

Cancer in the Seventies

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Introduction

Cancers should perhaps be divided into two classes, those that affect people or during the prime of life and those that, if left untreated, kill people who are past their prime. These two categories of cancers not only give rise to entirely different social problems but differ in biological significance.

Cancer competes with old age as a cause of death. Had I been able to predict great advances in the prevention or treatment of cancer during the nineteen-seventies, then I would at the same time have had to warn that degenerative diseases and senility would become more serious problems during the nineteen-eighties.

Definition of Cancer

It may not have escaped your notice that I have already been using the plural 'cancers' rather than the singular 'cancer'. The majority of biologically or medically trained cancer scientists now regard cancer as a group of diseases rather than as a single disease entity. Cancers vary widely in causation, in rate of growth, in manifestation, in structure, in response to treatment and in every measurable feature such as chromosome complement, cell-turnover time and antigenicity.

The concept of cancer as a single disease has, in many ways, been counter-productive. An ill-conceived search for what has been called "the final common pathway" has reduced otherwise competent scientists to the level of alchemists. Scientists anxious to justify the relevance of their efforts in terms of what they conceive as a single cancer problem have without justification developed general theories from observations made in simple model systems that bear little or no resemblance to other model cancer systems, let alone to cancer in man.

Cancers consists of cells derived from the host's own cells; they grow by the formation of new cells – by cell-division – taking place at a faster rate than old cells are lost. The cells of which cancers consist have the ability to invade and destroy surrounding normal tissues; and in some cases, after passive transport in lymph or blood to distant sites, cells derived from cancers survive and proliferate to form secondary deposits (or metastases).

Theoretically, cancers may arise because of the emergence of abnormal-

ly behaving cell mutants or because of faulty regulation of cell behaviour. In practise, both mechanisms seem to be operative to varying degrees in the genesis of all cancers. It is usually possible to detect multiple structural and functional abnormalities in the cells of which cancers are composed and apparently impossible to restore cancer cells to a state of normal structure and behaviour. In other words, the change from normal to cancerous seems to be irreversible.

Cancers are Diseases of the Whole Body

In an attempt to satisfy a popular thirst for good news about cancer, ill-informed science writers manufacture headlines from laboratory findings derived from experiments conducted under artificial conditions. Often the laboratory findings are not even scientifically sound, and it is rarely justifiable to make sweeping generalizations from them. Confusion would be less prevalent if cancers were conceived not only as many different diseases, but also as diseases of the whole body rather than of cells or of sub-cellular elements. Theories developed on the basis of results of surveys or studies conducted at other levels may be misleading unless verified at the whole animal level. How many chemicals, at one time hailed as cancer cures on the basis of their effects on cancerous cells in tissue culture, have foundered on the rocks of reality when given to patients in a cancer clinic?

The Future Arises out of the Past

Less than 9 years of the seventies remain and, despite what we're all a bit brain-washed to believe, cancer research that has direct relevance and benefit to man is progressing only very slowly.

The relative risk of death from infectious disease fell dramatically after the discovery of antibiotics and the development of effective vaccination procedures. As a consequence, average life-span increased, and the relative risk of the word 'cancer' being on the death certificate rose to its present level or more than 20%. If during the next decade anyone is misguided enough to find out how to prevent kindly death from coronary thrombosis, the relative risk of uglier death from cancer will increase still further.

Cancer and Occupation

In 1968, the widow of a toolsetter who died at the age of 43 from cancer of the scrotum as a direct result of exposure to mineral oils, was awarded £10,000 in the high Court. This case has had many consequences, most of

them beneficial. The conditions of work for men in many engineering firms has been improved by the provision of proper washing facilities and protective clothing. Men have been effectively warned of the danger of mineral oil, and systems of regular medical examination have been introduced. Safer, more highly refined — and incidentally more expensive — oils have begun to take the place of more dangerous, less — refined oils. The benefits of these improvements should begin to show during the seventies. So, one hopes, will the effects of the introduction of codes of practice for handling asbestos.

In the past when men who handled asbestos were exposed to the dust without any protection many of them developed fatal asbestosis and died in their early 50's. Partial protection from the dust delayed death from asbestosis long enough for lung cancer due to asbestos to develop. Today although asbestosis is less common than it was, the risk of a man who has developed the disease also developing lung cancer has increased to over 50%. During the past decade it has become known that a fairly rare form of cancer, known as mesothelioma and derived from the pleural or peritoneal serous membranes, is almost always associated with previous exposure to asbestos. In some cases the exposure is slight and even indirect (for example in a woman who only came into contact with asbestos because she washed her husband's overalls). The use of asbestos has been increasing exponentially during the last 20 years and the point has now been reached that none of us can completely avoid inhaling some particles of it. As a result of the codes of practice prepared by the Asbestos Council, the next ten years should see a decreased incidence of asbestos cancers among workers engaged in the production and use of asbestos products, but insofar as the dangers are not even now widely recognised, for instance, by workers demolishing premises in which pipes are lagged by asbestos, it is certain that further new cases will occur.

Improved and more sensitive epidemiological techniques have recently been revealing other cancer hazards attributable to dust inhalation. Thus we now know that the cabinet workers of High Wycombe and the boot and shoe makers of Northampton are at specially high risk of developing cancer of the nasopharynx. Gas workers, chromium workers and haematite miners are at special risk of developing lung cancers. The seventies are bound to witness further significant discoveries in the field of occupational cancer hazards.

On April 20th of this year, Judgment was given in another very important High Court case. The black rubber of which motor tyres are made contains antioxidant substances as preservatives. In the past some of the

antioxidants used have been powerful bladder carcinogens. An epidemic of bladder cancer among men in the chemical industry led many years ago to the cessation of the manufacture of the carcinogenic substances responsible. But their use continued in the Rubber Industry until much more recently. Unless the Judgment is reversed on appeal, the award of damages of £15,000 to one bladder cancer victim and £6,000 to another against the chemical firm that provided the dangerous chemical without warning that it was hazardous is a landmark in the history of the protection of workers against cancer hazards.

At the present time bladder cancers are still rising in rubber workers but we do not yet know whether these are due to exposure to carcinogens that are no longer used or to unsuspected carcinogens still in use.

Cancer of Children

Earlier I distinguished between cancers that occur in old people and those that kill people before and during the prime of life. Cancers in children are especially tragic. Because other threats to the survival of children have receded, cancers are nowadays second only to accidents as causes of death in childhood.

A small proportion of childhood cancers, including some cases of leukaemia, may be due to events occurring before birth. Exposure to X-rays during the measurement of the size of the mother's pelvis by radiography is thought to be one factor that increases the risk of cancer development in the child after it is born. The effects of drugs taken during pregnancy are under close scrutiny in this and other regards.

Improving knowledge of genetic factors that predispose to childhood cancers will enable prevention by eugenic counselling. For years we seem to have been on the brink of discovering that a virus or group of viruses is responsible for one or more forms of leukaemia. We seem even closer to making this discovery now that the cause of infectious mononucleosis (glandular fever) is established as the Epstein-Barr Virus.

It is possible that before the end of the seventies we shall know how to reduce the risk of leukaemia in children. We might by then also know of several types of human cancer that are caused by viruses. We might even recognise a venereally-transmitted virus as a significant causative factor in relation to cancer of the uterine cervix.

'The Pill' and Cancer

And this brings me to another delicate matter, 'the pill' and cancer. Hormones are powerful regulators of cellular proliferation and, theoretic-

cally, exposure to progestational agents and oestrogens for 21 days out of every 28 might significantly either enhance or reduce the risk of cancer development in various organs. Laboratory animal studies are not necessarily helpful since the cyclical changes in hormonal status associated with reproduction are rather different from those in women. In mice, for instance, ovulation isn't suppressed by continuous exposure to progesterones + oestrogens in high dosage. The truth is we shall not really know whether the pill increases or reduces the risk of cancer, until the epidemiologist and clinician tell us from their observations on women.

We already know, however, that cancer of the uterine cervix increases in incidence with multiplicity of sexual partners and with younger age at time of first sexual intercourse. Direct contact between the cervix and the penis, especially if the latter is uncircumcised, is thought to increase the risk of cervical cancer. Insofar as the use of the pill enables couples to dispense with the use of contraceptives that impose a physical barrier between the penis and the uterus its use is likely to increase the risk of cervical cancer. But it will be difficult to judge the influence of this factor alone against the background of the effects of generally greater sexual licence, and of earlier start to sexual activities.

Doubtless, the cervical smear test will have become universally available before the end of the seventies. I do not believe that a simple chemical test of vaginal fluid will replace the smear test. Nor do I think that the computer will have replaced the microscope and the trained eyes that are now needed to detect cancer cells in smears. But there could well be a number of important methodological advances which help to make the time-consuming job of searching for cancer cells among acres of normal smear material less tedious than it is at present.

To return to the pill, in ten years from now it may well have been superceded. The danger of cerebrovascular haemorrhage or thrombosis is real and, in the long run, unacceptable. We can but hope that, if new methods replace the pill, they are safer from all points of view.

Food and Cancer

The vastly different death rates from cancers of the stomach, oesophagus, colon and pancreas in different countries strongly suggest that environmental factors influence risk of development of cancers of these organs. Furthermore, it is reasonable to suspect that differences in diet are important determinants.

Theoretically differences between, say, Japanese and White Americans in death rates from these various types of cancer may be either genetic

or environmental in origin. However, the dramatic changes in cancer mortality rates in Japanese who take up residence in the United States point strongly to environmental factors being the more important.

The few of us who can still afford the time to live directly off the land or who are old enough to remember the pre-pre-packed, pre-supermarket, family-grocer and local baker days, mourn the lack of fresh food smells and shudder at the unwholesomeness and sheer monotony of the artificially coloured food stuffs by which we are surrounded. Nevertheless there are no good grounds for translating our sorrow for the loss of these joys into suspicion or fear that the shelves of our supermarkets are loaded with carcinogens. The death rates for stomach and colon cancer are falling and that for liver cancer is very low both in the United States and in Western Europe, where food manufacturing processes are the most sophisticated. Most experts would nowadays agree that more suspicion attaches to certain naturally-occurring ingredients and contaminants of food-stuffs and, perhaps, to traditional food-preservation methods than to changes introduced during the past ten years.

The last 10 years has seen the discovery of *Aflatoxin*, the most potent carcinogen known to man, as a natural contaminant of ground nuts and other cereal crops. Aflatoxin is produced by the mould *Aspergillus flavus* which is widely dispersed in nature. Under conditions of high temperature and humidity the mould can flourish in a wide variety of cereals and the concentration of aflatoxin can rise to significant levels wherever storage conditions are poor. It is not yet certain that any form of human cancer is due to aflatoxin, but the main reason for the uncertainty lies not in the lack of cancers of the liver, stomach and oesophagus, for which it might be responsible in certain oriental countries and in parts of Africa, but in the surfeit of other naturally-occurring carcinogens that might also be implicated.

Since some of these carcinogens find their way into milk, eggs and meat it might be more reasonable to regard with suspicion, for instance, the "free-range" egg than the egg with the "little lion" on it, on the grounds that one has no control over what the hen that laid the former has eaten or on where it has been!

Nitrosamines

During 1961, Norwegian fishermen encountered a glut of herrings. They stayed out longer than usual and returned to port heavily laden only to find that all the fish silos were full. They, therefore, had to wait to unload their catches or sail further along the coast to do so. At that

time Norwegian fisherman were permitted to add up to a certain levels of nitrite and formalin to fish as preservatives. Because of the length of time at sea and the delays in unloading, some of the skippers added more than the prescribed amount of nitrite.

When fish decays, trimethylamine is formed, and under the conditions of heat needed for processing herring into herring oil and fish meal for cattle feed, trimethylamine may react with nitrite to form dimethylnitrosamine, a potent toxin and carcinogen. The levels of dimethylnitrosamine in some batches of Norwegian herring meal in 1961 were sufficiently high to give rise to liver poisoning in sheep and cattle and to kill large numbers of mink on fur farms in Norway and Britain.

I tell this sad tale not to excuse any rise in the cost of mink coats, but because nitrite is used as a preservative of bacon, corned beef, many other meat products and some cheeses. Moreover, nitrite levels are naturally high in spinach and are raised in other crops by the use of nitrates as fertilizers.

Do significant levels of carcinogenic nitrosamines occur in human foodstuffs? Does the use of nitrates and nitrites as fertilizers or food-preservatives increase the risk of nitrosamine formation in food? Answers to these questions are urgently needed, and are likely to become available during the next few years. If research shows that the use of nitrites increases the risk of nitrosamine formation to a dangerous degree, there must follow a revolution in meat preservation methods. At present the use of nitrites not only provides colour advantages but is the main safeguard against that deadliest of all forms of food-poisoning, *botulism*.

The discovery of the carcinogenicity of the groups of chemicals, referred to collectively as the nitrosamines, is one of the major breakthroughs of the last 15 years. Not only are several members of the group among the most potent of carcinogens known, but animal experiments have shown that nitrosamines may give rise to cancers of a wide variety of tissues and sites.

Personally, I am intrigued by the following two facts. Man is almost unique in the animal kingdom in experiencing a high incidence of cancer of the large bowel—the colon and rectum. Man is also unique in that he eats cooked foods. Does cooking—which destroys all manner of parasites, bacteria and heat-labile toxins—favour the formation of a carcinogenic nitrosamine which causes cancer of the colon and/or rectum? What do the Japanese do differently that lowers their risk of colon cancer but increases their risk of developing cancers of the oesophagus and stomach.

Dr. Issels' Ringberg Klinik

During the past year we have been subject to all the Hooahh of what may well come to be known as "the Issels Affair". There are, scattered throughout Germany, at least 20 or 30 private medical clinics run on authoritarian lines, in some cases by doctors whose dedication is unmatched by scientific prowess. In this country, the authoritarian approach to medical teaching and practice, has, happily, to a great extent been superseded by a situation in which doctors, medical students and paramedical personnel of all ages and degrees of experience are encouraged to question the efficacy of both traditional and new methods of diagnosis and treatment.

The Report on the Ringberg Klinik prepared for the Department of Health and Social Security by Professor Sir David Smithers and the 6 others members of a visiting team deserves special attention because of the excellent balance it strikes between scientific objectivity and the need for compassion as an essential ingredient of the doctor-patient relationship. I quote from the final page of the report "The fact that so many patients go to this clinic to find something they fail to receive at home is really more a reflection on the medical service they leave than a credit to Dr. Issel's particular treatment".

Cancer Treatment

Are the seventies likely to see major advances in the treatment of all or any forms of cancer? Surgery is the preferred form of treatment for patients with localized cancers that have not disseminated to distant sites, although radiotherapy and chemotherapy are as efficacious as surgery for some cases of local cancer. Chemotherapy, hormone-therapy and immunotherapy are at present mainly reserved for the treatment of patients with disseminated cancers.

There will always be limits to the amount of body tissue that a surgeon can remove, if a patient is to survive with the prospect of a life of acceptable quality. X-rays kill normal cells along with cancer cells. In the case of disseminated cancer there seems to be no prospect of being able to kill all cancer cells with doses of X-rays low enough to permit sufficient survival of normal tissues for worthwhile life.

All the chemotherapeutic agents at present available are more or less non-specific cell toxins. They kill dividing cells irrespective of whether the latter are cancerous or normal. Some tissues of the body, for example, the lining of the gut and the bone marrow normally proliferate as rapidly as, or even more rapidly, than, the cells of some cancers. The

gut lining and the bone marrow are therefore hard hit by chemotherapeutic drugs and the risk of toxic effects attributable to damage to them limits the doses of drugs that can be given.

The growth of cancers of certain hormone-producing and hormone-influenced tissues—e.g. the breast, uterus, prostate, adrenal,—may be greatly influenced by changes as in the hormonal status of the host. This may be achieved either by the administration of hormones or by the removal of hormone-producing glands from the body. On the whole, however, it is the less malignant cancers—those that have not completely escaped from the control mechanisms which regulate the activity of normal tissue cells—that are most likely to respond to manipulation of hormonal status.

One of the characteristics of cancerous growth is that because of faults in the process of cell-division, growths come to consist of a mixed population of cells—of cells which differ from each other in ability to survive changes in the environment. It is a biological principle that, wherever there is a mixed population of living entities competing for survival against a limited supply of nutrients, the fittest will survive. In the case of growing cancers this means that there is a tendency for more autonomous cell lines to survive preferentially. This is probably the explanation of the phenomenon known as *tumour progression* by which cancers tend to become increasingly malignant with time.

There is a danger that the administration of hormones will help to “select out” more-malignant, less-hormone-sensitive, cell lines for survival whilst discouraging the growth and survival of less-malignant, hormone-sensitive, cell lines.

This is of course also a danger of all chemical and of some immunotherapy approaches to cancer treatment. In view of this danger, some doctors favour short, hard-hitting regimes of treatment rather than prolonged treatment with lower doses of drugs.

Transplantation Surgery

Stemming largely from concepts developed by Sir Macfarlane Burnet in Australia the theory of *immunological surveillance* has become widely accepted as plausible and important in relation to the development of cancers. The multicellular organism may be conceived as living in an environment full of mutational and carcinogenic hazards. The effect of exposure to these hazards is that the conversion of normal cells to potentially cancerous cells is a common event. An early manifestation of transformation from a normal to a cancerous state is that abnormal

proteins—which are also antigens—appear on the surface of affected cells. According to the immunological surveillance theory, wandering lymphocytes, like policemen on the beat, spend their time inspecting the surfaces of cells for abnormal antigens. Wherever an abnormality is discovered, a sequence of events is initiated which results in the destruction of the abnormal cell, or at least in the prevention of its undergoing cell-division.

According to this theory cancers may arise either because the capacity of the immunological surveillance system is overwhelmed by excessive exposure to carcinogens or mutagens or because the immunological surveillance system itself is faulty because of age-changes or damage by unfavourable environmental factors.

Dramatic and tragic evidence of the likely truth of this concept has come from observation of patients with kidney disease who are the recipients of transplanted kidneys and who have been kept for prolonged periods in a state of immunological suppression so that the grafts are not rejected. The incidence of cancers in kidney-graft-recipients aged under 50 years is more than 100 times higher than in healthy people within the same age range. The cancers that arise are of many different types—some arising from epithelial tissues and some from connective tissues.

In view of these observations, I think I may be forgiven for not being very optimistic that *transplantation surgery* has much to offer in the treatment of cancers. However, I could be wrong. If a method is developed for rendering graft-recipients specifically tolerant to the grafted tissue without impairing their state of immunological competence generally, then it may become possible for patients to have cancerous organs totally replaced by grafted organs without greatly increasing their risk of developing further cancers.

Immunotherapy

Can we expect any advances in the treatment of cancers by immunological methods? It seems clear that benefit is only likely to arise from forms of therapy that favour the rejection of cancer cells by lymphocytes that have recognised the presence of abnormal antigens on their surfaces. Benefit is unlikely to accrue from stimulation of the production of circulating antibodies active against cancer-cell antigens. Indeed such stimulation may make the situation worse. The abnormal antigen on the surfaces of cancer cells may be masked by antibodies sticking to them so that the cells concerned are no longer recognised as abnormal by the lymphocytes that could have destroyed them.

Is there any way of stimulating the immunological rejection of

cancerous cells by lymphocytes? The position at present seems well summarised at the end of a paper by Gordon Hamilton Fairley, published in the British Medical Journal in 1969:-

“ attempts at immunotherapy in patients with advanced disease are doomed to disappointment, for animal experiments suggest that one needs a powerful immunological reaction to combat even a small number of malignant cells”.

“ at the present time immunotherapy should be used only as an adjuvant for the removal of residual malignant cells after other forms of treatment have been used”.

Early Diagnosis

Cancers are difficult to treat effectively if the disease has spread too far locally, or is already widely disseminated, at the time of first diagnosis. Can methods for diagnosing cancers earlier be developed? If so, will they really help to make treatment more effective?

I am certainly hopeful that the seventies will see advances in the earlier diagnosis of cancers. There is already abundant evidence that early diagnosis may be associated with improved prognosis.

The value of cervical smear testing for the early diagnosis of cancer of the uterine cervix, although not formally proved, is already sufficiently likely that a nation-wide service is well on the way to becoming available. Perhaps the most room for hope in the field of early diagnosis, however, lies the development of better methods for the detection of abnormal antigens and other substances derived from cancer cells in the blood or urine. For such methods to have any value, they must clearly point to the tissue in which the cancer is located. Moreover the methods must be simple and painless if apparently healthy people are to be asked to submit to being screened for cancers.

The three main snags with the “early-diagnosis” approach are:- Firstly, patients who are apparently in perfect health, but who in fact have early cancers, are not prepared to submit themselves for tests. Secondly, some types of cancer spread to distant sites before they achieve any great size or cause any disturbance at the site at which they arise. Thirdly, tests indicate the presence of cancer in a large organ, such as the colon or the lung, but it may not be possible to locate the cancer exactly to enable limited surgical removal to be carried out.

Concluding Remarks

It has often been said that the problems of understanding cancerous

disease are as complex as those of understanding life itself. I not only subscribe to this view, but believe that cancerous diseases are natural forms of death that man interferes with at his peril. Of course, every effort should be made to prevent the tragedy of death from cancer in childhood and the development of cancer by persons in the prime of life. I am less certain of the wisdom of heroic treatment of old people with cancers. Death from senility and the loneliness of old age are not objectives necessarily worth the price of mutilating or extensive spare-part surgery. Interest in the quality of life is increasing. Perhaps we should now turn attention also to what I would call the "quality of death".

EVOLUTIONARY CONTINUITY

In *The Times* for October 15 two events were recorded which are linked through the ages of evolutionary development. One was that for this year, the Nodel prize for medicine had been awarded to Dr. Earl Sutherland, of Nashville, Tennessee. This is the first occasion in the last ten years that the award has not been divided – an act of special distinction "For his discoveries concerning the action of hormones."

The other announcement was that in a cave in the Pyrenees, not far from Perpignan, a group of French Archaeologists had discovered a collection of remains of a very primitive and distinctive type. As a whole they show affinities with early forms of Neanderthal Man as well as Java Man and Pekin Man dating back about 400,000 years. The French scientists that because of the distances in between, this kind of man on lines of its own. The skull is very primitive, with massive brow ridges, a flat forehead, more horizontal than erect and a narrow elongated brain case from which the jaw protruded strongly.

Scattered around were the remains of the man's armoury, simple stone points for knives and hand axes, yet along with these were the bones of a great variety of animals, which the people must have killed and eaten – horse, Rhinoceros, bear, turtle, deer, elephant, cow, rabbit, birds. These are evidence enough of this early man's mental and physical capabilities: indeed we can say that the roots of Dr. Sutherlands manipulatory skills and theoretical sophistication had been established 400,000 years ago. It is these which will enable him to go down in medical history as the first man to identify cyclic adenosine monophosphate (cyclic AMP) and found that it is of crucial importance in cellular activities since it in turn controls other hormones.

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