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## **Boveri and cancer: prescient views of molecular mechanisms**

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ESSAY REVIEW

BOVERI AND CANCER: PRESCIENT VIEWS OF MOLECULAR  
MECHANISMS

by

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Sir Henry Harris (transl. and annot.), *Concerning the Origin of Malignant Tumours* by Theodor Boveri. The Company of Biologists Limited and Cold Spring Harbor Laboratory Press, 2008. Pp. vi + 89, \$24 (paperback). ISBN 978-087969788-4.

This is much more than a new edition of Boveri's monograph. Henry Harris's authoritative new translation has reawakened a sleeping giant, but perhaps as importantly his incisive subscript comments break new ground in how to present and interpret older literature. Harris's translation and annotation reminds us of the power of the monograph form itself: the power of logical thought and sieving of evidence resulting in speculation from a single author on a specific, important topic with wide implications. This form of publication has almost disappeared from the biomedical sciences literature. Moreover, the word speculation has become a negative; a derogatory term used by reviewers and journal editors to decline or shorten publications.

In these respects this is a bipartite review. It has to deal with both the Boveri monograph and the Harris translation and annotation. It is a review of two books—one within the other, like a pair of Russian dolls—Boveri and Harris.

Boveri produced this monograph in Germany in 1914, one year before his death. It was only in 1929 that his widow, Marcella Boveri, an American, translated it.

The thesis within the monograph is defined in the introduction—the first of six chapters in 82 pages—as a further, in-depth, analysis of a speculation that Boveri had made in a 1902 publication—'that malignant tumours might be the consequence of a certain abnormal chromosome constitution, which in some circumstances can be generated by multipolar mitoses.'

Boveri's introductory chapter sets out the landscape in clearly defined language. He explains his lack of clinical training and the fact that he comes at this problem as a zoologist, basing much of his thought on studies of normal and abnormal chromosome behaviour in sea urchins. Boveri draws distinctions between benign and malignant tumours and declares malignancy to be a cellular phenomenon. The introduction contains some real gems. On page 9 Boveri defines malignancy as involving a loss of cellular function and not a gain-of-function phenomenon. It is in this section that the power of Harris's translation and annotation shows through. Harris is an individual of wide accomplishment—not only in science but also in writing about science and scientists. Still

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active in Oxford as a Regius Professor of Medicine Emeritus, Harris has many scientific achievements to his credit including some, such as use of cell fusion assays to define tumour suppressor activity, that speak directly to Boveri's topics of discussion.

However, Harris is also an accomplished author who has written extensively on scientists, science in general and cell science in particular. It is in this introduction that Harris lays the groundwork for this most successful publishing venture. His translation is clear, careful and uncomplicated. The venture is massively enhanced by his series of footnotes and the manner in which they are displayed. At central points in the manuscript Harris, and his publishers, the *Journal of Cell Science*, have inserted a small footnote reference number in parentheses. This relates to a footnote placed at the bottom of that page in which Harris draws attention to either the historical context of a statement by Boveri or places its importance, and often its priority, in terms of our modern molecular understanding of cancers or chromosome biology. A key feature is that the footnote reference number and the footnote are in red. This simple device is stunningly successful. It sets Harris's modern footnote additions aside from the original Boveri text yet integrates them beautifully into the narrative. Harris should also be applauded for using this device sparingly. There are only 60 short footnotes in the whole translation. They make a stunning addition for the expert and non-expert.

An early example of the power of the footnote comes in numbers 8 and 11, where Harris puts Boveri's views of malignancy as a loss-of-function phenomenon into context and rehearses the modern discoveries (some by Harris himself) that provided evidence for such phenomena being characterized by tumour suppressor genes.

In chapter 2 Boveri rehearses chromosome biology, often from his underpinning experimental cytology observations. Boveri's own work was very much focused on sea urchins, and there is little doubt that he would have been delighted to have observed how big a role these animals, and other model systems such as the yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*, played in enabling talented researchers in the last 25 years of the twentieth century to unravel the molecular events of normal and abnormal control of the cell cycle.

The prose is precise, clear and simple with few technical words and is therefore very refreshing to read. Boveri is careful to rehearse caveats and to be precise that he viewed aneuploidy itself as being an important requisite but not the cause in itself. His argument that chromosome variability greatly increased the probability that cancer, a rare and stochastic event, might occur is again placed in context by Harris in footnote 15. These arguments are still being played out today. It is this high current interest in molecular explanations of early tumour events that makes this monograph translation and annotation so timely. Harris's positioning of Boveri's comments both in their historical perspective and prescient insight makes the monograph required reading for all young cancer biologists.

Chapter 2 then moves on to apply his chromosomal biology insights to the study of tumours. Again, this chapter contains some gems, and Harris picks them for small insightful notes. Two small examples suffice: Boveri clearly believed in an underlying biology of chromosomal behaviour: what can be learned from lower organisms will apply to vertebrates. Second, he prophesied the arrangement of a large number of Mendelian genes aligned along a chromosome in a specific order.

The chapter reviews chromosomal abnormalities in the context of tumours and ends with clear statements of his views on their importance and positional timing in the journey to malignancy.

Chapter 4 is a major part of the monograph and Boveri rehearses the explanatory value of his hypothesis. He focuses on arguments that support his views ‘particularly well’ or seem to ‘contradict it’. The debate here encompasses views of the malignant defect as a nuclear event; hereditary and spontaneous cancers; characteristics of individual tumours; individual chromosomes determining different metabolic reactions; the influence of a cancer cell on its environment; and the influence of the age of the cell or organism on cancer development. Clearly, Boveri often thinks in terms of chromosomes and not of mutations in genes on chromosomes. Again, it is in this chapter where Harris’s footnotes make a big impact in placing Boveri’s comments in their historical context, particularly with regard to the concept of the gene and gene mutation. They also serve to emphasize the importance of small statements—for example, individual chromosomes being damaged by chemical treatments, randomness of damage and the two-hit model of tumorigenesis.

The current topicality and timeliness of this nearly 100-year-old essay are not in doubt. But again, to emphasize this point, Harris draws out the similarity of the current debate on pluripotent stem cells and Boveri’s coverage of the possibilities of embryonic remnants (‘embryonale Reste’) having a role in some malignancies.

Chapter 5 is shorter and deals with a ‘consideration of some objections’ to his hypothesis. Here Boveri often challenges the lack of rationality and stringency in the interpretation of cytological observations by certain individuals and professors! Harris makes some nice supportive remarks here that many will agree with.

Chapter 6 is the conclusion and gives a brief review of the sequence of ideas within it and the hypothesis on malignant tumours and abnormal chromosome constitution.

In summary, therefore, this is an excellent contribution by Henry Harris. It will make Boveri’s thoughts and analysis available to a wide readership. It brings insight and context to Boveri’s writing. As rehearsed earlier, it is an excellent read and one that every young cancer biologist should be familiar with. In passing, one might observe that it would make an excellent subject for a journal club series in a research group or an excellent term reading paper for an undergraduate course. It has the power to make people think clearly about basic concepts and detailed evidence in cancer biology. The layout, presentation and Harris’s footnotes are hugely complementary. The book is also a reminder that we have rather lost the short, single-author monograph. The thoughtful, reflective interpretations of a good mind can do a lot to advance a research field. Currently we are rather mired in a sea of original literature rehearsed within large numbers of reviews that are neither opinionated, integrative nor speculative. Science and scientists seem to be working for the publishing industry rather than the other way around. This small publication was important when it was first published early in the previous century. This excellent new version is timely in many ways and could become a paradigm for the first part of this century.