

re Genetics + Cancer

2/20/94  
PS  
#5 ↓

I remember Haddow was a strong advocate of the somatic mutation theory.

Reprinted from SCIENCE, November 1, 1946, Vol. 104, No. 2705, page 428.

**A Nutritional Concept of Cancer**

While the etiology of cancer has been categorized under infection by a transmissible virus on the one hand and gene mutation on the other (not to mention a host of other hypotheses), there has been relatively little speculation on the biochemical mechanisms whereby any of these events could lead to the process recognized as neoplastic growth. Recent studies by Beadle, Tatum, and others, on the genetic control of biosynthetic reactions in the fungus, *Neurospora*, have provided a foundation for new concepts of the biological regulation of growth. In particular, a study by Ryan and Lederberg (*Proc. nat. 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 speculative analogy with neoplasia.

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

Following ultraviolet treatment, a mutant strain of *Neurospora*, #33757, 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.

Occasionally, cultures of leucineless *Neurospora* grown on limiting 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*.

JOSHUA LEDERBERG

Osborn Botanical Laboratory, Yale University, and  
College of Physicians and Surgeons, Columbia University

(oncogene)  
some models

\* This was still problematic as late as 1946! Even Van Potter was talking of nutrient exhaustion and the biochemists would have none of it.