CANCER
(1) A STUDY IN MUTINY AND SABOTAGE

No disease is more feared and less understood than cancer. Until recently it was scarcely talked about, and even today unemotional discussion of this scourge which strikes many of us and our families is difficult. The environmental aspects of cancer, and its prevention, diagnosis and treatment will be discussed in the second part of this double article. Here, in the first part, Dr Francis Roe describes the fundamental nature of the disease and outlines the modern theories which cancer research scientists have developed to explain it

Cancer should be regarded as a *type* of disease rather than as a single disease entity, and the borderline between cancerous and non-cancerous diseases is indistinct. Man has been afflicted with cancer since his evolutionary birth, as were his forebears in the evolutionary tree; diseases of an undoubtedly cancerous nature occur in all but the lowest vertebrates.

One definition of cancers is: 'Diseases of multicellular organisms, characterised by the seemingly uncontrolled multiplication, and spread within the organism, of apparently abnormal forms of the organism's own cells.' This definition draws attention to the three principal characteristics of cancers: first, expansion by the multiplication of cells; secondly, invasion of surrounding normal structures by cancer cells; and thirdly, the autonomous nature of the process. It is important to realise that all three characteristics are important and significant and none by itself is sufficient.

When death cannot keep pace

It would not be possible to define cancer in terms solely of the multiplication of cells. The body grows by cell division from a single cell, the fertilised ovum, so cell multiplication is a normal and essential process. In a mature animal there is a constant turnover of cells in most organs and tissues of the body. Old, worn-out cells die and are replaced by new cells produced by the process of cell division. In some tissues, such as the lining of the gut and the bone marrow, the rate of cell turnover is more rapid than in others such as skin and lung; in yet others the normal rate is very slow and in some, like the brain, certain types of cell never divide. Cancers may increase in size because of incidents such as hemorrhage into them, or because they become infected and inflamed. But the growth of cancers that really matters is that due to cell division *unaccompanied by cell loss at a comparable rate.*

Where cells are multiplying more rapidly than they are being destroyed, but are not invading surrounding tissues or spreading to other sites, they do not constitute a malignant cancer. They will merely give rise to a well-circumscribed lump which can often be removed by simple surgical operation and which is referred to as a benign tumour or benign neoplasm. Even without treatment, benign tumours rarely kill unless they interfere with some vital function; they might, for instance, block the gut or prevent the circulation of blood. However, because there is a danger that benign tumours will progress to malignant ones, it is usually wise to remove them.

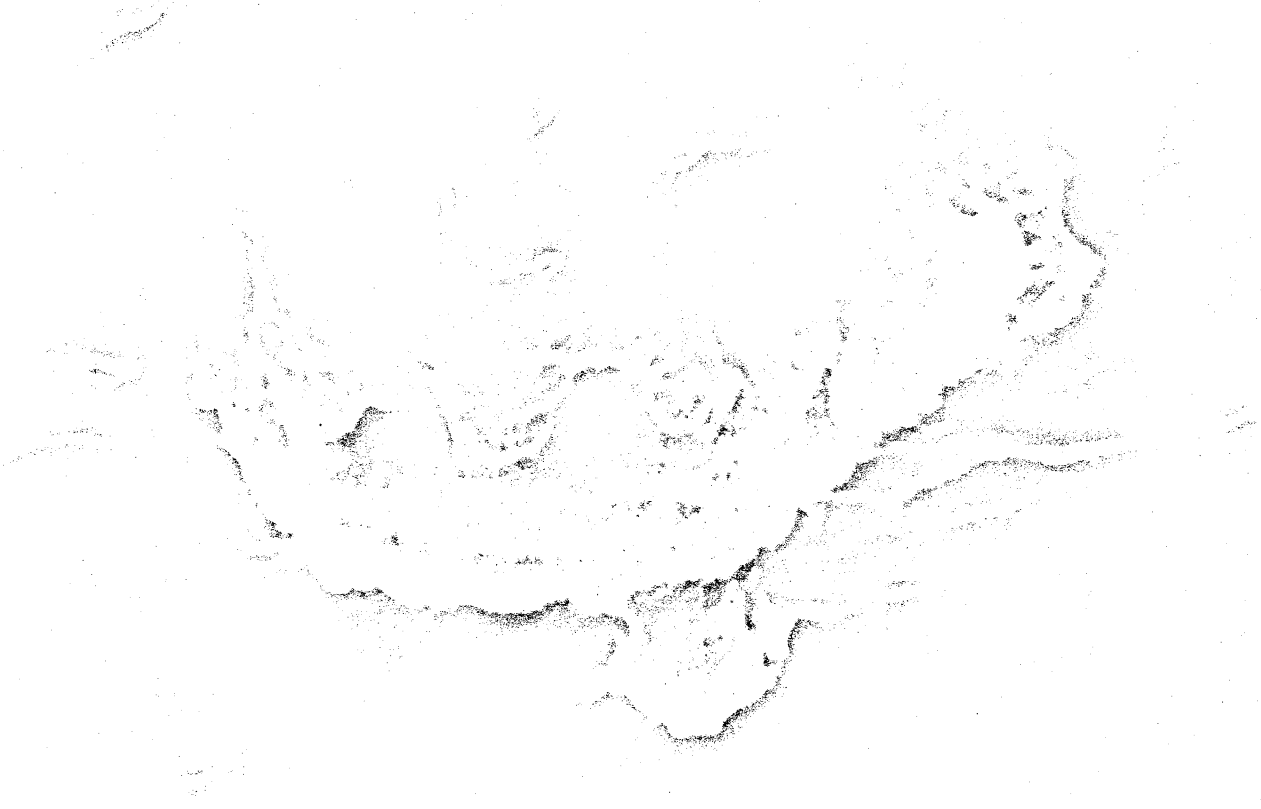
The feature of cancer that makes it a lethal disease is invasiveness. Normally in the body, cells of different types remain in their appointed places: liver cells remain in the liver, skin cells remain in the skin, and so on. Cancer cells do not obey this rule. Instead they invade surrounding structures, colonising them and destroying them. And if cells of a malignant cancer happen to invade a blood or lymph vessel, they may be carried in the vessel to more distant sites and set up new colonies there. This process of colonisation of distant sites is known as *metastasis.* The ability to invade other tissues, however, is not the sole property of cancer cells, since several types of quite normal body cells possess this ability. The white cells of the blood, for instance, can wander in and out of blood vessels and through the tissues. They may even form colonies in places where they are needed to repair damage or to defend the body against a foreign invader. But the white blood cells cause no damage, and when they have performed their function they leave, whereas cancer cells destroy and replace the tissues they invade.

Cells that know too much

It might be possible to define cancers solely in terms of *autonomy* (independence) if this were a property that could be measured. The nucleus of every normal cell in the mature organism has, as far as we know, all the information necessary for reproducing the whole organism. Under normal circumstances the great majority of this information is not expressed and most of it is kept suppressed – tightly locked up in safes for which there are few or no keys. If this were not so, all the cells of the body would look alike, and the evolution of complex multicellular organisms could not have occurred. The normal body cell therefore, lives a closely regulated life. Although it has the 'knowledge' to perform all sorts of tricks, it is only permitted to do a limited number of them. Its 'sex-life' is limited to cell division at a rate sufficient to compensate for losses due to the wear and tear of the tissue of which it

A cancer cell collapsing and disintegrating, as a result of being attacked by one of the body's white blood cells. This view is obtained by means of a scanning electron microscope

Transworld



forms a part, and its movement is severely restricted by the attachments it makes with other cells of its own type.

Much lower down the evolutionary scale than man, experiments have shown that if the nucleus of a fertilised ovum is replaced by the nucleus from a cell of an embryo that has developed to the multicellular stage, a normal organism may result. This experiment provides dramatic support for the view that the blueprint for the whole organism is present in each cell of multicellular organisms.

Another finding of great importance in this connection is that, in some cases of cancer of the bronchus in man, cancer cells have been shown to secrete hormones that are normally only produced in the pituitary gland. It seems that in these cases the cancerous process is associated with the release or activation of genetic information that is normally suppressed.

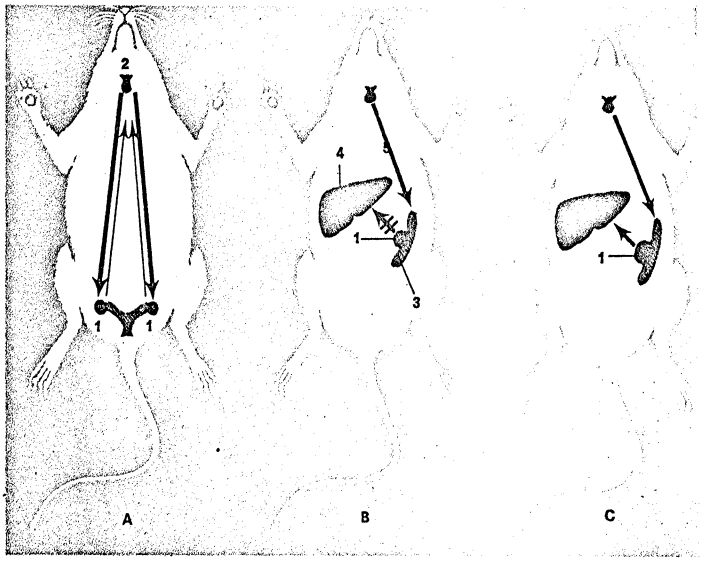
Thus the cancer cell, which proliferates irrespective of the needs of the organism as a whole, which fails to form firm attachments to neighbouring cells, which invades and preys upon surrounding tissues and which, in some cases, expresses genetically acquired information that is normally suppressed, may be described as *autonomous.*

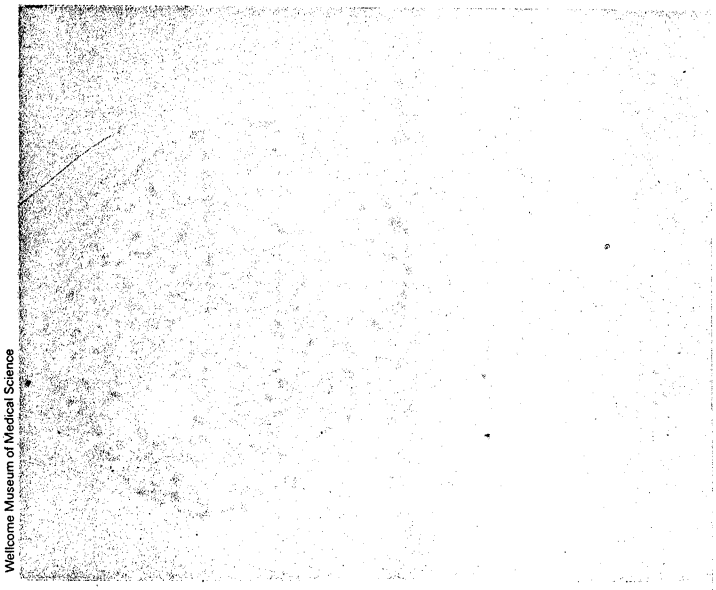
Cancers clearly differ widely in the degree of autonomy which their constituent cells enjoy. In some cancers, no cancer cells stray far from the main group. It is as though they need to be members of a group in order to survive and thrive. In other cases, even single cancer cells seem to have enough vigour to survive on their own without contact with others of their kind. These different capacities to survive on their own are reflected in the results of tumour transplantation studies in laboratory animals. It is possible to transmit the most vigorous cancers by transferring just a single cancer cell from one animal to another, but to transfer less invasive and less vigorous cancers many cells have to be transplanted. Between these two extremes are all grades of autonomy.

The growth spurt

It cannot be said too strongly that cancers are not diseases of cells but diseases of the whole body, and the questions which the scientist asks himself are: 'Why does a group of cells suddenly start multiplying and behaving in a way that is of no benefit to the body? Is it a fault of the cells that they do not respond to normal regulatory mechanisms, or have the regulatory mechanisms gone wrong, or both?'

The cells of which virtually all cancers are composed are unquestionably abnormal, and the fact that all the cells of a particular cancer may have the same obvious defect provides strong evidence that a cancer may arise from a single cell. This kind of observation supports the *somatic mutation theory* of cancer. For some reason there is a

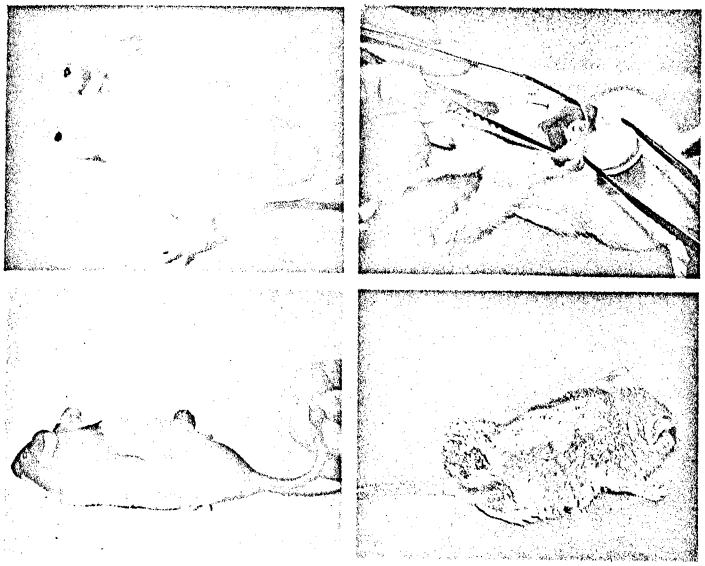




Wellcome Museum of Medical Science

John Harrison

Top. A. Normally, the ovaries (1) are controlled by a trophic hormone from the pituitary (2), which monitors how much estrogen they are producing. B. When an ovary is put into the spleen (3), its hormonal secretions are destroyed in the liver (4). C. The pituitary now receives no estrogen, and so it produces more trophic hormone to stimulate the ovary. This may cause an ovarian tumour. **Centre.** *A cancer cell in sputum. Bottom. Bronchial cancer, which may produce hormones*



All pictures Ken Moreman

sudden change (mutation) in the genetic information within a previously normal cell, such that it becomes transformed into a cancer cell. Thereafter, by successive cell divisions, a cancerous lump develops. The presence in the environment of chemical mutagens and of *carcinogens* (cancer-producing substances), and the fact that none of us can escape exposure to potentially carcinogenic cosmic rays, seem to make this theory plausible even if it is postulated that a sequence of mutations is required for the conversion of a normal cell to the cancerous state.

It would be very difficult to accept a completely opposite view of the nature of cancer – that cancers arise solely as a result of failure of regulatory mechanisms. If this were so, one would expect cancers to consist of apparently normal cells. Moreover, one could reasonably expect to be able to distinguish particular forms of cancer as being associated with specific lesions of the regulatory system. Only in the case of certain tumours of endocrine origin are these expectations even partly fulfilled.

One of the greatest difficulties in accepting the somatic mutation theory as the sole reason for cancer development is the fact that a long time may elapse between a single exposure to a carcinogen and the development of a cancer. It is difficult to believe that the interval is due to the need for a sequence of mutations, since in laboratory experiments a few animals may develop tumours very soon after exposure to a carcinogen. Also, since the cancers that appear in different animals exposed to the same substance differ widely in appearance, growth rate and so on, one must postulate that a wide variety of mutations can occur.

The phenomenon known as *tumour progression* has also to be taken into account in any general consideration of the nature of cancers. Sometimes, a tumour suddenly starts to grow more rapidly, as a whole or in one region of a large cancer, and this may happen several times during the natural history of a cancerous growth. Under the microscope, the more slowly growing parts of tumours consist of cells which look quite normal, whereas those from the regions growing more rapidly show less resemblance, not only to the tissue of origin, but also to each other. The suddenness of these changes in growth rate suggests that they could be due to mutations, but it is difficult to believe that this is the whole explanation.

A mutation is a definite event – a change from one definite state to another – and the extent of cell-to-cell variation within some cancers is not consistent with such a specific change. On the other hand, the same variation does offer a clue to events that may occupy the latent interval. Where, for one reason or another, there is a mixed population of cells competing with each other for survival, one must expect that the rules of *natural selection* will operate and that more vigorously growing and dividing

Top left. *A white mouse with an experimental parotid tumour.* ***Top right.*** *A rat being used to store cancer cells. The capsule has tiny pores, allowing nutrients from the rat's body to enter and keep the cells alive, without them escaping to affect the rat.* ***Lower left and right.*** *Skin tumours produced by chemical carcinogens.* ***Left.*** *Two of these rats have been kept in an atmosphere of tobacco smoke. Substances in the smoke, some of them known to be carcinogenic, have accumulated on the fur*

cells will replace less vigorous ones. Furthermore, if one postulates that a feature of cancer is defective cell division, so that cells give rise haphazardly to all sorts of oddities, then one comes close to an acceptable explanation of all the observed characteristics of cancers. Certainly cellular oddities abound in many of the most malignant forms of cancer – cells with abnormal numbers of chromosomes and with bizarre chromosomes, too much cytoplasm, too little cytoplasm, and so on. If such a cellular oddity by chance possesses exceptional vigour and autonomy, then its appearance within the tumour could lead to a sudden change in growth rate or to the sudden appearance of a region of rapid growth.

There is a great need for better knowledge concerning the ways in which cellular behaviour is normally controlled. We know about some influences – hormones, growth regulators and others – but it is difficult to believe that these are of primary importance in producing cancers.

Old and creaky defences

A concept both popular and widely accepted amongst cancer scientists at the present time invokes *immunological surveillance* as a factor of major importance in almost every aspect of cancerous disease. Cells recognise each other as belonging to the same or different types, by reason of their surface ANTIGENS. Also one type of white blood cell, the lymphocyte, like a policeman on patrol, strolls around checking that all the surface antigens of cells are of a normal nature. If, as a result of mutation, a cell begins to sport an abnormal antigen on its surface, lymphocytes gather around and destroy it. It is now widely thought that immunological surveillance is an important defence mechanism against cancer. Mutations of cells from the normal to the potentially cancerous state are taking place at a slow rate all the time because of exposure to environmental carcinogens, but the abnormal cells are being destroyed as fast as they are formed, and most of us remain free of cancer.

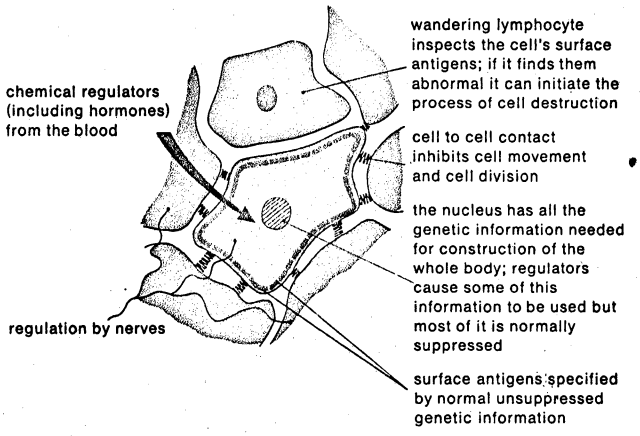
Evidence that supports this view of cancer is accumulating rapidly. First, the presence of abnormal antigens has been demonstrated in a large number of cancers both in laboratory animals and in man. Secondly, it has been shown that damage to the lymphoid system may predispose to cancer. A particular example of this concerns human recipients of kidney grafts, who are given drugs to suppress their immune response so that the grafts are not rejected. Cancer of a certain type – *reticulum cell sarcoma* – has a significantly high incidence in these patients, and it is possible that they have been susceptible to it for years without running into any trouble, because their lymphoid system was intact. Only when the activity of the lymphoid system is suppressed does cancer emerge.

It is well known to clinicians that the apparently successful removal of a cancer of pigmented cells – known as a *melanoma* – may be followed as long as 20 years later by the appearance of secondary colonies (metastases) in other parts of the body. In these cases it seems that, before the surgical removal of the primary tumour, tumour cells find their way to distant sites. Although they survive in these sites, for some reason they cannot, or do not, multiply until a very much later date; it seems that they are 'contained' by lymphocytes, but not actually killed. In all probability, containment involves mechanisms other than purely immunological ones.

It has been suggested that natural ageing predisposes to the development of cancer, since the latter usually develops during the later part of the life span. We can picture man as going through his life gradually accumulating potentially cancerous cells, some of which are destroyed and some merely contained. With advancing age, the immunological

How a normal cell can become a cancer cell

normal cell:
1. immobilised because of contact with neighbouring cells
2. only divides if it is permitted to do so by various regulators
3. has normal surface antigens and no abnormal ones

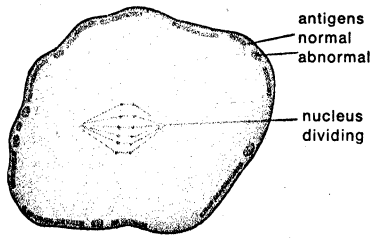


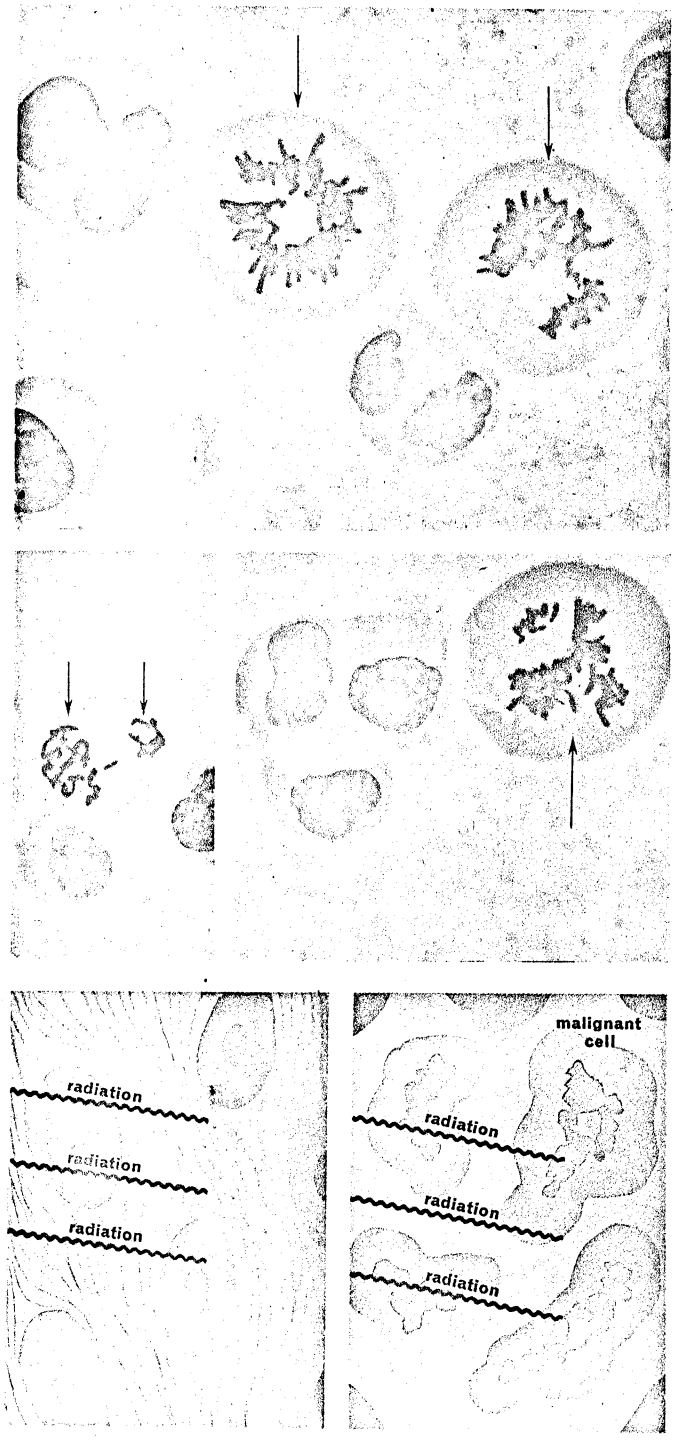
but when environmental influences or ageing lead to:

either, a breakdown in cell regulation:
1. by expression of information that is normally suppressed
2. by failure in cell contact, hormone or nervous control
3. by failure of lymphocyte surveillance after abnormal antigens have developed

and/or an abnormality in genetic information:
1. because of the presence of a virus
2. because of mutation, altering the cell's genes
3. by loss of genetic information and therefore of normal surface antigens

the result may be a cancer cell:
1. moves freely around, as it has few or no cell contacts
2. divides according to its own whim
3. has abnormal surface antigens, or has lost some of its normal ones





Left. *Some of the possible ways in which various influences can interact to transform a normal cell into a cancer cell.* ***Top.*** *In a cancer cell, cell division may be abnormal, and this can be seen in the pattern of the chromosomes, which are irregularly distributed.* ***Centre left.*** *In this dividing cancer cell, at a different stage, the migration of the chromatids to each end of the cell is abnormal.* ***Centre right.*** *In this case, the chromosomes have migrated into three poles, instead of the usual two.* ***Above left.*** *A drawing of cartilage cells. The effect of radiation on normal cells may be to make them malignant.* ***Above right.*** *The cells then become disorganised and perhaps cancerous*

surveillance system and the other regulatory mechanisms, which normally work in harmony to maintain the body's status quo, cease to function properly. The result is that, sooner or later, one or more of the dormant cancer cells escapes control, and proliferates to form a cancer. Some support for this view is provided by the demonstration that ageing is associated with a decline in immunological competence and that this is particularly evident in old people who have developed cancers.

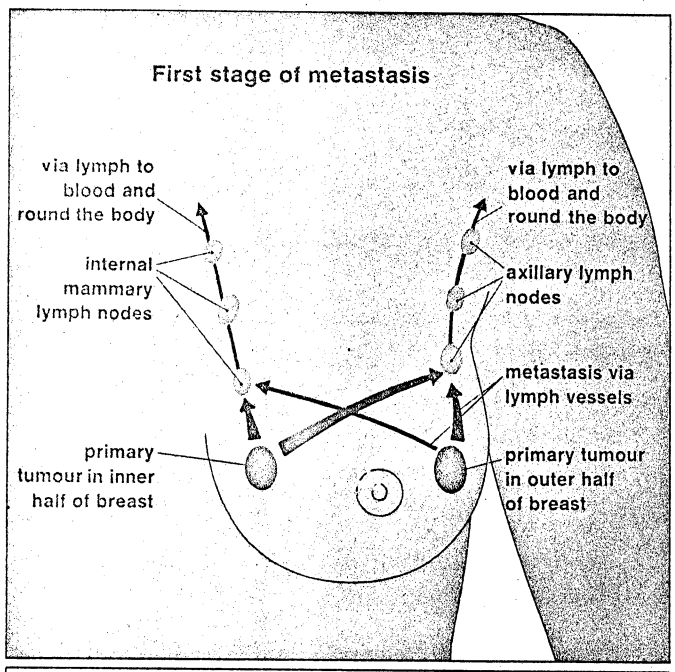
Can you be born with it?

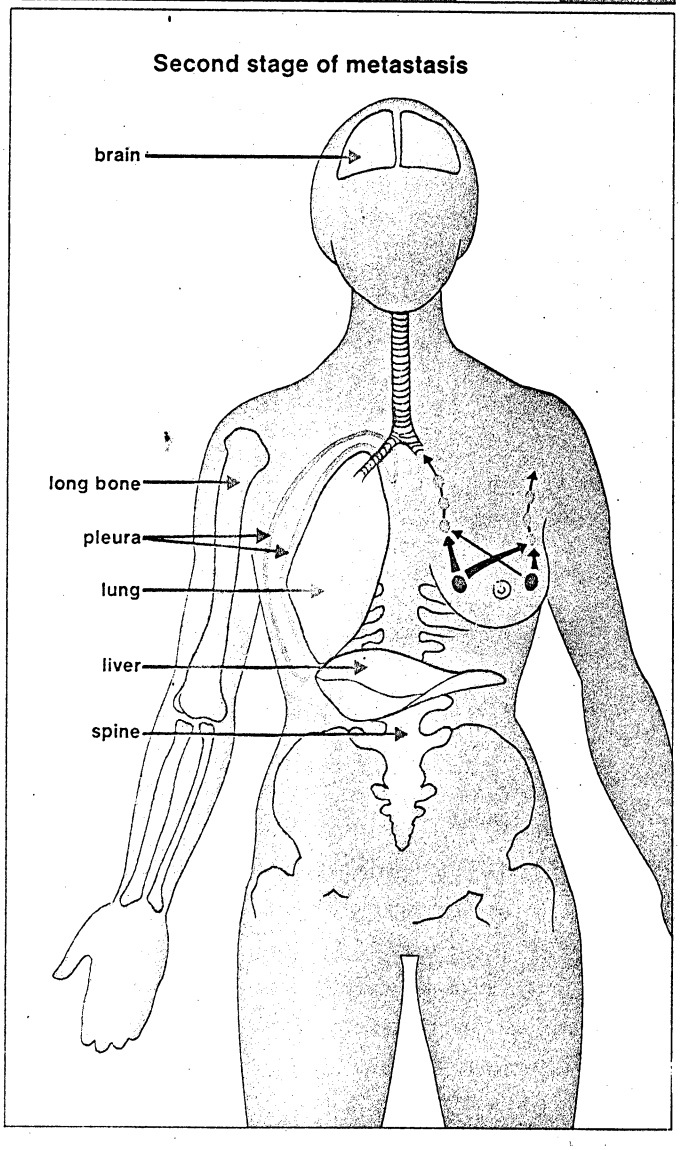
It is sometimes loosely stated by the ignorant that the cause of cancer is not known. The difficulty is quite the reverse: far too many causes of far too many varieties of cancer are known. Nevertheless, it is possible to assemble our knowledge of causation in a reasonably logical and meaningful form. Doctors and scientists often divide diseases into those of *genetic origin* and those of *environmental origin.* In practice both genetic and environmental factors are commonly simultaneously implicated. This is as true of cancers as it is of diseases of other types.

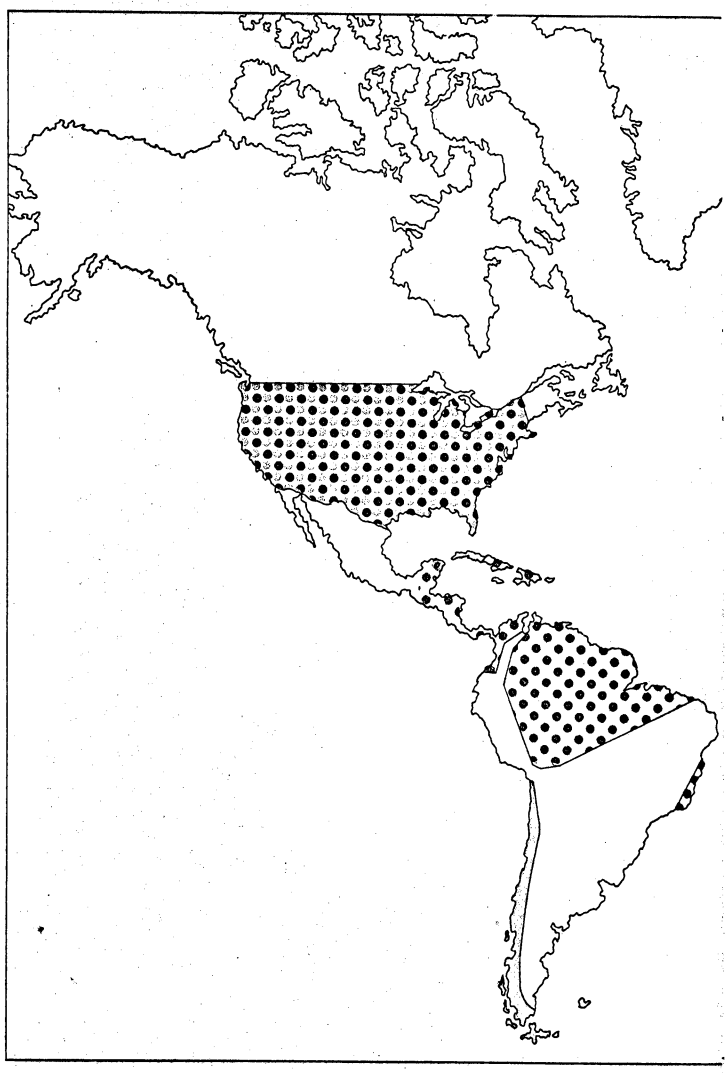
In the laboratory, different pure strains of animals show quite different propensities to develop different forms of cancer. In mice, for instance, there are high and low leukemia strains, high and low breast cancer strains, high and low liver tumour strains and so on. Strains in which all the animals develop cancers of particular types are well known, and in the case of both breast cancers and leukemia in mice, it is now clear that particular viruses are implicated. These viruses are transmitted from parent to offspring either through the placenta or in the milk. The transmission of viruses from mother to fetus via the placenta is known as *vertical transmission.* There is at present no information with regard to the vertical transmission of cancer viruses in man, but their discovery could well be an important landmark in the future. It is difficult even in the mouse to distinguish between the effects of inherited genes and of vertically acquired viruses, and such a distinction poses far more serious difficulties in man.

Despite these difficulties, we already know of some important genetic factors associated with cancer susceptibility in man. There is a disease called *xeroderma pigmentosa* which is associated with the inheritance of a so-called *recessive gene* from both parents. Neither of the parents suffers from the disease because each of them has a normal gene which is *dominant.* The double inheritance of defective genes, however, deprives the unfortunate *xeroderma pigmentosa* child of the ability to repair damage to the skin caused by exposure to the Sun's rays. Progressive destructive and inflammatory changes occur in the skin and eventually multiple cancers appear.

Another example of the influence of genetic factors on human cancer is the high incidence of cancer of the colon in *familial polyposis.* The underlying disease is due to the inheritance of a single defective dominant gene, and a person who has inherited this gene develops multiple polyps (benign tumours) from the lining of the large intestine and rectum. Sooner or later one or more of these polyps undergoes a secondary change with the resultant development of a malignant invasive cancer.



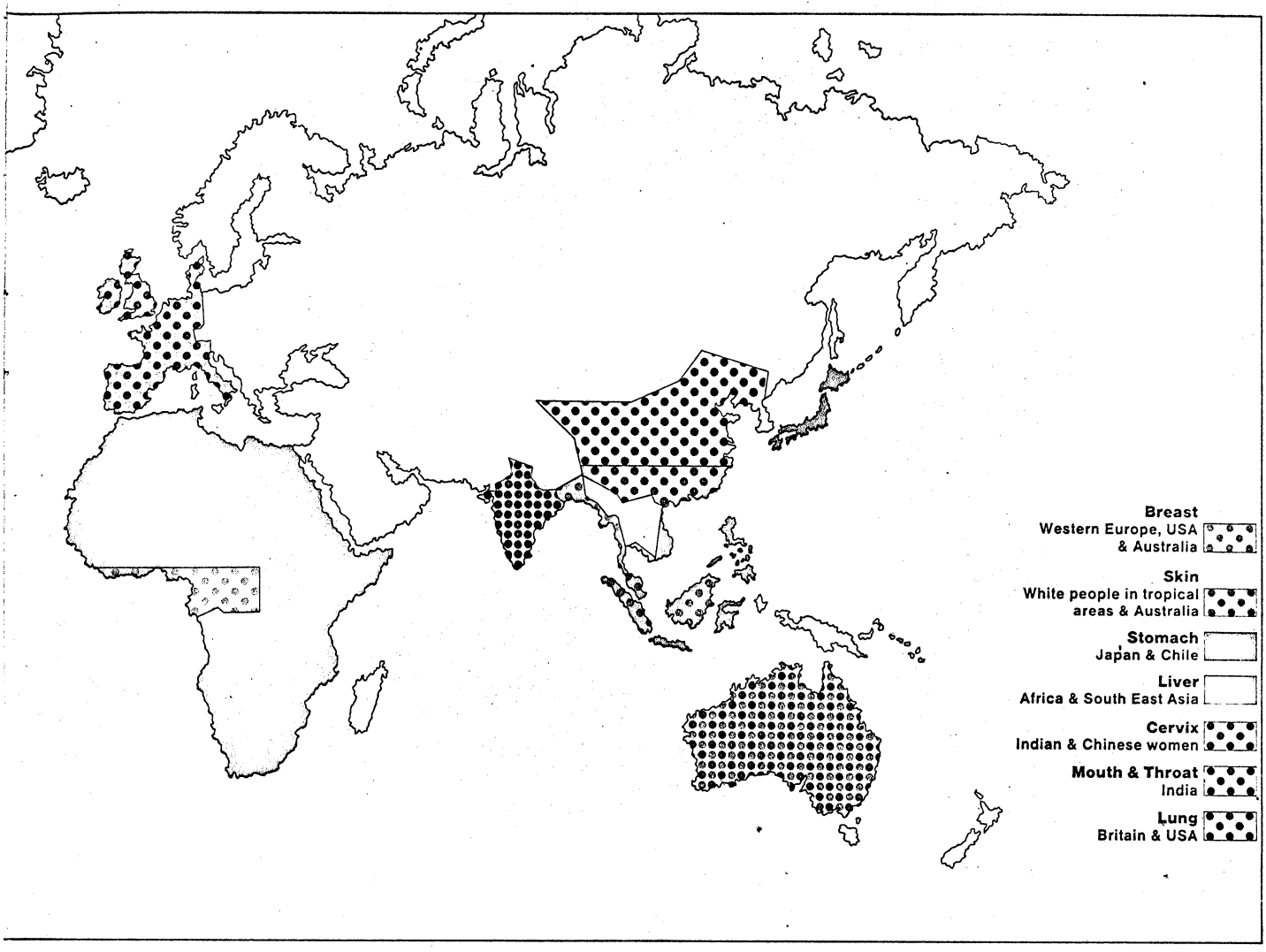




Left. *Metastasis is the process of spread of cancer cells round the body. From a breast cancer, for example, the cells first have to pass through lymph nodes which act as a first line of defence. The spread may be arrested at this stage, but once past the lymph nodes, the cancer may spread to many parts of the body – the second stage of metastasis.* ***Above.*** *A world map of the distribution of different forms of cancer. The coloured areas show which cancers are most prevalent in each country*

Other examples of genetic influence in man could be quoted, although in most of them the influence of genes on cancer susceptibility is marginal. For most of the more common forms of cancer it is the consensus view that environmental factors are more important than genetic ones.

Many hundreds of chemical substances, a wide variety of viruses, and certain forms of ionising radiation have been shown to predispose to cancer in laboratory animals. Some of the same factors have been shown to predispose to cancer in man, indeed there is a long list of known occupational cancer hazards. Exposure to ultraviolet light of certain wave-bands predisposes to skin cancer; certain drugs are known to have caused cancer in man; certain food additives, food contaminants and environ-



mental pollutants are suspected of doing so; and X-irradiation from a variety of sources has been a potent cause of human cancer. These environmental influences are discussed more fully in CANCER (2), along with the prevention, diagnosis and treatment of cancer in man.

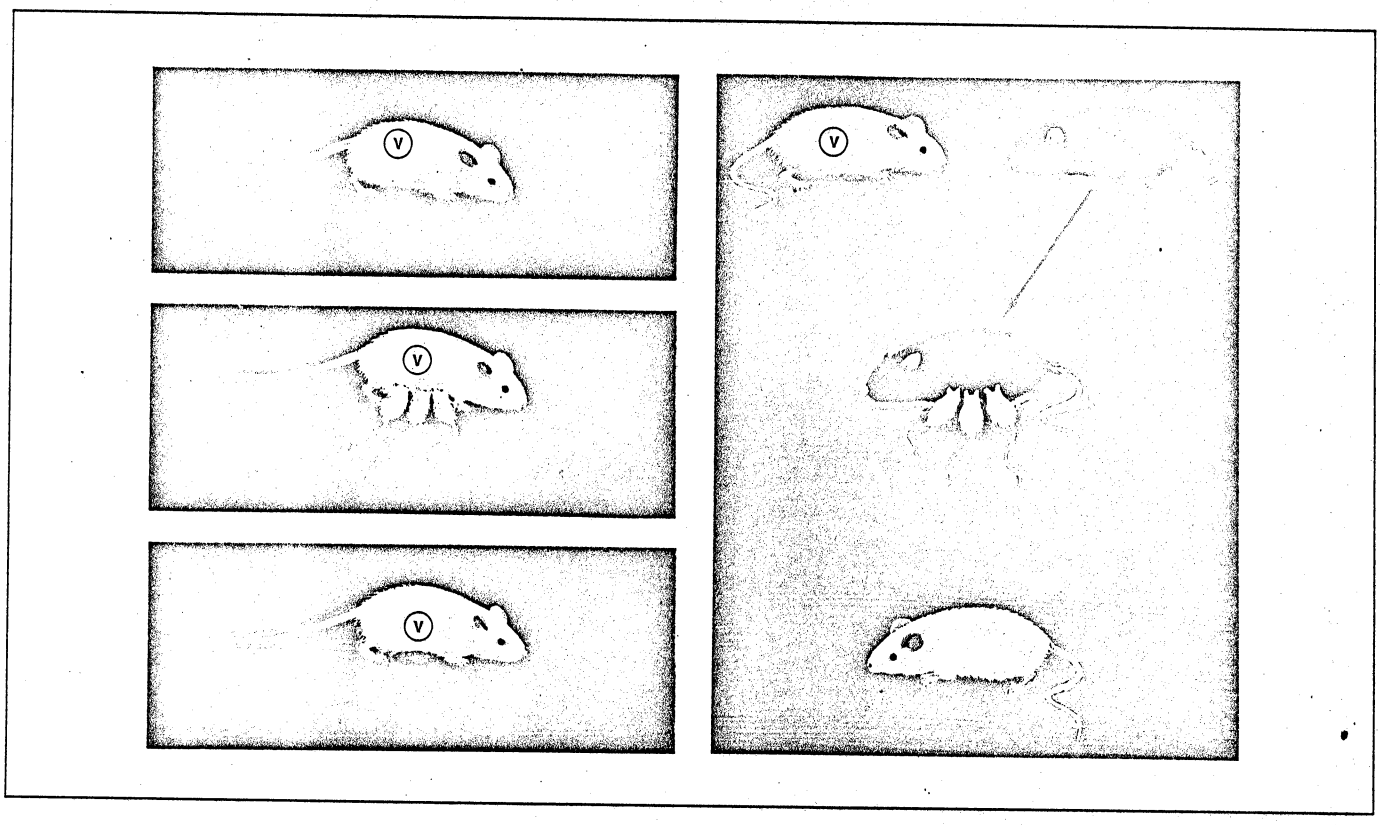
A subject of considerable current interest is whether virus infections (*horizontally transmitted viruses*) may cause cancer in man as they can in some other species. It is strongly suspected that the Epstein-Barr virus (EB virus), which causes INFECTIOUS MONONUCLEOSIS (glandular fever) in a proportion of those infected with it, may under certain rare circumstances give rise to a form of cancer of the lymphatic system, known as BURKITT'S LYMPHOMA.

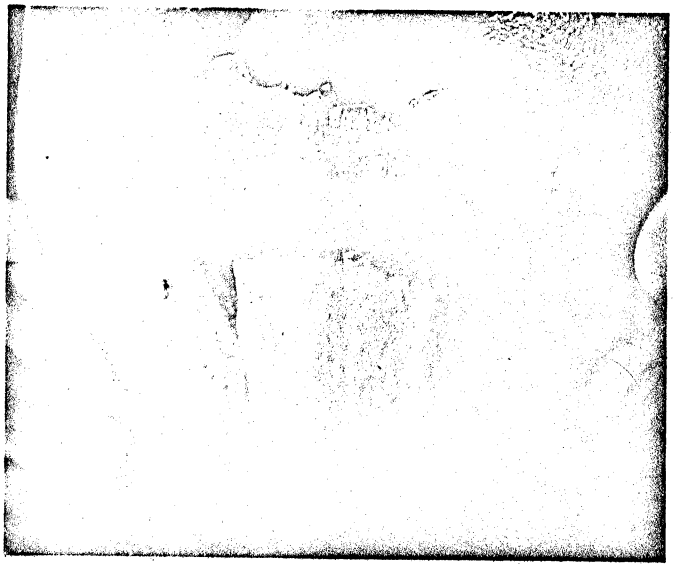
It is certain that there awaits discovery a rich harvest of fascinating and important facts concerning the environmental causes of human cancers. This is exemplified by the fact that Japanese living in Japan experience a high incidence of cancers of the stomach, esophagus and cervix, but a low incidence of cancer of the colon. If they migrate into the environment of the United States or Hawaii, the risk of their developing cancers of the stomach, esophagus and cervix falls dramatically, and the risk of their developing cancer of the colon undergoes a correspondingly dramatic rise.

More pieces of the puzzle

To relate the various types of causative factor with the whole background of cancer, we may assume that environmental factors act either by increasing the mutation rate of cells (*carcinogenesis*), or by damaging control mechanisms, or in both ways simultaneously; defective genes may act by rendering the cells more susceptible to damage by environmental factors; and viruses may alter the responsiveness of the cells to regulatory controls. Clearly the theoretical possibilities for interactions of these factors are legion. Moreover, in the induction of specific forms of cancer in laboratory animals, experiments show that many factors can be involved in an infinite variety of combinations.

A special case of this interaction is where exposures to two different factors can give rise to cancer only if they occur in the right order. This has led to the two-stage theory of carcinogenesis: the first stage (*tumour initiation*) is regarded as sudden and irreversible, perhaps a mutation; the second stage (*tumour promotion*) is a longer and partially reversible process, perhaps the breaking down of the regulatory processes which seek to prevent the cancer cell from proliferating. Cancer can be induced in animals by exposing them to a sequence of more than two factors,





Wellcome Museum of Medical Science

Top. *Breast cancer in mice can be transmitted from mother to young females via the so-called Bittner virus in the milk (left). If the young are fostered (right) they are less likely to develop the disease. Evidence for a similar transmission of cancer in man is not conclusive.* ***Above.*** *Xeroderma pigmentosa, here seen on the tip of the tongue, is a hereditary cancer*

and a confusing series of terms has been invented to describe the observations made in different laboratory experiments. Of these, the most widely used is *co-carcinogenesis*; this means the encouragement of tumour production by any means, after it has been started by a carcinogen. *Anti-carcinogenesis* has exactly the opposite meaning.

So far, we have considered cancer in the whole body, in organs and in individual cells. There are, however, two other aspects of the subject which should be discussed: its epidemiology and its molecular biology.

It is, of course, of vital interest to know whether cancers are occurring more commonly today than in times past. Except for cancer of the lung, the risk of death from most forms of cancer, standardised for age, has either remained virtually steady or has declined during the past 60 years. Improved methods of treatment and, in some cases, decreased incidence are responsible for these falling rates. During the same period there has been a revolution in our knowledge of how to prevent and treat many other fatal diseases, and dramatically lower death rates from these have led to the prolongation of life and hence to a greater chance of the eventual cause of death being cancer.

It seems certain that the most exciting developments in the future of fundamental cancer research will be in the field of molecular biology. These will be concerned with the structure of genes, how they mutate, how genetic information is suppressed, and how a normal cell is transformed into a cancer cell. These intricate problems have not been considered in detail here, because research at the molecular level only has meaning if it is related to the whole animal. Cancer is a disease of the body, not of cells, and most certainly not of subcellular particles.

Dr F. J. C. Roe was for ten years Senior Lecturer in Cancer Research at the London Hospital Medical School, and spent a further ten years as Reader in Experimental Pathology in the Chester Beatty Institute of Cancer Research, London. He has written several books and numerous articles on cancer, and is a member of several expert committees. Dr Roe is now Research Co-ordinator to the Tobacco Research Council