Introduction

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No theory, description, or view of human cancer has thus far gained universal acceptance or served to guide effectively research and development to successful treatment or prevention of this disease. This would appear to both justify and require that many alternatives be carefully stated and intercompared. Disagreements precisely stated generate new experiments.

In this series of symposia we have attempted an examination of ideas which have not yet been precast into large programs, with the aims of stating and examining concepts, collecting both supporting and contrary data, and generating new relevant information. The single guide has been Ockham's razor: the simplest explanation consistent with the facts must be given preference.

The starting point must be a consideration of human cancer cells themselves: their salient feature, so well reviewed by Foulds (1), is their extreme variability, individuality, and plasticity. No common point defect has been discovered, such as the deletion of one well-defined gene product, the addition of a new one due to mutation, or the introduction into the cell of extraneous genetic information. Given no single molecular defect such as characterize many other human diseases, we are forced to conclude that multiple molecular changes characteristically occur, and this indeed is the primary conclusion of cancer biochemistry. Two possibilities must then be explored. Either the pattern of changes produced is the result of chance clustering of accidents, such as a critical sequence of mutations, or the pattern of alterations reflects change or damage to whatever control mechanisms govern the pattern of gene expression. The former should yield mutant proteins which could be isolated and intercompared with the normal ones to show what substitutions have occurred. This has not been done in any tumor, animal or human, of which we are aware. While this does not prove that such do not occur, it is hazardous to base programmatic research on zero evidence. Thus an overwhelming mass of data points to heritable alterations in DNA as characteristic of cancer, with no conclusive evidence in man that any abnormal gene products are made. We are forced, therefore, to consider that the fundamental alterations affect mechanisms concerned with the control of gene expression, i.e., the errors are in programming (2). This at once raises the question of whether DNA devoted to this function indeed exists, a question addressed by Davidson and Britten (3) in this symposium. Despite the infancy of investigations on the control of gene function, the simplest considerations of gene numbers and of the informational requirements for the organization of the human body lead to the conclusion that the orchestration of gene expression is exceedingly complex, even if we do not know with certainty what or where the score is. The number of new combinations of gene expression possible as a result of single program errors or accidents is a direct function of program complexity.

Should our reasoning be correct to this point, we must then ask several very simple questions regarding the program of development and differentiation. Broadly viewed, it could be organized in at least 2 ways. The 1st is an additive program, with a few genes turned on in the fertilized egg and more genes turned on as differentiation proceeds until some maximal number is reached in a fully differentiated cell line. This "maximal set" would be different in each cell type; it would include, therefore, in a given cell type only a fraction of the total genome, and all sets would overlap to some extent. The 2nd type of program involves not only selective gene activation during development, but also selective gene repression. Such a program could be described in terms of branching Markov chains, and suggests that not only organ-, tissue-, or cell-specific genes exist, but also time-specific genes may be expressed transiently during differentiation. If one were to define a central question in cancer, it would, in our opinion, be the choice between these 2 (not totally exclusive) views. The reason this is crucial is, 1st, that the collapse or reversal of additive programs should lead to recognizable cells from an earlier stage in a cell's lineage, and 2nd, since the entire gene library would be expressed in the adult, there would be no library of genes inactive in adulthood. New antigens appearing in tumors must then be the products of neogenes, probably of viral origin. If, in contrast, a large library of genes exists concerned only with specific stages of development, then many new antigens and structural or behavioral properties exhibited by cancer cells could be the result of reactivation of genes normal to an earlier stage of development.

In a simple Markov chain program, each link is dependent on information in that link and in the preceding one. In a complex chain, in contrast, progression is dependent not only on information from the preceding link, but also on
information from other antecedent links, from other parallel chains, and from totally external sources. In such complex chains, a very large number of signals are possible which could permanently reactivate an early part of the chain and which would result in massive changes in other portions of it. One would expect, however, that interference or injury at some specific sites would tend to produce a unique program collapse, while multiple collapse patterns would exist for others. Thus if oncogenic viruses produce transformation by interaction with specific DNA sites concerned with early programming, then similar or identical tumors might be produced by some viruses, depending on the nature of the site interacted with. However, any consideration of uniqueness relative to program collapse (transformation) must take into account the fact that diploid organisms possess 2 copies of the program and that they are not identical except in isogeneic animals. It appears that the nonidentical redundancy of outbred diploid organisms may act to prevent virally induced program collapse and may indeed have been evolved for this purpose. Should this be true, much of what has been learned from the study of virus induction of tumors in highly inbred animals will become of great importance when the treatment of cancer in laboratory and domesticated animals becomes our central concern. However, since we have not progressed to that point, our interest here is with the less elegant problem of program collapse in outbred species such as man, where the results are as yet unpredictable in detail and where a stable pattern of gene expression is often not reached at once, resulting in the slow alterations characterized as tumor progression.

Given the ground rules we have set, each gene product must be considered to be that of a normal gene until proven otherwise. To allow any protein, no matter what its interest, to be freely ascribed another source without rigorous proof leads only to chaos. Careful study of alterations in isozymes, tRNA's, and a variety of antigens shows them to be normal to some stage of embryonic development. While much searching remains to be done, no antigen systematically shown to be absent from normal tissues at all stages of development has thus far been found for human tumors. Part of the problem is that definitive proof of absence is difficult to obtain.

The exploration of transformation-associated differences as ectopic gene expressions immediately raises a variety of questions which include the following.

1. Are there obligatory phase-specific antigens in human embryos?

2. Are these autoantigens the same as those found in tumors?

3. How does the maternal immune system deal with them, and how does the fetus escape? Do tumors, if they express embryonic autoantigens, use the same escape mechanism that the fetus does?

4. What is the relationship between pregnancy and cancer? Can fetal cells be used to immunize against cancer? Does immunization against tumor challenge affect pregnancy? Does multiparity affect cancer incidence? Can tumors be classified according to the degree of their regression along defined (ectodermal, mesodermal, and endodermal) pathways? Are these lines of descent ever transgressed, for example, by the ectopic synthesis by a tumor of a hormone produced by an endocrine gland of a different germ layer origin?

5. Is the information which makes a virus oncogenic obtained from the host genome in the first place? Interaction between the viral genome or its products and the host genome appears to be very specific, and specificities involving fairly long nucleotide sequences are unlikely to be the product of accidents. Do virus-embryo commonalities denote for certain viral infection of embryos, or the inclusion of normal embryonic information into oncogenic viruses?

These and other questions are among the topics of this conference. Hopefully, we can develop ideas, concepts, and data which, coupled with new experimental approaches, will lead to measurable improvements in the prevention, detection, and treatment of cancer in man. Hopefully, also, we can learn to abandon programs, concepts, and management arrangements that fail.

References

