certainly be a help however.

The therapeutic and financial consequences of success in this field will be enormous. Albumin and factor VIII form the stimulus for commercial and national plasma-fractionation programmes. Thus the biogenetic synthesis of either of these proteins will profoundly influence fractionation policy as well as provide potentially virus-free therapeutic agents. It is not difficult to see why the biotechnical commercial conglomerates jealously guard their secrets to the frustration of mere academics and clinicians. □

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Cancer

Chromosome aberrations and oncogenes

from Fred Gilbert

THE status of the chromosome localization of the cellular homologues of retroviral oncogenes (the c-*onc* genes) has recently been summarized in these pages[1]. The review points out that the breakpoints of many of the consistent rearrangements that characterize individual cancers involve the specific bands to which different c-*onc* genes have been assigned. Although a role for c-*onc* genes in mammalian cancer has yet to be proved, a possible relationship between chromosome changes, alterations in *onc* gene activity and cellular transformation can be deduced from what is known of the genetics and cytogenetics of cancer in man, and from studies of *onc* genes in man and other species. The observations contributing to the scheme I shall propose can be summarized as follows.

First, chromosome abnormalities in human cancer can be grouped into three major classes: reciprocal translocations, deletions and duplications (the latter including duplications of whole chromosomes, chromosome segments and gene sequences, as in the structural analogues of gene amplification, homogeneously staining regions and double minutes; ref. 2 and F. Gilbert, in preparation). Examples of each of these have now been associated with presumed changes in *onc* gene activity. As well as the translocations and deletions cited by Rowley[1], amplification of an *onc* gene, c-*myc,* has been demonstrated in a human promyelocytic leukaemia cell line, HL-60, known to contain double minutes[3,4].

Second, in many, if not all cancers, both tumorigenesis and tumour progression probably involve multiple gene changes. This seem to be true in certain solid tumours of children — retinoblastoma, neuroblastoma and Wilms' tumour — each of which has been associated with chromosome rearrangements involving different specific segments[5-7] and for each of which it has been postulated that (at least) two gene changes are required[8]. It is also clear that more than one putative oncogene may be active in a single cancer cell; a number of leukaemias and lymphomas have now been found to contain DNA sequences capable of inducing transformation of the mouse cell line NIH 3T3 (when transferred by transfection[9]) in addition to the transcriptionally active retroviral *onc* genes previously identified in each[10,11].

Third, cellular differentiation can be viewed as a series of step-wise changes in which the potential for (and pattern of) phenotypic expression is altered with successive cell divisions[12]. In particular cell lineages, terminal differentiation (the expression of the fully differentiated programme) may also be associated with the cessation of cell division[13]. Control of the individual stages of development is (at least partially) genetic and among the genes which may play a part in this process are the *onc* genes. Recent reports have documented the differential expression of particular c-*onc* genes during pre- and postnatal development in the mouse[14] and during liver regeneration in the rat[15]. That there may be a relationship between differentiation, specific chromosome aberrations and malignancy is also suggested by the demonstration that rearrangements involving homologous segments in certain B-cell tumours of man (Burkitt lymphoma) and mouse (plasmacytoma) result in the translocation of the same *onc* gene from one chromosome to another[1].

The synthesis of these observations leads me to propose the following scheme: the development of a chromosome abnormality, if it involves a segment containing or adjacent to a c-*onc* gene, can produce an alteration in the pattern of expression of the gene different from that seen in the normal course of cellular differentiation. The chromosome abnormality may develop as a germinal change[16], a *de novo* event, or following an underlying mutation which increases instability at that site[17]. The alteration in c-*onc* gene expression may be manifest in decreased gene activity (in deletions of the structural locus[18]), in increased activity (in deletions of a putative *onc* gene suppressor, in duplications, amplification and some translocations[19]), or in the transcription of an abnormal mRNA (postulated in other translocations[20]). Aberrant *onc* gene expression may, in turn, produce an alteration in the pattern of cell division. Instead of the programmed cessation of division, the cells may continue to divide; with continued division, the statistical likelihood of additional gene changes (through mutations and further chromosome rearrangements) increases.

The accumulation of specific gene changes is postulated to result in tumorigenesis; those changes which occur following tumorigenesis are presumed to contribute to tumour progression. The primary gene changes leading to tumorigenesis are likely to include those resulting from chromosome rearrangements characteristic of particular tumours, such as the 8;14 translocation in Burkitt lymphoma[1]. The secondary gene changes involved in tumour progression are likely to include those resulting from chromosome abnormalities that are not unique to any one tumour type: trisomies for chromosomes 17 and 1, for example[21].

Two caveats must be added: changes in gene activity can clearly be produced by mechanisms other than chromosome rearrangement (for discussions of the possible significance of point mutations in *onc* genes see refs 22,23) and *onc* genes (probably) constitute only one category of genes involved in cancer. However, recombinant DNA probes specific for *onc* genes are available and can be used, in conjunction with permanent cell lines containing defined chromosome rearrangements, to determine precisely how such rearrangements alter the expression of *onc* gene activity in individual cases. The *onc* genes therefore represent a model system with which to study the part played by single-gene changes in the development of cancer. □

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0028-0836/83/230475-02$01.00

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