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Abstracts from the 3rd Conference on Aneuploidy and Cancer: Clinical and Experimental Aspects

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Overview of the 3rd Conference on Aneuploidy and Cancer in Berkeley, CA, USA in 2017

(Organized by Peter Duenberg, Department of Molecular and Cell Biology, University of California at Berkeley and David Rasmick, Oakland CA; sponsored by philanthropist Robert Leppes, San Francisco CA USA) Ashel Comish-Bowden (acomish@imm.cmr.uio.no)
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David von Hanseemann noticed in 1890 that all of the cancer cells that he examined were aneuploid and suggested that the aneuploidy might be the cause of the cancer [1]. Based on Hanseemann's observations and his fundamental discovery that individual chromosomes have different genetic functions, Theodor Boveri advanced the first genetic cancer theory in 1914: cancer is caused by the loss of specific growth inhibitory or the gain of specific growth stimulatory chromosomes [2]. For half a century this remained the prevailing genetic theory of cancer, despite strong opposition from Thomas Morgan, who considered that no instances of chromosomal faults were known to give rise to uncontrolled growth of cells [3]. After the causative agent of Peyton Rous's chicken sarcoma was discovered to be a retrovirus that inserted an oncogene into the host genome [4], many cancer researchers discarded the aneuploidy theory, considering the dispute to be resolved in favor of oncogenes and viruses. Since then the field has been dominated by the view that cancer is caused by virus-related or virus-unrelated cellular oncogenes.

The difficulty that many researchers had with the chromosomal or aneuploidy theory was that no consistent stimulatory or inhibitory chromosomes could be found in cancers. As a result Boveri's theory seemed to be stranded on the same reef that prevented the theory of continental drift from being accepted by geophysicists, even though the close fit between Africa and South America had been obvious to anyone who looked at a world map since sufficiently accurate maps became available. In the absence of a credible mechanism, the hypothesis was rejected by most geophysicists, and the fact that Alfred Wegener had no recognized expertise in geophysics doubtless contributed to the skepticism. (Actually, Benjamin Franklin suggested a plausible mechanism similar to the modern theory of plate tectonics as long ago as 1782 [5]).

Returning to cancer, there are also serious difficulties with the oncogene theory. The number of cells in the human body is so large, and the frequency of random mutations in somatic cells is so high, that it is certain that any conceivable oncogene, in its supposedly oncogenic state, is already present in every person, but does not lead to cancer. Such difficulties tend to be brushed aside, just as Wegener's evidence for continental drift was brushed aside

in favor of supposed land bridges that had disappeared. The second problem with oncogenes is that overexpression of single genes almost never has any metabolic effects, and under-expression usually has only minor effects. That is why about 85% of mutations in, say, yeast, are "silent" [6, 7]; eliminating them from the genome usually produces no change in phenotype. When "knock-out mice" first became available [8] it was expected that the function of any gene could be revealed by observing the effect of eliminating it, but most such experiments led to disappointment. When a mouse completely lacks a protein such as myoglobin, which has a well-understood function in muscles, it can remain healthy, even when exercised [9].

The almost negligible effects of altering the activities of single genes can be easily understood in terms of metabolic control analysis, an approach to metabolic regulation introduced by Henrik Kacser and Jim Burns in 1973 [10]. Before then, and for considerable time afterwards, because the new ideas did not become immediately accepted, it was assumed that each metabolic pathway had a "key enzyme" or "rate-limiting enzyme", and that altering the activity of this enzyme would alter the flux through the pathway in proportion. Kacser and Burns realized, even before many experimental tests were available, that that could not be correct: flux control is shared between all of the enzymes in the system, and if the system is taken to be a whole cell or a whole organism, this means that most shares must be very small, so that altering a typical enzyme activity should have little or no effect. When techniques for genetic manipulation became available, Jürgen Heinrich and colleagues overexpressed phosphofructokinase (widely regarded as the key enzyme in fermentation) in yeast by a factor of 3.5, and observed no effect on the flux to ethanol [11]. This contradicted what was widely expected, but it was not a surprise for people who had understood the principles of metabolic control analysis.

The expectation of no effect, however, is the expectation of what will happen when the activity of a single enzyme is altered. But aneuploidy alters the activities of many enzymes at a time, and the analysis is not so simple. Even in Down syndrome, with fewer than 2% of genes affected by trisomy of the smallest chromosome, the effects are not negligible. Cancer cells are far more aneuploid than those of Down syndrome patients; for example, colon cancer produces cells in which many chromosomes are triploid, some are tetraploid, and some are damaged. This is a vastly larger perturbation than trisomy of one small chromosome, and altering the activities of a vast number of enzymes must inevitably create large metabolic disturbance. Down syndrome illustrates the severe effects that even a minimal degree of aneuploidy can produce, but people who believe that changing a single enzyme activity, or a small number of activities, can lead to cancer need to explain why Down syndrome patients are as normal as they are when they have hundreds of genetic alterations.

Fundamentals Of Electricity For Agriculture An Asae Textbook

**Amitava Rakshit, Harikesh Bahadur
Singh, Avijit Sen**



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