Commentary on Sandberg et al., “The In Vivo Chromosome Constitution of Marrow”

Bayard D. Clarkson

See related article by Sandberg et al., Cancer Res 1961;21:678-89.

German pathologists in the late nineteenth century appear to have been the first to publish observations of mitotic abnormalities in many types of human cancers and to suggest that they might have an important role in their pathogenesis (1). About two decades later, Theodore Boveri published his famous monograph (2) on the basis of his meticulous studies of mitotic abnormalities in sea urchins. Boveri hypothesized that mammalian tumors might be initiated by mitotic abnormalities, resulting in changes in the numbers of chromosomes in cells, called aneuploidy, that tumors might originate in a single cell, and that there might be causative submicroscopic genetic alterations not involving entire chromosomes. However, proof of these clairvoyant hypotheses had to wait several more decades for technological improvements in the resolution of chromosome analysis, including determining that the correct number of human chromosomes is 46 rather than 48 as had been proposed and widely accepted earlier (3, 4). The first human tumor clearly shown to have a consistent chromosomal abnormality, a minute chromosome, was chronic myelogenous leukemia (CML). The approximate 4-fold increased incidence of leukemia in mongols had been published earlier in 1956, and they speculated that the characteristic “trisomy G22 mutation” is probably a predisposing factor for development of leukemia. They also compared their findings with all the published cytogenetic reports then available. Overall, they found a higher incidence of aneuploidy (56.4%) in the leukemic marrow cells (56.4) than in the control (12.2%) marrows, with the highest incidence (77%) in ALL. Two of the treated aneuploid ALL patients who had marrow smears during hematologic remission had “almost normal” diploid chromosome counts, probably one of the first observations of cytogenetic remissions. They also observed in nine leukemic marrow samples processed both immediately after aspiration and after 10 hours of incubation that the percentage of diploid metaphases increased from 59% to 84%, suggesting that the presumably normal diploid cells resumed dividing before the “less adaptable” aneuploid, presumably leukemic cells. Almost nothing was known in 1960 about differences in the cytokinetic behavior of normal and leukemic cells, but their prescient observation that normal cells might enter mitosis faster than leukemic cells foreshadows later more extensive and detailed cytokinetic studies showing that acute leukemic stem/progenitor (S/P) cells almost always proliferate considerably slower than normal hematopoietic S/P cells (10).

In confirmation of other reports, 9 of 10 patients with AML studied at Roswell Park had “more or less pronounced normal modes at 46 chromosomes.” At the time, there was a fair amount of controversy about whether chromosome changes had any role in initiation of tumors, although most observers acknowledged that changes might contribute to tumor progression. However, the Roswell Park scientists presciently noted that it was difficult to define where “initiation ends and progression begins.” They also found no consistent karyotypic pattern in the different types of leukemia, treated or untreated or in remission or relapse, one of the earliest observations about the heterogeneity of human leukemias and other cancers. Interestingly, in the eight CML patients studied at Roswell Park, three were apparently in blastic phase and had aneuploid model karyotypes, whereas five apparently chronic phase CML patients had 46 chromosomes. Surprisingly, there is no mention of their observing the minute chromosome in the CML marrows that Nowell and Hungerford had consistently found in their seven CML patients and that was referenced in the Roswell Park article. This omission is probably because the authors were primarily focused on studying aneuploidy rather than paying attention to Nowell’s key finding, a common fault if the sole focus is overly concentrated on a single parameter. (In a follow-up article in 1966, Sandberg did acknowledge the Ph1 chromosome’s consistency and importance in CML; ref. 11).
Consistent with Boveri’s concept (2), they concluded that “the existence of leukemias without any recognizable departure from the diploid somatic constitution of the species clearly eliminates gross karyotypic changes as a necessary precondition of neoplasia,” another observation that has proved to be correct.

These careful observations and conclusions reported in 1961 of the largest study and survey of leukemia cytogenetics then conducted of course may seem rather naïve and unsubstantial in today’s light, but the experiments were performed with the best technology and procedures then available, and the authors could not possibly have foreseen all of the technological and conceptual advances that were going to take place in the evolution of cytogenetics and other discoveries during the next half century (12). It was another 13 to 24 years before Janet Rowley demonstrated that the Ph chromosome resulted from a translocation between chromosomes 9 and 22 (13, 14), and a few more years before the fusion genes were identified as the v-abl Abelson murine leukemia viral oncoprotein homolog (ABL) on chromosome 9 and the breakpoint cluster region (BCR) on chromosome 22 (15). The product of the BCR–ABL fusion gene was not shown to be a constitutively active tyrosine kinase (TK) responsible for the sustained hyperproliferation of Ph+ S/P cells until 1990 (16), and it then took another 10 years before the structural mechanism responsible for the specificity of imatinib’s and other TK inhibitors’ (TKI) inhibition of the tyrosine kinase domain of c-abl was demonstrated (17, 18). The clinical efficacy of imatinib in CML was first reported about the same time (19, 20). Whereas imatinib and subsequently even more potent inhibitors of BCR/ABL have greatly improved survival in the chronic phase CML and delayed or prevented blastic transformation, these TKIs are usually not curative and have only limited usefulness in blastic phase CML. An even more dramatic example of the importance of identifying specific chromosomal rearrangements was Rowley’s discovery of the t(15;17) translocation in acute promyelocytic leukemia in 1977, which eventually led to discovery of the driving PML/RARα transcript and fusion protein and the near universally curative therapy with all trans-retinoic acid and arsenic trioxide, which, in turn, may eventually lead to inspired new and more correct concepts. So not only do the primary paramount scientists such as the Roswell Park cytogeneticists also deserve considerable credit and recognition for their careful work in providing new technological discoveries and solid experimental evidence to confirm correct hypotheses, discard defective ones, and sometimes develop new concepts that are more accurately in accord with the ever-expanding experimental data.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
The author thanks Ms. Lucinda Lewis for her help with typing the manuscript.

Grant Support
This work at MSKCC was supported in part by The Enid A Haupt Charitable Trust, The WestRock Foundation, and The E/J. Sinda Lymphoma Research Fund to B.D. Clarkson.

References
Commentary on Sandberg et al., "The In Vivo Chromosome Constitution of Marrow"

Bayard D. Clarkson


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/76/5/991

This article cites 19 articles, 5 of which you can access for free at:
http://cancerres.aacrjournals.org/content/76/5/991.full.html#ref-list-1

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.