The Prevention of Cancer

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Fifty years ago, cancer was the certified cause of one death in nine; today it is certified as the cause of one in five. This increase, which has been particularly marked in childhood (Fig. 1), is largely due to the progressive elimination of other diseases, and the age-specific death rates from cancer have hardly increased at all (Fig. 2). Indeed, from 30 to 54 years of age, when cancer of the cervix used to be the predominant type in women, the rates have actually fallen.

That the rates have not fallen more generally, despite improvements in treatment, is in part an artefact due to improved diagnosis and more complete case-finding. In part, however, it is the result of a real increase in the incidence of some cancers that has more than compensated for a decrease in others. But no matter the reason, the fact remains that cancer is now such a major cause of ill-health that, in the absence of other causes of death, 33 per cent of men and 25 per cent of women will develop it before 75 years of age, which is slightly less than the age that half the population now achieves. In the presence of other causes, it is responsible for nearly 25 per cent of all deaths under 75 years of age,
and those that die of it lose, on average, 18 years of life. Cancer was never just a disease of the old, but its treatment and prevention have now become a matter of serious concern for the young and the middle-aged.

Until recently, cancer specialists concentrated on teaching people to recognise the first signs of disease, in the belief that earlier treatment would lead to improved results. Too many cancers, however, are incurable by the time they draw attention to their presence for it to be possible to make any major impact by this means. The weight of effort is, therefore, now being switched to the development of programmes for examining the healthy population, in the hope that cancers can be detected before they have produced symptoms or, better still, that pre-malignant states can be detected and treated so that invasive cancer does not have a chance to appear. Programmes for the examination of vaginal smears for the presence of abnormal cells have been introduced in many countries, and the experience of British Columbia, where population screening was first introduced on a large scale, provides evidence that a useful reduction in the mortality from cancer of the cervix can be achieved by such means. It is less obvious, however, that similar programmes should be introduced for other types of cancer. We have to consider not only whether the limited funds at our disposal are best used in this way but also whether the medical benefit may not be outweighed by the harm of the diagnostic process. We have to consider the
carcinogenic effect of X-rays and the discomfort and anxiety produced by repeated physical and instrumental examinations and the surgical intervention that is liable to follow. No one who has examined the facts could be impressed by Illich's (1975) criticism of modern medicine; but there is much to be said for his contention that the really healthy man is one who takes responsibility for his own body until there is some positive reason to seek professional aid.

An alternative programme, which, in my opinion, is more likely to succeed, is one that aims to prevent cancer by eliminating the factors that cause it. Whether we shall ever be able to do this absolutely, in the way that we can now prevent poliomyelitis and scurvy, depends on the mechanism by which the disease is produced, and that is still not known. There is, however, ample evidence that the disease can be prevented in the practical sense that we can reduce the frequency with which it occurs by a particular age.

CAUSES OF CANCER

Industry and Medicine

Some 20 physical and chemical agents have been recognised as causing cancer when used in industry or as drugs (Tables 1 and 2). Most are weak carcinogens in that the disease is seldom produced until after prolonged and intensive exposure; but even so, several of them have caused cancer in between a third and a half of all the workers employed on the specific process. Nearly all these risks have now been brought under control, either by stopping manufacture or use of the material (as with 2-naphthylamine, 4-aminodiphenyl, thorotrast, and chlornaphazine) or by altering the process so as to reduce exposure (as with the manufacture of asbestos textiles).

The Role of Environment

Several of these agents are also found in the general environment. The greatest risk has probably arisen from domestic smoke, which was the principal source of polycyclic hydrocarbons in town air. Even so, urban residents were not exposed to more than one hundredth of the amount that was regularly inspired by gasworkers, who experienced an 80 per cent increase in lung cancer, and the effective difference is likely to have been much more (Lawther et al., 1965). Asbestos has been brought home by workers on their clothes, and at least 37 cases of mesothelioma of the pleura, which is almost pathognomonic of exposure to asbestos, have occurred in household contacts in nine countries (see Anderson et al., 1976). Home pollution can also be produced by sawing and drilling asbestos board, but the amount that is generally inspired in town air (2 mg/m³) is only a millionth of that which has been regarded as an acceptable concentration in the asbestos industry for some years. As for vinyl chloride, the amount absorbed in food from PVC containers is estimated to have been fifty million times less than that received by the men who made PVC and who have been at risk of developing

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Table 1. Occupational Cancers.

| Agent                        | Occupation                                      | Site of Cancer |
|------------------------------|-------------------------------------------------|----------------|
| Ionising radiations:         |                                                 |                |
| Radon                        | Certain underground miners: uranium, fluorspar, haematite | Bronchus       |
| X-rays, radium               | Radiologists, radiographers                     | Skin           |
| Radium                       | Luminous dial painters                          | Bone           |
| Ultraviolet light            | Farmers, sailors                                | Skin           |
| Polycyclic hydrocarbons      | Chimney sweepers                                | Scrotum        |
| in soot, tar, and oil        | Manufacturers of coal gas                        | Skin           |
|                              | Many other groups of exposed industrial workers  | Bronchus       |
| 2-Naphthylamine              | Chemical workers                                | Bladder        |
| 1-Naphthylamine              | Rubber workers                                  | Bladder        |
|                              | Manufacturers of goal gas                        |                |
| Benzidine                    | Chemical workers                                |                |
| 4-Aminobiphenyl              | Asbestos workers                                |                |
| Asbestos                     | Chemical workers                                |                |
|                              | Shipyard and insulation workers                 |                |
| Arsenic                      | Sheep dip manufacturers                          | Skin           |
|                              | Gold miners                                     | Bronchus       |
|                              | Some vineyard workers and ore smelters           |                |
| Bis (chloromethyl)           | Makers of ion exchange resins                   | Bronchus       |
| Benzene                      | Workers with glues, varnishes, etc.              | Marrow         |
|                              |                                                  | (leukaemia)    |
| Mustard gas                  | Poison gas makers                               | Bronchus       |
|                              |                                                  | Larynx         |
|                              |                                                  | Nasal sinuses  |
| Vinyl chloride               | PVC manufacturers                                | Liver          |
|                              |                                                  | (angiosarcoma) |
| Chrome ores                  | Chromate manufacturers                           | Bronchus       |
| Nickel ore                   | Nickel refiners                                 | Bronchus       |
| Isopropyl oil                | Isopropylene manufacturers                      | Nasal sinuses  |
| *                            | Hardwood furniture makers                        | Nasal sinuses  |
|                              | Leather workers                                 | Nasal sinuses  |

* Specific agent not identified
Table 2. Iatrogenic Hazards.

| Agent                                      | Site of cancer                                      |
|--------------------------------------------|----------------------------------------------------|
| Diagnostic and therapeutic X-rays          | All sites                                          |
| Thorium                                    | All sites                                          |
| Thorotrast                                 | bone                                               |
| Polycyclic hydrocarbons in:                | R.E. system of bone and liver                      |
| ointment                                   | Skin                                               |
| liquid paraffin (?)                        | Stomach, colon, rectum                            |
| Arsenic                                    | Skin (? lung)                                      |
| Oestrogens                                 | Vagina, corpus uteri                              |
| Stilboestrol                               | breast (male)                                      |
| Steroid contraceptives                     | Liver                                              |
| Phenacetin                                 | Renal pelvis                                       |
| Chlornaphazene                             | Bladder                                            |
| Immunosuppressive drugs                    | Reticulosarcoma (?: all sites)                     |

angiosarcoma of the liver (Barnes, 1976), although a somewhat higher dose may have been received by residents in the immediate neighbourhood of factories where the material was made. Taken all in all, the agents that are responsible for occupational hazards can have caused only a very small proportion of all the cancers diagnosed each year. It seems unlikely, however, that these agents are all special cases, and it is only reasonable to assume that other chemical agents are responsible for other cancers in other circumstances. Indeed, it now seems certain that environmental agents, of one sort or another, are responsible for the great majority of all cancers everywhere.

That this is so has been demonstrated by the way in which the incidence of cancer varies from place to place and from time to time. The extent of this variation is shown in Tables 3 and 4. Cancers common enough in Britain for them to be considered a more than one per cent risk of either men or women developing them by 75 years of age (in the absence of other causes of death) are shown in Table 3. For most of them the range of variation is twenty-fold or more, and there are other countries where the risk is around 1 per 1,000 or less. The range is never less than seven-fold and the minimum rate is never more than 9 per 1000. Other cancers that are common enough for the risk to affect at least 1 per cent of men or women in some other countries are shown in Table 4. Again, variation is the rule, and the range is usually large.

Some of this variation is, of course, genetic in origin. Migrant groups, however, show that genetic factors are not usually the principal cause, particularly the
Table 3. Range of variation in the incidence of cancers common in Britain: cumulative risk by 75 years of age in the absence of other causes of death.

| Type of Cancer | Area | High incidence | Low incidence | Range of variation |
|----------------|------|----------------|---------------|--------------------|
| Skin           | Queensland | 20 | India, Bombay | 0.1 | x 200 |
| Bronchus       | England   | 11 | Nigeria       | 0.1 | x 100 |
| Stomach        | Japan     | 11 | Uganda        | 0.2 | x 50  |
| Cervix uteri (♀) | Colombia | 10 | Israel, Jewish | 0.6 | x 20  |
| Prostate       | U.S.A., black | 7 | Japan | 0.3 | x 20  |
| Breast (♀)     | U.S.A., Connecticut | 7 | Uganda | 0.9 | x 7   |
| Colon          | U.S.A., Connecticut | 3 | Nigeria | <0.1 | x 30  |
| Rectum         | Denmark   | 2  | Nigeria      | <0.1 | x 50  |
| Bladder        | U.S.A., Connecticut | 2 | Japan | 0.6 | x 4   |
| Ovary (♀)      | Denmark   | 2  | Japan        | 0.2 | x 8   |
| Corpus uteri (♀) | U.S.A., Connecticut | 2 | Japan | 0.2 | x 9   |

Table 4. Range of variation in the incidence of cancers common outside Britain: cumulative risk by 75 years of age in the absence of other causes of death.

| Type of cancer | Area | High incidence | Low incidence | Range of variation |
|----------------|------|----------------|---------------|--------------------|
| Oesophagus     | N. E. Iran | 20 | Nigeria       | <0.1 | x 300 |
| Liver          | Mozambique | 8  | Norway        | 0.1  | x 70  |
| Nasopharynx    | Singapore, Chinese | 2 | England  | <0.1 | x 40  |
| Buccal cavity  | India   | 2  | Denmark      | 0.1  | x 20  |
| Penis          | Uganda, part | 1 | Israel, Jewish | <0.1 | x 300 |
| Pancreas       | New Zealand, White | 1 | Uganda       | 0.3  | x 4   |

groups of black Africans and Central Europeans who moved to North America, the Japanese who moved to California and Hawaii, the Indians who moved to South Africa or Fiji, and the Northern Europeans who moved to the tropics. Sometimes the migrant groups have retained the habits of their homelands and the same hazards of cancer. More often, their way of life has changed and their experience of disease has changed with it.

Variation with time provides even more convincing evidence of the influence of environmental agents, but it is more difficult to demonstrate, partly because it is difficult to compare the efficiency of case-finding at different periods, and partly because a high standard of case registration has existed for more than ten years in only a few places — the most notable being Denmark and Connecticut, U.S.A. We have, therefore, to rely to a large extent on trends in mortality, which may also be influenced by changes in the efficacy of treatment.
Some changes are so gross that it is impossible to doubt that there has been a real change in incidence: for example, the increase in lung cancer in all developed countries, the increase in oesophageal cancer in the black population of South Africa, and the decrease in gastric cancer in the U.S.A. Many lesser changes have taken place in Britain during the last 20 years. These are shown in Table 5, which

Table 5. Changing mortality rates from different cancers* England and Wales, 1958 to 1973.

| Type of cancer | Males | Females |
|----------------|-------|---------|
| Melanoma       | +95   | +47     |
| Myelomatis     | +65   | +70     |
| Lung           | +29   | +94     |
| Pancreas       | +19   | +20     |
| Testis         | +19   |         |
| Oesophagus     | +16   | +17     |
| Stomach        | −25   | −34     |
| Buccal cavity  | −38   | −24     |
| Cervix         |       | −23     |

* All cancers with rate of change equal to or more than one per cent per year.

lists all those cancers for which the mortality rate, standardised for age, has changed by more than one per cent a year between 1958 and 1973. Several of the changes are difficult to dismiss as artefacts, particularly when the diagnosis is easy and the death rate has increased despite improving treatment (as with cancer of the testis). In sum, the evidence suggests that all common cancers have varied in incidence from time to time just as they vary from place to place.

Social Causes
Although we know that environmental factors are responsible, there is still only a minority of cases in which the cause has been identified (Table 6). Three of the factors are limited to Asia and have been known for many years. One, the chewing of a variety of materials, is responsible for the vast majority of cases of one of the commonest cancers throughout the large parts of Central and South-East Asia. Another, aflatoxin, appears to be a cause of the commonest cancer in tropical Africa. That it might be so was suggested as a result of investigating an outbreak of poisoning which killed 100,000 turkeys in British farms. The outbreak was traced to a consignment of peanut meal contaminated with Aspergillus flavus. The fungus produced aflatoxin as a metabolite and this was found to produce acute liver failure in poultry and cancer of the liver, when given in minute doses, to a wide variety of animals. Human liver cells contain the enzymes necessary to
Table 6. Cultural hazards

| Agent                      | Site of Cancer                          |
|----------------------------|-----------------------------------------|
| Sunlight                   | Skin                                    |
| Use of 'kangri'            | Skin of abdomen and thigh               |
| Reverse smoking            | Soft palate                             |
| Chewing betel, tobacco, lime | Mouth                                  |
| Aflatoxin                  | Liver                                   |
| Schistosomiasis            | Bladder                                 |
| Alcoholic drinks           | Mouth, pharynx, larynx, oesophagus      |
| Smoking tobacco            | Mouth, pharynx, larynx, bronchus, oesophagus, bladder. |

produce the epoxy-metabolites of aflatoxin, which are the active agents, and *Aspergillus flavus* frequently contaminates foodstuffs stored under hot and humid conditions. Now, in Thailand, Singapore, Kenya, Swaziland, and Mozambique, it has been shown that the incidence of the disease increases in proportion to the amount of aflatoxin in the diet (van Rensburg *et al.*, 1974; Peers *et al.*, 1976). The vagaries of daily diet make it unlikely that we shall ever be able to establish the relationship in individuals, but the evidence is strong enough to justify applying the crucial test that one would naturally apply in industry, that is, to reduce exposure and see if the disease disappears.

Another factor (the consumption of alcohol) interacts with tobacco smoke and other agents to cause a variety of cancers of the upper respiratory and digestive tracts in a manner that is still not understood. It is also related in a more obscure way to cancer of the liver (through the production of cirrhosis) and possibly to some cases of cancer of the pancreas and rectum. Estimates of its total effect are difficult to make, but it may account for some 5 per cent of all fatal cancers in men. Pure alcohol is not carcinogenic to animals and it seems probable that alcohol solubilises another agent, or that the actual agent is another component of alcoholic drinks. If this is so, it should be possible to identify it by comparing cancer incidence rates in different regions where different types of drink are consumed.

The highest incidence of oesophageal cancer in Europe is found in Brittany and Normandy, which are characterised by the consumption of cider and cider-based liqueurs, and the role of these and other alcoholic drinks in that area is now being investigated by the International Agency for Research on Cancer (1975). Preliminary estimates, based on a comparison of the histories given by patients with oesophageal cancer and a random sample of the general population, suggest that the risk of developing the disease increases both with the amount drunk and with the amount smoked until, among men who drink 81 or more grams of ethyl
alcohol (equivalent to 7 whiskies) and smoke 20 or more cigarettes a day, the risk is 45 times that in men who drink less than 40 grams and smoke less than 10 cigarettes a day. Until recently, few attempts have been made to explain the association between the consumption of alcohol and the development of cancer, although the existence of a relationship has been recognised for 50 years. We can, however, now reasonably hope that current research will identify the responsible agent and lead to some practicable means of prevention short of abandoning the use of alcohol altogether.

Last on the list is the smoking of tobacco, which is a cause of cancers of the mouth, pharynx, oesophagus, larynx, and, possibly, bladder and, when smoked in the form of cigarettes, is a principal cause of cancer of the lung. Observation of mortality rates in people with different smoking habits suggests that, in the absence of smoking, the mortality from lung cancer in men would be reduced by between 90 and 95 per cent, and from all cancers by about 40 per cent. Among ex-smokers, the mortality from lung cancer rapidly falls behind the rate in continuing smokers until, after about 20 years, it is only slightly more than that in lifelong non-smokers of the same age. That stopping smoking has, indeed, a measurable long-term benefit is demonstrated by the observations on British doctors that my colleagues and I have made over the last 25 years.

Our study began at the end of 1951, when a questionnaire was sent to all doctors who were resident in Britain (Doll and Hill, 1954, 1964). Nearly 35,000 men replied, giving details of their smoking habits in a standard way. They were subsequently followed for 20 years and further details of their smoking histories were obtained in 1957, 1966 and 1972. With these data and national data reported by the Tobacco Research Council and the Registrar-General, Doll and Peto (1976) have compared the trends in the number of cigarettes smoked and the mortality from lung cancer in both the doctors and the total male population of the country. In brief, the results showed that the doctors were smoking somewhat more cigarettes than other men in 1951 and slightly less than half the number of other men 20 years later. In parallel with this change, the mortality from lung cancer in doctors fell from about 60 per cent of the national rate to under 40 per cent. The doctors’ mortality was at all times somewhat less than would be expected on the basis of the current number of cigarettes smoked per day. This, however, is not surprising. It can be accounted for partly by a three-year difference in the age at starting to smoke and, partly perhaps, by a tendency for people with more money to smoke each cigarette less intensively and to throw away a longer butt than people with less money to spend on smoking.

A similar but less marked effect is observed in the country as a whole, as a result of the changes that have taken place in the type of cigarette and the relative numbers smoked by men and women. First, there has been a phenomenal increase in the sale of filter-tipped cigarettes, which began in the early 1950s and continued — aided by their cheaper price — until 1973, when they accounted for
83 per cent of the total sales. Secondly, the industry began to manufacture cigarettes that yielded less tar and nicotine so that by 1973 the tar yield per cigarette averaged 40 per cent less than it had in 1965. Thirdly, the combined effects of a decrease in smoking by young men and an increase in older men has led to a stabilisation of male consumption at the level it had reached at the end of the war, while the rise in female consumption, which began in 1920 and became more rapid during the war, has continued ever since. As a result, the consumption per adult woman, which was only 7 per cent of the male figure in the early 1930s, had risen to 33 per cent twenty years later, and to 58 per cent in 1973. The changes that have taken place in the mortality from lung cancer, which has been influenced very little, if at all, by treatment, are shown for the quinquennia 1956-60 and 1969-73 in Fig. 3. Between these two periods the mortality from lung cancer in men under 60 years of age fell, and under 45 years of age it fell substantially. In women, it fell slightly under 40 years of age, but at other ages it

Fig. 3. Change in mortality from lung cancer in England and Wales between 1956-60 and 1969-73, by sex and age (Wall, 1976).
rose, and over 45 years of age it rose considerably. Whether or not these changes can be accounted for entirely by the changes that have taken place in the number and type of cigarettes smoked is impossible to say, owing to our ignorance of the exact differential effect of inhaling, or duration of smoking cigarettes with different yields of tar. Qualitatively, however, they correspond closely to what would have been predicted on our present imperfect knowledge.

A possible cause of cancer that has not yet been established is the nature of the Western diet which is distinguished by a high proportion of meat, fat and refined carbohydrate and a relative deficiency of fibre. Burkitt (1969) suggested that a low residue diet might be responsible for a whole group of diseases that affect the large bowel, are common in developed countries and rare in rural Africa, including appendicitis, diverticulitis, ulcerative colitis, polyps, and cancer. That the difference in diet has an effect on the colon is demonstrated by the greater bulk of stool and shorter transit time on a high residue diet than on a low, and it is not difficult to believe that these physical differences affect the tone of the gut and the development of diverticulae. It is less easy to see why they should affect the incidence of cancer of the colon so grossly unless they also produce some change in its chemistry. Stimulated by Shiner's interest in bacterial flora as a cause of gastrointestinal disease, Williams and his colleagues (Aries et al., 1969) examined the bacterial flora in faeces from healthy adults in different countries. The same broad groups were found in all specimens, save that Sarcina ventriculi was present only in the faeces of vegetarians, while anaerobic bacteroides were characteristic of areas in which cancer of the colon was common. Some members of the latter group degrade steroids by dehydrogenating the alpha-hydroxyl groups, and the amount of the metabolic products in pooled faeces, particularly the hydroxycholanic acids, correlated very closely with the incidence of cancer of the colon in the community in which the donors resided. Investigations are now aimed at comparing faecal contents of patients with and without cancer. Preliminary results suggest that the risk of the disease may be many times higher in patients whose faeces contain bacteria with this metabolic capacity and at least 6.0 mg bile acids per gram dry weight, than in those whose faeces contain neither (Hill et al., 1975). If these results are confirmed we shall need to see whether the faecal contents can be used to predict the risk of cancer in later life (as Hart is already trying to do in South Wales) and whether the flora, the steroid metabolites, and the incidence of the disease can be modified by, for example, adding cereal fibre, or subtracting fat or meat.

That diet is an important cause of cancer has long been suspected. Many investigators have sought causes in the polycyclic hydrocarbons produced by frying, grilling and smoking, and the addition to food of colouring agents, preservatives, sweeteners, and hormones has been strictly controlled. I suspect, however, with Cleave et al. (1969) and Burkitt (1971), that industrialisation is more likely to have affected cancer incidence by the mass refining of
carbohydrates than by the addition of minute amounts of specific chemicals. Such dietary changes may not only be relevant to the production of colonic and rectal cancer, they may also contribute to the geographical variation in breast cancer, which is too great to be accounted for by different fertility patterns, by creating conditions in the bowel that are favourable to the production of steroidal oestrogens (Hill et al., 1971).

Oncogenic Viruses
In all these examples, the immediate causes are physical or chemical agents. There is, however, another group of agents that raises the possibility of a different method of prevention. The evidence that viruses can produce cancer in man is, as yet, wholly circumstantial and inferential: but it would be surprising if they never did in view of the wide distribution in nature of the many viruses that cause cancer in animals.

Of those tumours that are likely to be due, in part, to viral infection, the most outstanding are Burkitt's lymphoma, carcinomas of the nasopharynx and cervix uteri, Hodgkin's disease, and childhood leukaemia. One virus, the Epstein-Barr (EB) virus, may, it seems, be a cause of both Burkitt's lymphoma and carcinoma of the nasopharynx. In epidemic areas these diseases are found only in individuals infected by the virus. Viral DNA is present in all the tumour cells and determines the expression in them of virus-coded neo-antigens, and virus production can be activated in some of the tumour cells in the laboratory. The EB virus is widespread in human society and is the cause of infectious mononucleosis, when it stimulates the proliferation of mononuclear cells of the lymphatic series. In vitro, it confers the property of continuous growth on normal human B lymphocytes in culture, in a way that is analogous to malignant transformation. Finally, it has been shown to cause malignant lymphoma in South American cotton top marmosets. The record is impressive, and it is doubtful if it can ever become much more convincing short of developing a vaccine that will prevent the disease (Epstein, 1976).

Of the other cancers to which I have referred, the most frequent is cancer of the cervix uteri, which is commonly associated with infection with herpes virus, type II. In this case, the laboratory evidence is less complete. We know, however, that the disease spares nuns and is most common in prostitutes, and that the risk of developing it increases with the number of marriages and with the age at which coitus first takes place. Yet there is no relationship with the number of pregnancies, nor with the frequency of intercourse within marriage. To these facts we can add Martin's (1967) observation that more of the husbands of affected women had extramarital intercourse than of husbands of control women, Beral's (1974) observation that the mortality from cancer of the cervix in cohorts of women of different ages varies with the incidence of gonorrhoea at the time they were 20 years old, and the accumulating evidence that obstructive methods of
contraception are protective (Vessey et al., 1976). The disease is apparently venereal in origin and the sum of the evidence can most readily be explained by infection with an oncogenic virus.

POLICY FOR PREVENTION
In this review, I have sought to provide an account of those causes of cancer that we must aim to bring under control if we wish to prevent the disease. In the future, when we have a more exact knowledge of the mechanism of carcinogenesis, it may be that we shall be able to intervene by, for example, helping the body to recognise and reject the malignant cell. It may be also that we shall be able to prevent some cancers by a vaccination programme comparable to the one that has already eliminated poliomyelitis. The obstacles in the way of developing a suitable vaccine are enormous but not necessarily insuperable. It may never be possible to develop a live viral vaccine for human use, like the one that has been used to control Marek's lymphoma in chickens (Churchill et al., 1969; Okazaki et al., 1970), because we cannot inoculate man with material that is potentially capable of producing tumours no matter how attenuated we believe it to be. Even a conventionally inactivated virus would be objectionable because of the virtual impossibility of proving that it is totally inactivated but still efficacious. It may be possible, however, to produce effective vaccines that consist of only some of the viral antigens, such as those formed on the surface of human lymphoid cells in culture after transformation by the EB virus.

In the immediate future there are only two methods open to us. We can institute some method for controlling the introduction of new carcinogens into the environment, and we can take steps to reduce contact with those physical and chemical carcinogens that are already there.

At first glance the proposal to prevent the introduction of new carcinogens is attractively simple. All that needs to be done is to set up an organisation like the Committee on Safety of Medicines and insist that any new chemical is submitted to exhaustive tests on animals before it is used outside the experimental laboratory; and something like this has, indeed, been suggested by the Environmental Protection Agency (1976) of the U.S.A. The difficulties with this proposal are multiple: first, the cost of long-term tests on a variety of laboratory animals is enormous: secondly, agents that are carcinogenic to man will certainly be missed, partly because of variation in the susceptibility of different species, and partly because the induction of cancer is a complex process, so that an agent that increases the incidence of cancer may do so by acting as a co-carcinogen or promoting agent, but only in peculiar and unforseen circumstances. Thirdly, many substances may be banned that have great value when used properly and are only very weakly, if at all, carcinogenic to man, like phenobarbitone, isoniazid, DDT, saccharin, and the minute amounts of stilboestrol that have been used to fatten cattle.
In considering restrictions of the sort proposed it is important to retain a sense of proportion. Industry has certainly introduced many powerful carcinogens that have had serious effects on its employees, and the Health and Safety Commission will want to make sure that workers are better protected than they are now when new materials are used in the future. But the proportion of cancers in the population as a whole that are caused by agents introduced by industry in the twentieth century is minute and there is no reason to suppose that the application of the most rigorous restrictions would do more than tinker with the real problem that is facing us.

What would be more practicable would be an arrangement for the pooling of information about the biological effects of chemicals, as envisaged by the Department of the Environment in its proposals for a data network on environmentally significant chemicals, combined with a system for testing materials by stages, like that proposed by Bridges (1973, 1974). Bridges's scheme (Fig. 4) is based on a correlation between carcinogenesis and mutagenesis, when the latter is tested for in bacterial culture. The bacteria have to be grown in the presence of microsomal fractions of mammalian liver cells, or some such material, so that the stable carcinogens are converted into their active metabolites; but when this is done an extremely close, though not complete, correlation has been obtained over a wide range of substances (McCann et al., 1975). The adoption of the scheme would require (a) that no generally mutagenic chemical should be released into the environment or be permitted to be used if there exists a satisfactory non-mutagenic substitute; (b) that the extent and rigour of the screening procedures should be related to the extent to which man is likely to be exposed to the agent, and (c) that mutagenic substances are used if the benefits

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**Fig. 4. Three-tier scheme for screening material for mutagenicity and carcinogenicity as proposed by Bridges (1973, 1974).**
are judged to be great enough to outweigh the hazards and if appropriate controls are exercised.

An accompaniment of the scheme, which would still be needed with a more restrictive one, is the provision of some mechanism that would enable any risk to man to be detected at the earliest opportunity and measured for comparison with the accompanying benefit. In fact, an embryo mechanism already exists in our Cancer Registers. To make it effective, however, we need to be able to match the names in the Register with the records of people exposed to the new material. This would be relatively easy if they were exposed at work or by medical prescription, as most are likely to be, but it could be very much more difficult if they were exposed in other ways. No scheme can be guaranteed to prevent the escape of any carcinogenic material into the environment, but we can certainly do much better than we do now.

The urgent problem is how to deal with the carcinogens already in the environment. These are not, for the most part, pollutants, but are bound up with what is commonly regarded as the normal way of life — however abnormal some aspects of it might have appeared to our ancestors. If we are to make any serious impact on the incidence of cancer we shall either have to stop smoking and stop taking alcohol or find a way to remove carcinogens from tobacco smoke and alcoholic drinks; we shall either have to reduce the extent of sexual promiscuity or protect the cervix from infection; and we may need to modify our diet by reverting to the use of less processed foods and reducing the content of meat and animal fat. This will not sound an unreasonable programme to the Seventh Day Adventist who has already adopted most of it, but it will hardly commend itself to the public at large. Life, it will be said, is for living. Different people enjoy it in different ways and few of them have any desire to emulate the hypochondriac who lived his life as an invalid so that he could die healthy.

Unfortunately, it cannot be assumed that more precise information about the nature of the effective carcinogens will necessarily solve the problem, as it may not be possible to remove them without destroying the attraction of the product. Moreover, a reduction in the content of carcinogens may lead to an increase in other components that are responsible for other diseases, as may be the case when low tar cigarettes which deliver a greater amount of carbon monoxide are manufactured.

In these complex circumstances our responsibility as biologists must be to ensure that the facts are both clearly established and generally understood. As doctors, however, it must be something more. We are not, nor should we seek to be, the arbiters of human behaviour; but neither are we without responsibility for trying to influence it. Two things we can do. First, we can show by our personal example the reality of the threat to health associated with a particular type of behaviour. Secondly, we can press government to ensure that neither commercial interests nor the pattern of taxation are allowed to encourage people to
undermine their health. As a minimum programme the public advertising of tobacco and the use of gift coupons should be prohibited, and taxation should be used to encourage smokers, who are unable to stop, to switch from cigarettes to the less harmful pipe — something the Chancellor began to do in 1976, despite the fact that the Treasury had long maintained that it was impossible.

If, in concluding, I have concentrated on the reduction of smoking, it is because it is the most practical way in which we can now make a major impact on the risk of death from cancer in Britain. In ten years' time, with further knowledge of environmental causes, I have little doubt that several other methods will be possible. I suspect, however, that they may prove to be equally unpopular.

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