre-cancerous states only helps in the avoidance of cancer if the affected tissue can be excised or the progression to malignancy halted. There is little doubt that it is of value in the case of carcinoma of the uterine cervix, for in this case local or even total excision is possible; but in patients with widespread leukoplakia in the mouth extensive excision is not possible. In this case all that can be done is to recommend the

avoidance of irritants which may be supposed to exacerbate the condition and hasten the onset of the malignant change, and to detect the onset of malignancy as early as possible so that it can be dealt with. Even in the case of carcinoma of the cervix it is now suspected that some cases are fulminating from the start and do not pass through a long phase of pre-malignancy in which they can be detected by cytological methods.

Hormones and Endocrine Ablation

It would be wrong, then, in looking to the future, to hope too much from advances in the traditional methods of treating cancer, or from the earlier diagnosis of cancer. Perhaps more is to be hoped from the development of entirely new approaches to cancer treatment. Until recent years the success of hormonal and other chemotherapeutic approaches has been limited to a few types of neoplastic disease. The administration of hormones and hormone-ablation therapy have profoundly affected prognosis, particularly in patients with cancer of the prostate and breast. Even so, cure of cancer by hormonal therapy alone cannot often be claimed. A possible development in this field is that more tissues and organs will be shown to respond to hormones as a part of normal homoeostatic control. Consequently, it will be reasonable to try to treat a wider variety of cancers than at present by hormones or hormone-ablation therapy. The first sign of this development is seen in the results of treating renal cancer with hormones (Bloom and Wallace, 1964). Another possibly important development is that methods may be evolved for the recognition of pre-cancerous states attributable to hormone imbalance. It is well established in laboratory animals that certain states of hormone imbalance predispose to a wide variety of types of cancer, and it is more than likely that some cases of cancer in man are attributable wholly, or partly, to the pre-existence of such states. Their recognition might well make a significant inroad into the problem of preventing the disease.

Hormone-induced tumours often begin as hyperplasia and advance through stages from benign to malignant tumours without abrupt or distinct separation of the stages. In addition, discontinuous progression, regression, either spontaneous or induced by hormone administration or deprivation, also occur. The life-span of the host may not be sufficient for the full sequence of changes to malignancy, so that at death latent and subclinical neoplasms are found. It is necessary to examine the processes which account for the development of a hormone-dependent tumour and its transformation into an independent and truly malignant tumour. This sequential process occurs when laboratory animals are given dimethylbenzanthracene to produce mammary tumours. Initially, such tumours tend to be of limited malignancy and hormone-dependent, as indicated by the fact that hypophysectomy prevents their appearance or causes them to regress. After a few weeks this operation fails to affect growth of the tumour because it is no longer dependent on a particular hormonal environment. We must now examine, by refined and subtle methods, the biological mechanisms operating in such tumours before and after this striking change from hormone-responsiveness to hormone-irresponsiveness, for it may become possible by physiological methods to avoid the change to autonomous growth.

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Leukaemias and Reticuloses

Chemotherapeutic agents other than hormones are at present used particularly in relation to the leukaemias and reticuloses—forms of cancer which tend to be widely disseminated from their inception. It is worthwhile to consider briefly how these conditions differ from other forms of cancer. Carcinomas in general and many forms of sarcoma (for example, chondrosarcoma, osteosarcoma) arise from tissues which are confined to certain anatomical sites and from cells which do not normally have the power to invade surrounding structures. If such cells multiply more rapidly than they are destroyed, a tumour results, but unless they also acquire the property of invasiveness the tumour will be benign and amenable to local excision. In the case of these tumours, therefore, the acquisition of invasiveness is the critical change which confers malignancy.

In contradistinction, the leukaemias and lymphomas arise from tissues and cells which under normal circumstances have the power to invade other tissues and to migrate throughout the body. It follows that hyperplasia could not be distinguished from cancer simply on the basis of the invasiveness. It may be that chronic myeloid leukaemia, for example, despite the apparent widespread dissemination of myeloid cells is, in the early stages at least, only a state of very marked hyperplasia, and that the success of chemotherapeutic drugs is attributable to this. This concept implies that some form of leukaemia and reticulosis may be pre-cancerous rather than cancerous in nature, and that a better understanding of the homoeostatic mechanisms which control the multiplication of myeloid and lymphoid cells could lead to the development of methods of preventing the subsequent onset of malignancy. Some cases of leukaemoid reaction induced by such agents as phenylbutazone (Thorpe, 1964) and certain antibiotics (Felistovich, 1960) may be examples of reversal of a process which would otherwise develop into fatal leukaemia.

Anti-cancer Vaccines

A spectacular development during recent years is the discovery that cases of Burkitt's lymphoma sometimes respond dramatically to small doses of chemotherapeutic agents (Annotation, 1966), and that apparently complete and permanent cures may sometimes result from the administration of single doses of methotrexate or cyclophosphamide. Large jaw and abdominal tumours have disappeared completely following such treatment. Why is the response to treatment so dramatic? It may be that the tumour is more of the nature of a hyperplasia than a neoplasm. Alternatively, it has been suggested that the immune response of the host is particularly strong in the case of Burkitt's lymphoma and that the body only needs a little help to eradicate the tumour.

A similar explanation has been put forward to explain the successful treatment of chorio-epithelioma by chemotherapeutic agents. The geographical pathology of Burkitt's lymphoma suggests that it may be caused by an insect-borne virus. If this is so, it is not unreasonable to expect that it would give rise to specific tumour antigens common to tumours in different patients. Early results suggest that serum from patients who have recovered

from the disease by chemotherapy caused marked regression of cancers in untreated cases.

Are these the first indications that some forms of cancer, especially virus-induced cancer, will be preventable by vaccination? Burkitt has suggested that, in those areas of the world where Burkitt's lymphoma is endemic, the disease is a rare manifestation of infection with a universally widespread agent, just as poliomyelitis is a rare manifestation of infection with poliomyelitis virus. As yet it is not proven that Burkitt's lymphoma is due to a virus; both reovirus 3 (Annotation, 1966) and a herpes type virus (Epstein and colleagues, 1965) have been associated with disease. The former has been implicated in the causation of lymphosarcoma in mice (Stanley and colleagues, 1966). If a viral aetiology is eventually proven the way may be open for the preparation of a vaccine to prevent, if not infection with the virus, then at least the lymphomatous response to such infection.

It is now to be regarded as likely that several forms of cancer in man, including Burkitt's lymphoma, are due to virus infection. Unfortunately, this does not mean that, in the general case, there are only two short steps to the production of a variety of preventive vaccines. Where viruses have been shown to be implicated in the aetiology of cancers in animals, special conditions have aided the initial observation. Thus, the Bittner milk factor which is involved in the aetiology of mammary cancer in mice, several of the murine leukaemia viruses, and the polyoma virus, have all been identified because it was possible to observe animals bred under controlled conditions. All these viruses are spread predominantly by vertical transmission, that is to say from parent to offspring before birth, after birth in the milk, or by other means during the early neonatal period. It would be very difficult to detect viruses transmitted in the same way in man.

Furthermore, in many cases the tumours which arise in response to infection with oncogenic viruses do not contain the virus itself, and it is suspected that the virus has become incorporated within the genome of the host cell. Under these circumstances it is difficult to see how a vaccine prepared from the virus is likely to prevent the disease, for the vaccine could not be given before infection with the virus, and antibodies to the virus would not be effective against cells with genomes altered by the presence of the virus.

As pointed out in Chapter 9, the hope that vaccines will be developed in relation to virus-induced tumours is more applicable to horizontally transmitted virus infections. In this case it may be difficult to decide when and to whom inoculations should be given. In qualification we visualize the possibility that we might be able to determine those persons at special risk to a particular form of virus-induced cancer and to define the nature and extent of the risk. This is likely to be true in the special case of Burkitt's lymphoma.

Another possible development involves the use of heterologous lymphocytes from animals inoculated with human cancer tissue (Delorme and Alexander, 1964). The principle underlying this method is that the introduction of cells from a tumour in man into an animal of another species, such as the sheep, is followed by the development within that animal of lymphocytes which produce antibodies to specific antigens present in the

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tumour tissue. Promising results have been obtained in laboratory animals by this method, but it is too early to be sure whether it has a human application.

CANCER EDUCATION

At present cancer education consists of the instruction of the public in the ways of recognizing the early signs and symptoms of cancer. We believe that this approach is too limited. The public should be given up-to-date information about cancer hazards and should be instructed in the avoidance of exposure to such hazards. In other words, we feel that an entirely new image of the cancer problem should be presented. However, this can only be done successfully if the new image is first accepted by the medical profession itself. The essential features of the new image are that *cancer is many diseases and not one, that many aetiological factors are involved, and that man really does have some control over whether he develops or does not develop the disease.* The old image of cancer as a single disease of unknown aetiology requiring treatment, which is usually unsuccessful, should be discarded for good. People must be shown that cancer is probably for the most part the effect of a cause-and-effect phenomenon and that, in many instances, we have good information with regard to the cause.

The lay press not infrequently presents the cancer problem as perpetually poised for a 'break-through'. We see not one but many problems, just as we see cancer as multiple diseases. We see ahead a long uphill struggle, questions asked and answered one at a time, numerous questionnaires, experiments on animals, and the critical statistical evaluation of clinical trials. It is for this type of painstaking and hard work that the public should be asked to give support. For there is still much to learn about the causes of cancer in man and much more effort should be put into the task of detecting weak carcinogens in the human environment—physical, chemical and viral agents which are responsible for inducing cancers in only one in a hundred or one in a thousand persons exposed to them. The more that the ordinary people know about cancer, the greater the chance that weak cause-and-effect associations will be observed.

CONCLUSION

Our main conclusion from this survey of the subject is that cancer prevention, based on knowledge of aetiology, should command far more interest and energy than at present, since it is from endeavour in this area of cancer research that much of the hope for the future lies.

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