

Hi, Al

This present work mode, as you see, precisely the opposite prediction from the current findings. When we go into hormonal control and derepression, it may still be justified. I would assume that

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asparagine-dependence, etc., are associated in some way with linkage of genes for the synthetic enzyme with other factors more directly associated with neoplasia.

General Concept of Cancer

The biology of cancer has been categorized under two main types: a transmissible virus on the one hand and a mutation on the other (not to mention a host of other theories). There has been relatively little speculation on the biochemical mechanisms whereby any of these could lead to the process recognized as neoplasia. Recent studies by Beadle, Tatum, and others on the genetic control of biosynthetic reactions in *Neurospora*, have provided a foundation for concepts of the biological regulation of growth. A study by Ryan and Lederberg (*Proc. Natl. Acad. Sci. Wash.*, 1946, 32, 163-173), on the "adaptation" of a *Neurospora* mutant deficient in the synthesis of leucine, has provided an experimental basis for an analogy with neoplasia.

Cells of *Neurospora* will grow on medium containing sugar, salts, and biotin, which is to say that they are capable of manufacturing all other essential metabolites. As the result of mutations of single genes, the capacity for synthesis of various compounds is lost. A similar process presumably accounts for the special requirements of higher forms.

By ultraviolet treatment, a mutant strain of *Neurospora* (No. 53757), has been isolated which is incapable of synthesizing leucine. As a consequence, this strain requires leucine, and its growth is quantitatively regulated by the available supply.

In cultures of leucineless *Neurospora* grown on media containing amounts of this amino acid will "adapt";

that is, an exceptional fragment of the mycelium will grow autonomously, irrespective of the available leucine, and may under certain conditions overgrow the culture until the sugar is exhausted. By genetic analysis of crosses between adapted and wild strains, it has been shown that adaptation depends on the mutation, or reversion, of the leucineless gene to an allele capable of mediating the synthesis of leucine.

A culture of leucineless *Neurospora* has, then, two growth potentialities: a regulated growth corresponding to the leucine externally available to it, and, exceptionally, autonomous growth on the basis of a gene mutation leading to the synthesis of that metabolite.

If one correlates normal tissue cells with a culture of leucineless *Neurospora*, both regulated by their environment, a simple analogy for cancer is evident—the newly found capacity of a cell to synthesize an essential metabolite otherwise available only in limiting and regulatory amounts.

While the *Neurospora* experiments suggest a mutational origin for this capacity, virus infection, by providing a missing link for a blocked enzyme system, could play a corresponding role. A consequence of this simple concept is that cancer cells may be found to differ in their growth factor requirements from cells of normal origin when they are grown *in vitro*.

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