(β-chloroethyl)amine hydrochloride." It is unfortunate that Demerec's original results are widely quoted and his subsequent retraction is frequently overlooked, possibly due to the restricted circulation of the journal in which it is published.

The effect of 20-methylcholanthrene on lethal mutation rate in the Oregon-R strain of *D. melanogaster* has been tested in our laboratory and reported previously (*2*). No increase in lethals was found after administration of this carcinogen. A scheme (*3*) was then devised for testing mutation rate and tumor incidence simultaneously after treatment of tumor strains of *Drosophila*. Failure to demonstrate an increase in mutation rate in the presence of increased tumor incidence (and vice versa) in this type of experiment should therefore constitute stronger evidence than negative results obtained in the case of either tumor incidence or mutation rate alone. Nitrogen mustard, stilbestrol, methylcholanthrene, and formaldehyde were tested. It was found that mutation rate and tumor incidence were both increased after administration of nitrogen mustard (*4*), only tumor incidence was higher after methylcholanthrene (*5*), only mutation rate was increased in males after formaldehyde (*6*), and neither mutation rate nor tumor incidence were increased after diethylstilbestrol treatment (*7*).

One should require that mutation rate and tumor incidence be correlated to validate the somatic mutation hypothesis. Otherwise one would expect to find four types of agents: those causing increased mutation rate and tumor incidence, those causing only tumor incidence to increase, those causing an increment only in mutation rate, and finally those affecting neither tumor incidence nor mutation rate. The results in *Drosophila* illustrate that these four types of agents do actually exist. In more recent experiments, introduction of the mutator, *hi*, into two tumor strains (*8*) also failed to reveal any correlation between mutation rate and tumor incidence. This eliminates the possibility that results may be explained by failure of the initiating agent to enter the cell. Other work in our laboratory on biochemical mutants in *Neurospora* treated by exposure to 1,2,5,6-dibenzanthracene and 20-methylcholanthrene (*9*) may be more easily explained by selection than any mutagenic effect of the carcinogen.

It is customary to arrive at a conclusion in a scientific problem by reviewing and evaluating all previous work in the light of personal observations. We are not, in this discussion, including a review, since that has been done elsewhere (*10*), but wish to point out omissions in Fardon's paper which we believe weigh heavily against his conclusions. The frailty of reason and limitations of methodology restrain any dogmatic pronouncements on the validity of the hypothesis in question. However, studies to date in our laboratory do not warrant any change in the view we expressed in this journal in 1950: "There would seem to be a reasonable doubt that there is necessarily a connection between mutagenic and carcinogenic effects of an agent or that carcinogens are necessarily mutagens. At the present time there are even more obstacles in accepting without reservation the hypothesis that tumors are the direct result of somatic mutation."

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Regarding the Somatic Mutation Hypothesis of Cancer

IN HIS RECENT article in SCIENCE, "A Reconsideration of the Somatic Mutation Hypothesis of Cancer in the Light of Some Recent Developments," J. C. Fardon[1] makes the following statement, ". . . it may be concluded with some degree of confidence that the somatic mutation theory of cancer does not oppose the facts that have so far been brought to light." This is a cautious, but at the same time a sweeping conclusion which should not go unchallenged.

One of the principal arguments used to support the somatic mutation hypothesis is that cancer tissue when transplanted maintains its character of malignant growth. This is construed to mean that the cancer cell has a new hereditary character (malignancy) and hence has mutated. The same argument might be applied to most differentiated cells in the adult organism, since, when transplanted, differentiated cells usually maintain their essential morphologic and other characteristics. Thus similar reasoning would lead to the conclusion that differentiation also means mutation. But differentiation is an event taking place at just the appropriate time in the developing organism in coordination with other developmental occurrences. Mutation, on the other hand, displays a high degree of randomness and uncertainty; this applies to the somatic mutations that Fardon cites in drawing his parallels with cancer. I do not believe biology can furnish satisfactorily conclusive evidence that differentation is to be explained in terms of mutation (this does not mean, of course, that differentiation is not genetically controlled). Lacking such evidence the transplantability of cancer tissue constitutes only equivocal support for the somatic mutation hypothesis. Remove that support and the analogies drawn

1 SCIENCE, **117**, 441–445 (1953).

between cancer and somatic mutation lose much of their significance.

But leaving aside this uncertainty, strong evidence against the somatic mutation hypothesis is comprised in quantitative studies of the induction of cancers by ultraviolet light. Repeated exposures to ultraviolet light are necessary to induce tumors. If it is assumed that each dose of radiation produces one or more mutant cells each of which proliferates by "unlimited cell division" to form a clone of cancer cells, it may be calculated that (if the proliferation rate is comparable to the growth rate measured after the tumors have appeared) only the first few clones would have any appreciable effect on the growth of the tumor. The rapid proliferation of the initial clones would swamp out any late-appearing clones, and hence after the first few exposures ultraviolet light should have no effect on the time of appearance of the tumor. Yet doses of ultraviolet light continue to accelerate tumor appearance long after the time they should be ineffective if we were dealing with somatic mutations. Furthermore, the data indicate that the process of carcinogenesis is continuous throughout the whole period of tumor development from the first dose of ultraviolet radiation to the appearance of the tumor, and that no sharp separation into periods of induction and growth can be made. These findings are difficult to fit with any form of the somatic mutation hypothesis.[2]

Most of the reasoning regarding the somatic mutation hypothesis disregards the quantitative aspects of tumor growth, and this constitutes an important weakness. Knowledge of the character of the growth rate is essential to the successful extrapolation back in time to the origin of cancer; and in this regard all cancer theories are extrapolations. The lack of such knowledge is a principal hindrance to our understanding the nature of cancer.

Taking these things into account it seems that there is strong evidence against the somatic mutation hypothesis of cancer; that there is a great deal to be learned before we can accept this or any other hypothesis; and that basic studies of growth and differentiation would seem logical (though perhaps far from smooth) avenues of approach to the problem of carcinogenesis.

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IN HIS REVIEW, "A Reconsideration of the Somatic Theory of Cancer" in SCIENCE, (**117**, 441–445 [1953]), John C. Fardon fails to call attention to certain recent publications which indicate that the "manifestations of cellular anarchy," which he ascribes to mutations, may in part be consequent upon the activities of a pathogenic microorganism of pleomorphic nature. The presence of this microorganism has been revealed by special methods described in the two papers listed below, which state that some of its forms are of viral dimensions, and that these forms have been demonstrated within the cytoplasm and the nuclei of cancer cells obtained from human as well as from animal specimens.

(1) "Cultural Properties and Pathogenicity of Certain Microorganisms Obtained from Various Proliferative and Neoplastic Diseases," by Virginia Wuerthele-Caspé, M.D., Eleanor Alexander-Jackson, Ph.D., James Hillier, Ph.D., Roy M. Allen, D.Sc., and Lawrence W. Smith, M.D. *American Journal of the Medical Sciences,* **220**, 638–648 (1950).

(2) "Some Aspects of the Microbiology of Cancer," by Virginia Wuerthele-Caspé, M.D., Eleanor Alexander-Jackson, Ph.D., and Lawrence Weld Smith, M.D. *Journal of the American Medical Women's Association*, **8**, 7–12 (1953).

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[2] H. F. Blum: On the mechanism of cancer induction by ultraviolet radiation, *Journal of the National Cancer Institute,* **11**, 463–495 (1950). The evidence against the somatic mutation hypothesis presented in this paper is derived independently of the author's own hypothesis of progressive acceleration of growth rate, which is also described there.

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