CHROMOSOMES IN CANCER*

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Many tumours are suspected of having some form of genetic origin. Retinoblastoma and epiloia, which is associated with multiple gliomata of the nervous system, are due to a genetic defect which leads directly to cancer. Intestinal polyposis and multiple neurofibromatosis, both examples of genetic defects, also provide the fertile ground on which malignant change may supervene. Furthermore, pedigrees have been compiled showing an increased incidence of breast cancer in certain families. These examples of malignant disease, coupled with the fact that strains of mice susceptible to cancer can be bred, suggest that changes in certain genes may give rise to cancer.[1]

An outwardly visible sign of a change to malignancy may be reflected in the chromosomes. The alteration may be either morphological or numerical.

VARIATION IN CHROMOSOME NUMBER

The variation in number can be either polyploid or aneuploid. Polyploidy is the presence of exact multiples of the basic haploid number. In man, the basic haploid number, as seen in the ovary or testis, is 23. All other cells in human tissue have twice that number (46) and are known as diploids.

A chromosome number of 92, known as tetraploid, results from multiplication of the haploid number 23, by a factor of 4. Aneuploidy is an irregular number of chromosomes. Some of the mechanisms producing these variations are endo-reduplication, multipolar spindle, absent spindle, lagging chromosomes and broken chromosomes.[2]

STRUCTURAL ABNORMALITIES IN CHROMOSOMES

There is a wide range of abnormalities which can result from fragments of chromosome breaking and rejoining in different ways. These may appear as V, J[3] or ring forms. Other changes include minute and extra-large elements, dicentrics and isochromosomes. Then there is the particular abnormality which has been called the Philadelphia chromosome, to be discussed in fuller detail below.

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Many tumours with normal structure and complement of chromosomes have been described.[4] Cells exhibiting aneuploidy as in mongols, Turner's and Klinefelter's syndrome, do not necessarily lead to malignancy.

CAUSES OF CHROMOSOME ABNORMALITY

X-rays

The effects of ionizing irradiation are assuming increasing importance as causes of cancer in clinical medicine. Following the atomic bomb at Hiroshima the incidence of acute leukaemia was increased after an interval of 5 - 7 years. A similar result was shown to occur following treatment of the spine for ankylosing spondylitis with X-rays. Within 24 hours of treatment with X-rays of this disease, chromosomal abnormalities were seen in the peripheral blood.[5] These abnormalities may persist for many months and in one case were observed 10 years after therapy. Fig. 1 illustrates 2 ring chromosomes in a single blood cell of a young African male, who had received deep X-ray therapy to the skull and spine, for an ependymoma.

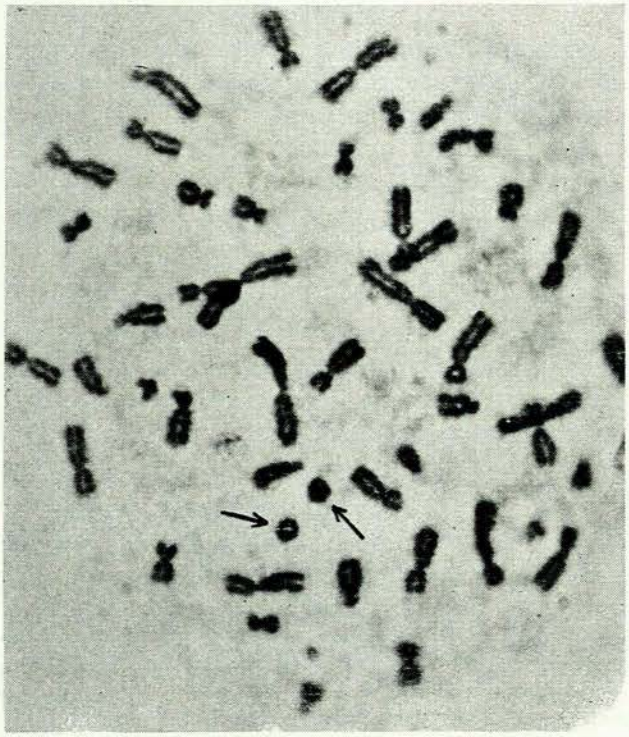

Fig. 1. Arrows indicate 2 ring chromosomes in the peripheral blood of a patient who had received spinal irradiation.

There have been reports that diagnostic X-rays produce chromosome damage.[6] Probably most of these abnormal cells are destroyed by the body's homeostatic mechanisms and through mitotic suicide. The affected cells may fail to divide and form multinucleate cells which eventually die. However, one should weigh carefully the need for repeated X-ray examinations of small children and infants. They are more likely to receive higher doses of irradiation than adults, because of the difficulty in maintaining correct position and shielding vital areas.[7] This would be particularly difficult in retrograde pyelograms and repeated barium enemas.

Chemicals

Certain chemicals form an important group producing chromosome anomalies. Radiomimetic drugs, such as nitrogen mustard,[8] and antimetabolites, like the uridines,[9] are examples of substances which act on the nucleus. Some of the drugs most effectively used in treating cancer also produce chromosome breakage, which can be detected in the rapidly dividing cells of the haemopoietic system.[10]

It is perhaps pertinent to also mention that the effect drugs may have on the foetus in pregnancy is still a gap in our knowledge.

Age

Although the study of the effect of age on the human chromosome is in its infancy, it promises to be a fruitful field for research. It has recently been shown that the number of aneuploid cells increase with age. This appears to be largely a result of errors in division involving the X chromosome in women and the Y chromosome in men.[11] It is well known that certain cancers occur at different ages. One would like to postulate that a virus acquired at an earlier age might lie dormant until the 'door' is opened, either by age, chemical or X-ray damage. The changes characteristic of malignancy then follow. It is interesting to note that whereas acute leukaemias, sarcomas and retinoblastomas have an incidence in early life, the tumours of the breast, cervix, prostate and uterus appear in the later years. It is tempting to speculate that the latter may be related to some change in the sex chromosome.

Viruses

Within the past decade an ever-increasing number of animal tumours have been shown to have a viral aetiology.[12] Certain bacteriophages are capable of attaching themselves to bacterial chromosomes. Instead of destroying the cell, they replicate with the host and may cause changes in cell character. This phenomenon, most common in lysogenic strains, is responsible for such bacterial genetic alterations as exotoxin production by *Corynebacterium diphtheriae*. If this could be shown to occur in the cancer cell, it would contribute greatly to our understanding of the induction of malignancy by viruses. The monkey virus known as SV_{40}, is being intensively investigated because it fails to produce a cytopathogenic effect in certain cells, where it appears to replicate with the host. SV_{40} is capable of transforming normal tissue cultures. It can initiate tumours in hamsters. Finally, it gives rise to non-random changes in the chromosomes.[13]

Many common viruses produce intranuclear inclusions. Of these, adenovirus types 12 and 18 have been shown to produce tumours in hamsters.[14] Large intranuclear inclusions are also characteristic of measles. Is it possible that a measles virus or other virus may attach itself to a chromosome in a young child giving rise to an abnormal clone of cells which may result in leukaemia? Using a method of acridine-orange staining which differentiates

chromosone DNA from RNA, we hope to elucidate the interaction of virus with the cell genome in cancer.[15]

ACUTE LEUKAEMIA

In acute leukaemia, the only consistent abnormality discovered so far, has been an increase in aneuploidy.[16] An extra chromosome in group C has been described in 4 cases[17, 18] and an extra chromosome in the D group in 2 cases.[19] A most remarkable feature, too, is the predisposition of mongols to develop acute leukaemia. As a group, these children have a 15-times greater chance of developing this disease than normal children. The polymorphonuclear leukocytes show an abnormality of lobulation and a raised alkaline phosphatase[20] in mongols. Although no abnormality of the 21st chromosome has been described in acute leukaemia, one wonders if the leukaemia susceptible gene might be located on this chromosome.

THE PHILADELPHIA CHROMOSOME

In chronic myeloid leukaemia, a most exciting discovery has been the finding of a consistent chromosome abnormality.[21] The change consists of the deletion of approximately half the long arm of one of the 4 smallest autosomes, probably the 21st. Myelofibrosis, polycythaemia vera and myeloid metaplasia, which may have leukaemia-like pictures complicating the diagnosis, do not have this abnormality.[22] Treatment may lower the number seen in the peripheral blood, but it will always be seen in the bone marrow.[23, 24]

Only the cells of the haemopoietic system exhibit this defective chromosome. Recently, it was suggested that erythroid cells, granulocytes and megakaryocytes contain the Ph^1 chromosome. These elements are derived from a common ancestral cell.[25] The abnormality is probably not inherited. Whether the Ph^1 change confers neoplastic properties on the myeloid cell, or whether it produces an element favouring the development of an abnormal cell, is not yet known. The change is consistent with that produced by ionizing radiation or other mutagenic agents which produce breakage. An interesting feature of chronic myeloid leukaemia is that the alkaline phosphatase is usually greatly reduced in this disease,[26] in contrast to the levels in mongolism in which they are elevated and there is a trisomy of the 21st chromosome.

The Christchurch chromosome, known as Ch^1, is a defect of one of the 4 small acrocentrics. The abnormality consists of the complete or almost complete loss of the short arm with apparent preservation of the centromere and long arm. This defect was demonstrated in 2 siblings with chronic lymphocytic leukaemia and also in several other members of the same family without evidence of leukaemia. It is suggested that this abnormality may predispose individuals carrying it to chronic lymphocytic leukaemia.[27]

HUMAN TUMOURS

There have been many investigations on the chromosome constitution of human tumours in tissue culture,[28, 29] pleural effusions[30] and solid material.[31, 32] Each tumour appears to possess its own characteristic karyotype, but this does not bear any relation to the histological origin.[33] The numbers range from hypodiploid to hypotetraploid, with a modal number for each tumour. The large extra chromosome that has been described in Waldenstrom's macroglobulinaemia provides, for the first time, a morphological basis of a genetic kind for a biochemical defect.[34]

Cells in tissue culture are probably undergoing a continual change in gene structure, according to the variation in temperature, nutrient media and pH.[35]

The response of these cells to a wide range of stimuli, including viruses, chemical and physical change, is providing an ever-increasing volume of valuable information.

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