Early references to the mutational origin of cancer
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Recently in this journal, Edler and Kopp-Schneider1 reviewed the origins of the mutational theory of cancer focusing mainly on the influential book by Karl Heinrich Bauer2 published in 1928. However, like Bauer, the authors failed to mention some previous papers in which scientists had suggested a possible role of somatic mutations in carcinogenesis. In fact, it was the pathologist Ernest E Tytzer3 (1875–1965) who in 1916 first used the term ‘somatic mutation’ with respect to a tumour. His observations on tumour immunity led him to conclude:

‘From the evidence in the biological character of tumors of a permanent modification of somatic tissue, it appears logical to regard a tumor as a manifestation of somatic mutation. As a basis for this, there may be modification of the relative value either by loss or addition, or in the nature of factors, any of which, if continuously transmitted thereafter in successive cell generations will constitute a type of mutation. […] The tumor […] may be regarded as a modification of the somatic tissue which may be termed somatic mutation’ (italics in the original) pp. 147–51.3

In 1919, two papers published by geneticists further expanded the view of somatic mutations in cancer. Whitman4 considered tumour cells displaying anaplasia as mutated cells; yet, anaplasia was earlier discovered as a hallmark of cancer by David Hansemann.5 Whitman states:

‘Anaplasia produces a cell different from any cell at any time normally present in the body. […] This cell, the cancer cell, is thus a new kind of cell’. In modern terminology it is, strictly and literally, a mutated cell. Since the process is, or at least may be, repeated itself from time to time, and here and there, in a tumor, it follows that the tumor cells themselves are by no means all alike in their biologic properties; that, on the contrary, an ever recurring process of mutation is taking place, with a tendency, however, to deviate more and more from the normal type. This explains why metastatic tumors, for example, are often more, but never less, malignant than the primary tumor, as well as other related phenomena of tumor growth’ (Whitman, 1919, p. 185).

Inspired by, and with reference to, Theodor Boveri6,7 Thomas H Morgan (1866–1945) and Calvin B Bridges (1889–1938)8 remarkably contributed to the discussion as follows (since the source is not available everywhere, the text is given in full).

‘Is cancer a somatic mosaic?

Into the difficult and obscure question as to the cause of cancer it is not our business to enter, but a suggestion made by Boveri (in 1902 and 1914) calls for a brief notice, since he appealed to a process akin to chromosome elimination as a possible explanation of the phenomenon. Boveri suggested that an imperfect or irregular division of the chromosomal complex might in certain cases produce combinations through loss of specific chromosomes that caused the different cells to run wild, so to speak, in the sense that factors that normally inhibit the rate of growth or proliferation of embryology that compression of a dividing cell may interfere with the normal distribution of the chromosomes to the daughter cells. At present, however, reference to such possible sources is too uncertain to be of great value, for there are no instances where irregularities of this kind are known to give rise to prolific growth processes. The cancer-like or tumor-like growth shown by a mutant race of Drosophila, discovered by Bridges and described fully by Stark,9 has not been shown to be associated with abnormal distribution of the chromosomes, although this point has not been sufficiently studied to exclude such a process. On the other hand, it has been shown that the growth in question is caused by a sex-linked Mendelian gene that is inherited strictly, as are all Mendelian sex-linked genes. This mutant lethal race of Drosophila arose as a mutation, presumably in the same way as other mutations. If it is not admissible at present to draw any analogy between this case and that of mammalian cancer, it is conceivable at least that mammalian cancer may be due to recurrent somatic mutation of some gene. Such a conclusion would, however, not invalidate the

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view that cancer is more likely to occur in certain families, or even be inevitable in them, because recurrent mutation in certain genes appears to be more likely than in other genes. But even if this view were maintained, the inheritance would be different in kind from the inheritance of ordinary Mendelian genes, because such a view involves a secondary step, viz, the likelihood of a mutation in a race containing the inherited gene in question. The whole problem of the causes of mutation is at present so obscure that a discussion of this possibility is purely theoretical. Added to this is the uncertainty of how cancer is inherited in those races of mice that appear to produce it with great frequency. Important as the work along these lines unquestionably is, the subject is not yet ripe for any positive statement. It may, nevertheless, be worth while to keep in view the possibility suggested above, viz, that what is inherited in cancer may be a gene or complex of genes in which somatic mutation is of sufficient frequency to give the appearance that a gene for cancer is itself inheritable.8

In his typical style, Morgan10 came back to these considerations a few years later in a book already mentioned by Edler and Kopp-Schneider. He wrote:

‘Suppose, as a theoretical possibility, that spontaneous cancer is due to a recurrent somatic mutation of a specific gene to a dominant one that leads to cancer. Then the proportion of individuals that develop spontaneous cancer in such a strain will depend on the frequency of mutation of this specific gene. [...] I am far from wishing to suggest that spontaneous cancer is a mutational process, despite certain rather obvious resemblances to mutational effects in plants and animals, but I should like to insist that the appearance of spontaneous cancer is in its nature so peculiar that one can not afford to ignore such a possibility in any discussion as to whether spontaneous cancer is or is not “inherited”.10

It must be emphasized that Boveri, in his monograph of 1914, made no mention of mutation or even of gene mutation. The mutational interpretation of his ideas was posthumously added (Boveri died in 1915), essentially by Morgan. In contrast to Boveri, Morgan had early become a proponent of Hugo de Vries’s mutation theory when it was published at the beginning of the 20th century.11 Although the de Vries theory was not able to stand the test of time,11 as was already becoming apparent in 1919, many authors—first and foremost the prominent Morgan—have for decades drawn the attention of cancer researchers in the direction of mutations as major cancer-causing events. Since 1927, after his discovery of the mutagenic activity of X-rays in Drosophila, even Hermann J. Muller (1890–1967),12 previously an early critic of the de Vries theory, suggested somatic mutation as a cause of cancer. In recent years, however, the always controversial somatic mutation theory of cancer has largely lost its attraction.13–15 To the contrary strong evidence in favour of Boveri’s far-reaching ideas concerning cancer causation has accumulated,16–21 leading to an astonishing resurrection of his cancer theory, highlighted, for example, by the editor of Nature:

‘A hypothesis about cancer initiation, first proposed nearly a century ago, has stood the test of time. German biologist Theodor Boveri suggested that a failure of cell division might produce tetraploid cells (containing a double chromosome quota) that then undergo multipolar mitosis, leading to genome instability that can trigger cancer’.22

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References