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This Week's Citation Classic™

Nowell P C & Hungerford D A. A minute chromosome in human chronic granulocytic leukemia. *Science* **142**:1497, 1960.
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This abstract described seven patients (five male, two female) with chronic granulocytic leukemia (CGL) in whom a similar minute chromosome was found in the neoplastic cells in each case. The finding suggested a causal relationship between the chromosome abnormality and CGL. [The *SCI*® indicates that this brief "paper" has been cited in over 510 publications since 1960.]

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After serving my country by doing 5,000 mouse autopsies, I joined the University of Pennsylvania faculty in 1956 and began culturing human leukemic cells using Edwin Osgood's method.[1] (This used phytohemagglutinin to get rid of the erythrocytes, but that's another story.) Being trained in pathology, I stained the culture slides and rinsed them under the tap to examine the cells. Unknowingly, I was reenacting the accidental discovery, by T.C. Hsu,[2] of the hypotonic treatment that made modern cytogenetics possible. My slides contained dividing cells with countable chromosomes, something I had never seen in ordinary tumor-tissue sections. I knew nothing of chromosomes or of the recent cytogenetic advances that had corrected the human chromosome number from 48 to 46, but I thought somebody might be interested. My inquiries ultimately led to David Hungerford, a graduate student at the Institute for Cancer Research, who was doing a thesis on human chromosomes and needed material. Our collaboration resulted: I cultured the cells, and he looked at them. Our first cases, of acute leukemia, were unrewarding. Then Dave spotted a small chromosome in cells from two male patients with chronic granulocytic leukemia (CGL). These findings were published[3] with caution (because the Edinburgh group had found no abnormality in CGL[4]) and with the suggestion that the "minute" chromosome might be an altered Y. Subsequent cases, including women and using an improved "air-drying" technique,[5] led Dave to assign the minute chromosome correctly to the larger pair of G-group autosomes, first numbered 21 and later changed, by convention, to no. 22. The additional CGL cases were being readied for publication when A.N. Richards asked us to present something at a National Academy of Sciences meeting he was organizing at Penn. Our abstract, published in *Science*, led to wide recognition (and citation) of the first example of a consistent chromosome abnormality in neoplasia. The Edinburgh group graciously suggested the name "Philadelphia (Ph) chromosome."

The next decade was frustrating. Cytogenetic studies in CGL proved of some diagnostic and prognostic value and provided key evidence of clonal evolution in tumor cell populations, helping to explain clinical tumor progression. But since other consistent chromosome changes in neoplasia were elusive, their significance in tumorigenesis was questioned and the term "epiphenomenon" frequently used. With the advent of chromosome banding techniques in the 1970s and of molecular genetic techniques in the 1980s, the story changed dramatically. Nonrandom cytogenetic alterations were recognized in many tumors and are now proving very useful for exploring oncogene involvement.[6] Chromosome studies remain a crude way of looking at genomic changes, but the early promise of the Ph chromosome as an indicator of specific genomic alterations important in human tumorigenesis is finally coming to fruition.

1. **Osgood E E & Krippaehne M L.** The gradient tissue culture method. *Exp. Cell Res.* 9:116-27, 1955. (Cited 70 times.)
2. **Hsu T C & Pomerat C M.** Mammalian chromosomes in vitro. II. A method of spreading the chromosomes of cells in tissue culture. *J. Heredity* 44:23-9, 1953. (Cited 105 times since 1955.)
3. **Nowell P C & Hungerford D A.** Chromosome studies on normal and leukemic human leukocytes. *J. Nat. Cancer Inst.* 25:85-110, 1960. (Cited 290 times.)
4. **Baikie A G, Court Brown W M, Jacobs P A & Milne J S.** Chromosome studies in human leukaemia. *Lancet* 2:425-8, 1959. (Cited 120 times.)
5. **Moorhead P S, Nowell P C, Mellman W J, Battips D M & Hungerford D A.** Chromosome preparations of leukocytes cultured from human peripheral blood. *Exp. Cell Res.* 20:613-16, 1960. [See also: **Moorhead P S.** Citation Classic. *Current Contents/Life Sciences* 26(7):21, 14 February 1983.]
6. **Nowell P C, Emanuel B S, Finan J, Erikson J & Croce C M.** Chromosome rearrangements and oncogenesis. *Microbiol. Sci.* In press, 1985.