problems. The first one is a factual one: Are the existing theories able to account for all the observed facts? The second one is of a more philosophical nature. Is it scientifically justified to consider in detail a theory of which one is aware that it cannot satisfactorily account for all the data for which it is trying to account? Palmer's answer to both questions seems to be an emphatic "no." Personally, I feel that the answer to the second question should be "yes" and that although the answer to the first question is "no," the situation is not as black as it is pictured by Palmer.

To take the last question first, I feel that only by thoroughly discussing and exploring all possibilities, and thus also the not so very profitable and even the incorrect ones, it is possible to arrive at satisfactory theories. If science is to advance at all, it must needs be by the suggestion and criticism of theories, and it would in my opinion not be in the interest of science, if only "final" theories could be published—even if it were possible to judge prior to publication whether a paper could be considered to give a "final" theory. Palmer's criticism seems therefore to me to be far too severe and to be unscientific.

Regarding the first problem, I fully agree with Palmer that at this moment no completely satisfactory theory exists, and I hope within the near future to give a more detailed account of the reasoning by which I have arrived at this conclusion. However, none of the points raised by Palmer play a role in arriving at this conclusion. His points are mainly concerned with (i) the distribution of angular momentum in the solar system, (ii) the condensation process leading to the planets, (iii) the loss of material from the solar envelope, and (iv) the inclination of the axes of rotation of the outer planets. I do not wish to enter into a detailed discussion at this moment but I may just briefly mention a few points which to my mind are relevant and which seem to have been overlooked by Palmer.

(*a*) The distribution of the angular momentum in the solar system is difficult to understand, but only in as far as the sun is rotating slowly (*2, 3*). It is, however, likely that this problem is not connected with the origin of the solar system, but rather with the more general question of the relation between spectral class and rotation (*4*).

(*b*) If one assumes condensation in the solar envelope to be due completely to supersaturation of part of the constituents (*3, 5*), none of the problems mentioned by Palmer in this connection remains serious.

(*c*) In the discussion of the loss of material from proto-planets or from the solar envelope, Palmer does not seem to take turbulence into account. This would have changed his estimates considerably, as turbulence is probably the most important factor in the development of the solar envelope (*3, 6, 7, 8*).

(*d*) If one takes into account that the height of the solar envelope at the distance from the sun corresponding to Jupiter is at least $10^5$ km (*3, 8*), one sees that the problem of the development of the proto-planets is really three dimensional rather than two dimensional and an inclination of the equatorial plane of the outer planets is no longer such an important problem.

Summarizing, it seems to me that even though no completely satisfactory theory has been developed, the situation has certainly been greatly improved by the publication of various theories such as those of von Weizsäcker (*6*), Kuiper (*8*), and Urey (*9*), to name only a few.

D. TER HAAR

*United College,*
*St. Andrews, Fife, Scotland*

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## The Somatic Mutation Hypothesis of Cancer Genesis[1]

COPIES of SCIENCE issued April 24, 1953, contain an article entitled "A Reconsideration of the Somatic Mutation Theory of Cancer in the Light of Some Recent Developments." No original data are presented and quotations only from selected papers appearing in various journals are included, one dated 1951 and the remaining 33 from previous years. The author, Mr. John C. Fardon, says: "In view of the experimental evidence collected in recent years, 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." With this statement and opinion we most heartily disagree. In support of this contention we wish to call attention first to a later paper by Demerec and coworkers (*1*) which negates the papers by Demerec quoted by Fardon in support of the somatic mutation theory and, second, to personal work (*2–10*) appearing in the literature, reference to which was entirely omitted.

Demerec, Wallace, Witkin, and Bertani (*1*) reported in 1949 that earlier reports on the increased lethal mutation rate in *Drosophila* after administration of carcinogens could not be confirmed. "The variability from experiment to experiment became alarming and only occasionally was it possible to obtain confirmation of previous experiments. The fourth period, encompassing all the past year, has been characterized by uniformly negative results, except in those experiments using nitrogen mustard, methyl-bis

[1] Supported by grants from the National Cancer Institute, U. S. Department of Health, Education, and Welfare.

(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."

WALTER J. BURDETTE

*Department of Surgery*
*Louisiana State University School of Medicine*
*New Orleans, Louisiana*

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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).