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EDITORIAL

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Chromosomes and cancer: Theodor Boveri's predictions 100 years later

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Boveri's contributions to clear thinking on cancer ranks closely to Mendel's contribution to clear thinking on genes.

Ruth Sager, 1983 [1]

A hundred years ago was an exciting time for researchers investigating chromosomes. Refined coloring techniques allowed previously unknown details in the interior of cells to become visible. In addition, Mendel's experiments were rediscovered in 1900. On both sides of the Atlantic, Walter Sutton, Theodor Boveri, and William Bateson conducted competitive experiments which led very quickly to a general theory of chromosomal inheritance. Within a few years the foundations were laid for a new discipline, which was named "genetics," following Bateson's suggestion in 1907. Boveri, who had been a professor of zoology in Würzburg, Germany, since 1893, played a crucial role in these developments by his exceptional ability to integrate different areas of research (Table 1).

As a model for his experiments Boveri used sea urchin eggs. In 1902 he published some of his important results in his seminal work, "On Multipolar Mitosis as a Means of Analysis of the Cell Nucleus" [2, 3]. This work on the development of double-fertilized sea urchin eggs (for a description in present-day terms see [4]) concluded with the surprising hypothesis that malignant tumors could be the result of an abnormal chromosome constitution caused by multipolar mitosis which leads to "out-of-balance cells" with a cancer-like phenotype. Since this view was treated skeptically by cancer researchers, Boveri decided to present his ideas in detail in his 1914 publication "About the Question of the Origin of Malignant Tumors" [5]. This was to be his last publication, as he died less than a year later. While the original German version was soon forgotten, the translation of his paper, arranged by his widow Marcella O' Grady Boveri (1863–1950) [6], received limited attention when it was published in 1929. It was only after 1970 that the publication began to receive increasing attention. However, it is doubtful whether an increased citation rate indicates that his study is read today. The richness of Boveri's thought can only be tapped by the "diligent" reader.[1]

Before Boveri, David von Hansemann (1858–1920) had described changes in the chromosomes of cancer cells [7, 8]. Boveri, however, who had seen similar aberrations in double-fertilized sea urchin eggs, went far beyond simple observation – he attempted to bring together findings from different research areas. He developed the first *genetic* theory for the cause of cancer strictly on the basis of chromosome anomalies [2, 3, 6]. This consisted of numerous partial theories and explicit predictions which were experimentally verified only many years later, but which in most cases have proven to be astonishingly correct (Table 2). Today, with hindsight, we can see that Boveri had not only expressed several ideas that were advanced for their time, but he was also the architect of a large "virtual" building based on many of the essential pillars of our present knowledge of cancer, which he had already suggested. In cancer research the paradigm shift in genetics which he had anticipated actually took place in 1970 [9]. However, the first model for the study of genetic factors in cancer, the Gordon-Kosswig fish melanoma system, had been established as far back as 1927 [10].

It is now routine to include the very common occurrence of chromosome aberrations associated with human tumors. The catalog by Felix Mitelman first published in 1983 now covers more than 30,000 cases [11, 12]. It is

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[1] This refers to the statement by the German poet, G.E. Lessing, on the works of his poet friend F.G. Klopstock, in *Sinngedichte* (1753): "Wer wird nicht einen Klopstock loben? / Doch wird ihn jeder lesen? – Nein / Wir wollen weniger erhoben / und fleißiger gelesen sein." ("Who would not wish to honor a man like Klopstock? / But who is reading him these days? No one / We need to honor men like him less / and read them more.")

Table 1 Early milestones in chromosome research (adapted from [23])

1869	Discovery of nucleic acids	Friedrich Miescher (1844–1895)
1876	Discovery of centrosomes	Edouard van Beneden (1845–1910) (named 1888 by Theodor Boveri)
1877	Discovery of chromatin	Walther Flemming (1843–1905)
1882	First use of the term "mitosis"	Walther Flemming
1883	Discovery of chromosomes	Edouard van Beneden (named 1888 by Wilhelm Waldeyer, 1836–1921)
1885	Transfer of a nuclear substance with a specific molecular structure essential for transmission	August Weismann (1834–1914)
1892	Chromosomal sets of maternal and paternal nuclei are equivalent	Theodor Boveri (1862–1915)
1901	Proof of chromosomal division at meiosis (the term "meiosis" was coined in 1905)	Thomas H. Montgomery (1873–1912)
1902–1903	Chromosomes are carriers of hereditary determinants	Walter S. Sutton (1877–1916) Theodor Boveri
1902–1904	Discovery of chromosomal individuality; proof of chromosomal continuity	Theodor Boveri
1904	First use of terms "allele," "homozygous," "heterozygous"	William Bateson (1861–1926)
1905	Discovery of sex determination by chromosomes	Nettie M. Stevens (1861–1912)
1909	First use of the term "gene," "genotype" vs. "phenotype"	Wilhelm Johannsen (1857–1927)
1911	First assignment of a gene to a specific chromosome	Edmund B. Wilson (1856–1939)
1911	Linear arrangement of genes on chromosomes First gene linkage analysis	Thomas H. Morgan (1866–1945) Arthur H. Sturtevant (1891–1970)

Table 2 A centenary review of Boveri's predictions (1902, 1914)

Boveri's prediction (page reference in [5])	First experimental verification: by year and author(s)	Prediction viewed by present-day knowledge or described in current terminology
Numerical chromosome imbalance (a mutational event) at the root of cancer (aneuploidy) (p 14, 18)	1927: H.J. Muller[b]; Radiation increases the rate of mutations [24] 1960: P.C. Nowell, D. Hungerford, Philadelphia chromosome [27] 1974: L.A. Loeb et al., Mutator phenotype [28] 1998: C. Lengauer et al. [17]	Somatic mutations initiate cancer: 1916 E. Tyzzer [25]; 1928 K.H. Bauer [26] Chromosomal abnormalities are common to human tumors Increase in mutation rate is an early event in tumorigenesis Aneuploidy: a driving force in cancer?
Cancer cells arise from normal cells (p 3)	1999: W.C. Hahn et al. [29]	Malignant transformation of human cells by specific gene combinations
Teilungsfoerdernde Chromosomen (growth stimulating chromosomes[a]) (p 14)	1976–1982: D. Stehelin, H.E. Varmus[b],] J.M. Bishop[b], P.K. Vogt [30	Proto-oncogenes and oncogenes
Growth stimulating chromosomes[a] may be amplified during tumor progression (p 16)	1983: M. Schwab et al. [31]	Homogeneously staining regions, double minutes
Teilungshemmende Chromosomen (growth inhibitory chromosomes[a]) (p 14)	1942: D.R. Charles, E.M Luce-Clausen [32] 1969–1982: H. Harris et al. [33]; A.G. Knudson [34]; E. Stanbridge et al. [35]	Tumor suppressor genes
Growth inhibitory chromosomes[a] may be lost in tumor progression (p 18)	1983: W.K. Cavenee et al. [36]	Loss of heterozygosity
Cancer susceptibility through inheritance of predisposing chromosomes[a] (p 29)	1986: S.H. Friend et al. [37]	Retinoblastoma as a prototype of familial cancer syndromes
Inhibitory mechanisms whose removal is required for unlimited proliferation (p 5)	ca. 1973–1990: L.H. Hartwell[b] et al. [38]; A.B. Pardee [39]; P. Nurse[b], Y. Bisset [40]; T. Hunt[b] [41]; T. Weinert, L.H. Hartwell [42], S. Mittnacht, R.A. Weinberg [43], others	Cell-cycle checkpoints which are deregulated in cancer
"*Ur*-cells" (first cells) of the tumor (p 22)	Circumstantial evidence, not yet identified	Cancer stem cells
Unicellular origin of tumors (p21)	1967: P.J. Fialkow et al. [44]	Clonal origin of tumors
Gradual changes in characters during tumor progression (p 32)	1954: L. Foulds [45] 1976: P.C. Nowell [46]	Clonal evolution of tumors
Causation of malignant tumors usually occurs in two stages which can be separated by long intervals of time (p 35)	1941: I Berenblum [47]; P. Rous, G. Kidd [48]	Two-stage mechanism, tumor initiation, tumor promotion

Table 2 (continued)

Boveri's prediction (page reference in [5])	First experimental verification: by year and author(s)	Prediction viewed by present-day knowledge or described in current terminology
The role of cell regeneration in tumorigenesis (p 36)	1922: H.T. Deelmann [49]	First stage of tumor promotion
"Lottery-like" nature of cancer causation (p 43)	1954: P. Armitage, R. Doll [50]	Stochastic models of carcinogenesis
Aberrant activity of centrosomes in tumors (p 19, 37)	1996: K. Fukasawa et al. [51]	Centrosome hypertrophy is linked to genomic instability and cell polarity of tumors
Age-dependent weakness of specific chromosomes with respect to mitotic control (p 30)	1990: N.D. Hastie et al. [52] 2001: D. Gisselsson et al. [53]	Shortening of telomeres at the end of chromosomes; telomere crisis and cancer
Permanent irreparable defect in cancer cells (p 20)	1968: J.E. Cleaver [54]	Defective DNA repair as important cancer predisposing factor
Interaction of tumor with surrounding tissue (p 23)	1999: A.F. Olumi et al. [55]	Functional role of stroma in tumor development

[a] If one puts "genes" in the place of "chromosomes," the relationship to proto-oncogenes or tumor suppressor genes becomes obvious
[b] Nobel prize winning discoveries (1946: Muller; 1989: Bishop, Varmus; 2001: Hartwell, Nurse, Hunt)

hard to imagine clinical research and the treatment of patients today without such data. With the advent of cancer genomics and high throughput technologies, whole genome detection of chromosomal gains and losses at high resolution is now possible using the array comparative genomic hybridization technique [13].

Recently centrosomes, which were once regarded by Boveri as the organelles of the cell, have again become a focus of interest. Their function concerns not only the organization of microtubules, as had been assumed until now. They also appear to play a key role in the cell cycle [14]. Many tumors contain superfluous centrosomes instead of the usual one or two in normal diploid cells [15, 16]. Boveri had suspected a mistake in the multiplication of the centrosomes as the cause of chromosome aberration in malignant cells (Table 2). Chromosomal imbalance (aneuploidy) was long considered an epiphenomenon associated with the formation of tumors. This is the most common manifestation of genomic instability, a hallmark of cancer. Recently there have been a increasing number of indications that aneuploidy is an early event, which could even be a driving force in cancer development [17, 18]. It is possible that it is a direct result of centrosome amplification [18]. Molecular scenarios for the origin of centrosome hypertrophy have been developed [15].

In light of the current discussion on stem cells [19], Boveri's comments on the "*Ur* -cells" of tumors is of particular interest. "As a consequence of an abnormal process," these cells possess "an incorrect combination of the chromosome constitution." "Above all, this is the cause of uncontrolled growth tendencies which are passed on to the daughter cells of the *Ur*-cells formed from regular mitosis splitting" [5]. Today, although definitive confirmation of cancer stem cells ("rare cells with indefinite potential for self-renewal which drive tumorigenesis" [19]) is still lacking, it appears entirely possible that, here too, Boveri was very close to the actual truth.

It is not possible to cover individually every prediction found in Table 2 in this essay. Many predictions concern problems which were at the very heart of cancer research in the twentieth century (see [20, 21, 22]. Some recent high points involve the discovery of the nature and function of "cancer genes" (proto-oncogenes, tumor suppressor genes), the cell cycle, the biology of telomeres, and cell-cell interactions, both functioning and nonfunctioning, in cancer cells. Many of these themes can be found in Boveri's writings.

Unlike his contemporaries, Boveri believed that the phenomenon of cancer was strictly a biological problem. He was therefore in the position to recognize very early on the potential use of genetics, a field which he helped develop, to help us understand cancer. As Boveri never worked with tumors or tumor cells, he considered himself as a person who looked on the cancer problem from the outside [5, 6]. Nevertheless, his impressive intuition and imagination, which are more apparent today than ever before, proved very helpful.

References

1. Sager R (1983) Genomic rearrangements and the origin of cancer. In: German J (ed) Chromosome mutation and neoplasia. Liss, New York, pp 333–346
2. Boveri T (1902) Über mehrpolige Mitosen als Mittel zur Analyse des Zellkerns. Verh Phys Med Gesellschaft Würzburg 35:67–90
3. Boveri T (1964) On multipolar mitosis as a means to analyse the cell nucleus. In: Willier BH, Oppenheimer J (ed) Foundations of experimental embryology. Prentice-Hall, New York (English translation of ref 2)
4. Surridge C (2001) Nature milestones: chromosomes to the fore http://www.nature.com/celldivision/milestones/full/milestone01.html
5. Boveri T (1914) Zur Frage der Entstehung maligner Tumoren. Fischer, Jena
6. Boveri T (1929) The origin of malignant tumors. Williams and Wilkins, Baltimore; Baillière, Tindall & Cox, London

7. Hansemann D von (1890) Über asymmetrische Zelltheilung in Epithelkrebsen und deren biologische Bedeutung. Virchows Arch Pathol Anat 119:299–326
8. Hansemann D von (1906) Über pathologische Mitosen. Virchows Arch Pathol Anat 123:356–370
9. Bishop JM (1995) Cancer: the rise of the genetic paradigm. Genes Dev 9:1309–1315
10. Anders F (1991) Contributions of the Gordon-Kosswig melanoma system to the present concept of neoplasia. Pigment Cell Res 3:7–29
11. Mitelman F, Johansson B, Mertens F (1998) Catalog of chromosome aberrations in cancer, 5th edn. CD-ROM version with annual updates. Wiley, New York
12. Anonymous (2002) Mitelman database of chromosome aberrations in cancer. Mitelman F, Johansson B, Mertens F (eds) http://cgap.nci.nih.gov/Chromosomes/Mitelman
13. Weber BL (2002) Cancer genomics. Cancer Cell 1:37–47
14. Doxsey S (2001) Re-evaluating centrosome function. Nat Rev Mol Cell Biol 2:688–698
15. Brinkley BR (2001) Managing the centrosome numbers game: from chaos to stability in cancer cell division. Trends Cell Biol 11:18–21
16. Marx J (2001) Cell biology. Do centrosome abnormalities lead to cancer? Science 292:426–429
17. Lengauer C, Kinzler KW, Vogelstein B (1998) Genetic instabilities in human cancers. Nature 396:643–649
18. Lingle WL, Barrett SL, Negron VC, D'Assoro AB, Boeneman K, Liu W, Whitehead CM, Reynolds C, Salisbury JL (2002) Centrosome amplification drives chromosomal instability in breast tumor development. Proc Natl Acad Sci USA 99:1978–1983
19. Reya T, Morrison SJ, Clarke MF, Weissman IL (2001) Stem cells, cancer, and cancer stem cells. Nature 414:105–111
20. Schwab M (ed) (2001) Encyclopedic reference of cancer. Springer, Berlin Heidelberg New York
21. Balmain A (2001) Cancer genetics: from Boveri and Mendel to microarrays. Nat Rev Cancer 1:77–82
22. Wunderlich V (2002) Krebs – von Hippokrates bis zur molekularen Medizin. Einige wichtige Etappen auf einem langen Weg. In. Ganten D, Ruckpaul K (eds) Molekularmedizinische Grundlagen von nicht-hereditären Tumorerkrankungen. Springer, Berlin Heidelberg New York, pp 405–425
23. Jahn I (1990) Grundzüge der Biologiegeschichte. Fischer, Jena
24. Muller HJ (1927) Arteficial transmutation of the gene. Science 66:84–87
25. Tyzzer EE (1916) Tumor immunity. J Cancer Res 1:125–155
26. Bauer KH (1928) Mutationstheorie der Geschwulstentstehung. Springer, Berlin
27. Nowell PC, Hungerford DA (1960) A minute chromosome in human chronic granulocytic leukemia. Science 132:1497
28. Loeb LA, Springgate CF, Battula N (1974) Errors in DNA replication as a basis of malignant changes. Cancer Res 34:2311–2321
29. Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW, Weinberg RA (1999) Creation of human tumour cells with defined genetic elements. Nature 400:464–468
30. Stehelin D, Varmus HE, Bishop JM, Vogt PK (1976) DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. Nature 260:170–173
31. Schwab M, Alitalo K, Varmus HE, Bishop JM, George D (1983) A cellular oncogene (c-Ki-ras) is amplified, overexpressed, and located within karyotypic abnormalities in mouse adrenocortical tumour cells. Nature 303:497–501
32. Charles DR, Luce-Clausen EM (1942) The kinetics of papilloma formation in benzpyrene-treated mice. Cancer Res 2:261–263
33. Harris H, Miller OJ, Klein G, Worst P, Tachibana T (1969) Suppression of malignancy by cell fusion. Nature 223:363–368
34. Knudson AG (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 68:820–823
35. Stanbridge EJ, Flandermeyer RR, Daniels DW, Nelson-Rees WA (1981) Specific chromosome loss associated with the expression of tumorigenicity in human cell hybrids. Somatic Cell Genet 7:699–712
36. Cavenee WK, Dryja TP, Phillips RA, Benedict WF, Godbout R, Gallie, BL, Murphree AL, Strong LC, White RL (1983) Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. Nature 305:779–784
37. Friend SH, Bernards R, Rogelj S, Weinberg RA, Rapaport JM, Albert DM, Dryja TP (1986) A human segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 323:643–646
38. Hartwell LH, Mortimer RK, Culotti J, Culotti M (1973) Genetic control of the cell cycle in yeast. V. Genetic analysis of cdc mutants. Genetics 74:267–286
39. Pardee AB (1974) A restriction point for control of normal animal cell proliferation. Proc Natl Acad Sci USA 71:1286–1290
40. Nurse P, Bisset Y (1981) Gene required for G1 for commitment to cell cycle and in G2 for control of mitosis in fission yeast. Nature 292:558–560
41. Evans T, Rosenthal ET, Youngblom J, Distel D, Hunt T (1983) Cyclin: a protein specified by maternal mRNA in sea urchin eggs that is destroyed at each cleavage division. Cell 33: 389–396
42. Weinert T, Hartwell L (1989) The RAD9 gene controls the cell cycle response to DNA damage in Saccharomyces cerevisiae. Science 241:317–322
43. Mittnacht S, Weinberg RA (1991) G1/S phosphorylation of the retinoblastoma protein is associated with an altered affinity for the nuclear compartment. Cell 65:381–393
44. Fialkow PJ, Najfeld V, Reddy AL, Singer J, Steinmann L (1978) Chronic lymphocytic leukaemia: clonal origin in a committed B-lymphocyte progenitor. Lancet 2:444–446
45. Foulds L (1954) Tumor progression: a review. Cancer Res 14:327–339
46. Nowell PC (1976) The clonal evolution of tumor cell populations. Science 194:23–28
47. Berenblum I (1941) The cocarcinogenic action of croton resin. Cancer Res 1:44–48
48. Rous P, Kidd JG (1941) Conditional neoplasms and subthreshold neoplastic states. J Exp Med 73:365–389
49. Deelmann HT (1922) Die Entstehung des experimentellen Teerkrebses und die Bedeutung der Zellregeneration. Z Krebsforsch 21:220–226
50. Armitage P, Doll R (1954) The age distribution of cancer and a multi-stage theory of carcinogenesis. Br J Cancer 8:1–12
51. Fukasawa K, Choi T, Kuriyama R, Rulong S, Vande Woude GF (1996) Abnormal centrosome amplification in the absence of p53. Science 271:1744–1747
52. Hastie ND, Dempster M, Dunlop MG, Thompson AM, Green DK, Allshire RC (1990) Telomere reduction in human colorectal carcinoma and with ageing. Nature 346:866–868
53. Gisselsson D, Jonson T, Petersen A, Strombeck B, Dal Cin P, Hoglund M, Mitelman F, Mertens F, Mandahl N (2001) Telomere dysfunction triggers extensive DNA fragmentation and evolution of complex chromosome abnormalities in human malignant tumors. Proc Natl Acad Sci USA 98:12683–12688
54. Cleaver JE (1968) Defective repair replication of DNA in xeroderma pigmentosum. Nature 218:652–656
55. Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR (1999) Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. Cancer Res 59:5002–5011