Peter C. Nowell (1928–2016)

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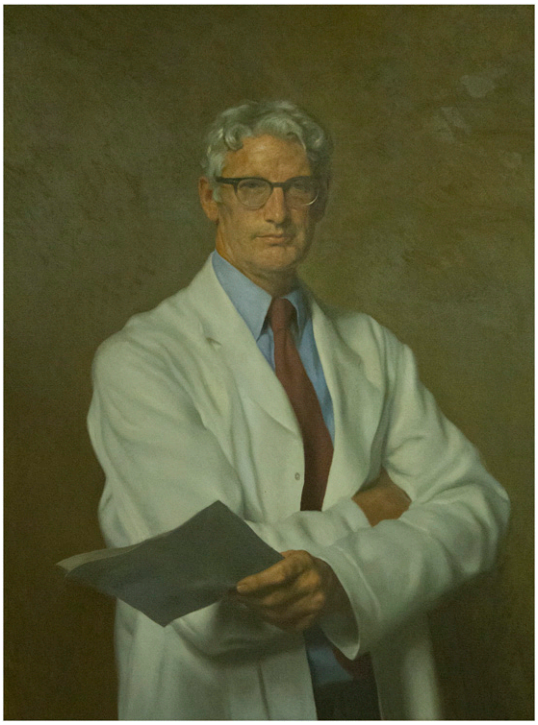
The pioneering cancer cytogeneticist, Peter C. Nowell, died on December 26, 2016, from complications of Alzheimer's disease at the age of 88. His work laid the foundation for the recognition of the genetic basis of cancer that paved the way for modern targeted cancer therapeutics. Nowell's observations of changes in chromosomal anatomy during progression of malignancies led him to predict that it was the accumulation of genetic abnormalities that underlies cancer progression, predating notions such as genomic instability as a fundamental hallmark of cancer.

Nowell was born on February 8, 1928, in Philadelphia. He attended Wesleyan University as an undergraduate and medical school at the University of Pennsylvania, graduating in 1952. He then performed a rotating internship at Philadelphia General Hospital and trained in pathology at Philadelphia's Presbyterian Hospital. Nowell was drafted into the military and spent 2 years studying the health effects of radiation at the Naval Radiological Defense Laboratory in San Francisco, before joining the faculty at the University of Pennsylvania in 1956, where he stayed for the remainder of his career.

As a pathologist, Nowell's primary tool for discovery was the light microscope. He contributed to development of methods for visualizing chromosomes in mitotic cells (karyotyping). In 1960, using his improved karyotyping methods, Nowell and his associate David Hungerford published their discovery of the first nonrandom chromosomal alteration in cancer: an abnormally small chromosome #22 that was present in all blood or marrow samples from patients with chronic myeloid leukemia (CML) (1). In the seminal paper describing this finding, Nowell wrote that this discovery suggested a causal relationship between the chromosomal abnormality observed and CML. This notion was met with great skepticism, but his prescient prediction was confirmed by numerous subsequent discoveries. This included Janet Rowley's work showing that this shortened chromosome 22, now called the Philadelphia (Ph) chromosome after the city in which it had been discovered, resulted from a reciprocal exchange of genetic material between chromosomes #9 and #22. This chromosomal rearrangement generates a fusion gene *BCR-ABL*, which encodes an activated tyrosine kinase. Befitting the seminal discovery of the Ph chromosome as the first cytogenetic abnormality in cancer, the first kinase inhibitor to be approved by the Food and Drug Administration and other health authorities for cancer treatment was imatinib mesylate (Gleevec), an oral small-molecule inhibitor of the BCR-ABL kinase that has transformed outcomes for patients with CML. Before imatinib, the median survival of patients with CML was typically 3 to 5 years; now the majority of patients achieve durable remissions and have a near normal life-expectancy.



Portrait of Peter C. Nowell. Image courtesy of the University of Pennsylvania Art Collection.

Nowell's observations on cytogenetic changes with tumor progression were profound, giving rise to the hypothesis that cancers begin with a small number of

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specific genomic alterations, then progressively become genetically heterogeneous, with subclones emerging that possess additional genetic changes on top of the original founding mutations. Nowell again made an accurate prediction that in a Darwinian-like fashion, those malignant subclones with added genetic lesions had a growth advantage and would compete with other neoplastic cells within tumors to emerge as the dominant population (2). These concepts are now widely accepted in cancer biology and include the recognition of genomic instability as a fundamental hallmark of cancer, and tumor heterogeneity as a common mechanism of resistance to therapy.

Among Nowell's most cited works was the discovery in 1960 of the mitogenic properties of plant lectins when applied to cultured human lymphocytes (3). In those days, lectins, such as phytohemagglutinin (PHA), were used by cytogeneticists to aggregate nonnucleated red blood cells, thus enabling cytogenetic analysis of nucleated cells. The discovery occurred when one evening Nowell found himself running late for a family obligation and left PHA-treated blood specimens overnight rather than proceeding to centrifugation. Upon returning to the laboratory the next morning, Nowell inspected the blood cells via light microscopy and noticed that the lymphocytes had undergone blastogenesis. Rather than set the peculiar observation aside, Nowell pursued it with vigor and soon thereafter published that lectins such as PHA could be used to stimulate proliferation of human lymphocytes. The discovery provided a robust cell-culture model for studying basic mechanisms of cell proliferation, laying a foundation for subsequent discovery of multiple cytokines, lymphokines, cell surface receptors, and ligands that orchestrate the complex process of lymphocyte cell cycle entry and cell division.

Referred to respectfully as "Dr. Nowell" (not Peter) by his colleagues, Nowell was a dashing figure with a deep resonant voice and a head of thick white hair. He wore a long, white, perfectly pressed laboratory coat from the moment he arrived in the office until departing at day's end. He was mentor to hundreds of students, always challenging them to focus on big questions and avoid the entrapments of mindlessly generating volumes of data using the latest technique. Nowell insisted that his students develop the critical skill of expressing their ideas in writing. Every student was given a copy of Strunk & White's *The Elements of Style* upon drafting their first manuscript: Nowell's "bible" for good writing practices, which included examples, instructions, and best practices of writing, such as E. B. White's three cardinal rules of writing: "avoid needless words, avoid needless words, avoid needless words." Nowell would debate with students for hours how a particular sentence should be structured or how a thought should be phrased. He spent as much or more time working on the text of documents with his students as he devoted to reviewing their data. In the laboratory, Nowell was a hands-off leader, who gave his students the freedom to explore and learn from their mistakes.

Naming the CML chromosomal anomaly after the city in which he worked, Philadelphia, rather than himself, was characteristic of Nowell's unpretentious and humble style. He never sought the spotlight, preferring to devote his energy to science and teaching. Nowell reluctantly served as chair of the Department of Pathology at the University of Pennsylvania, School of Medicine from 1967 to 1973, then voluntarily stepped down after a highly successful tenure, setting a precedent that department chairs should have term limits and not pursue life-long careers as administrators.

Nowell was intensely devoted to his family: his wife Helen and their five children. Their first child, Sharon, was severely stricken with cerebral palsy. The Nowells cared for Sharon in their home for 35 years, with Peter personally dressing and feeding Sharon each morning before leaving for the laboratory and then again, in the evenings, feeding her dinner and putting her to bed. In this and many other ways, Nowell was a role-model for his students on the challenging topic of work–life balance. At their annual backyard summer party for the laboratory staff and students, Nowell's wife Helen would regale young couples with stories about their child-rearing methods, while Peter graciously made self-effacing remarks about his subordinate stature in the Nowell household. He enjoyed a gin-and-tonic nightly after work, and was a deadly lawn croquet player who eliminated opponents with ease.

Over the course of his career, Nowell earned numerous awards, including the Albert Lasker Clinical Medical Research Award (1998), the Franklin Medal in Life Science (2010), and the Albany Medical Prize (2013). In recognition of his devotion to his trainees, his family donated the winnings from the Albany Medical Prize to establish a scholarship fund in his name at the University of Pennsylvania.

Many universities and medical centers attempted to recruit Nowell over the years of his productive career, but he chose to remain at the University of Pennsylvania. An oil-painting portrait of Nowell hangs in the John Morgan Building of the University of Pennsylvania campus, the same building where America's first medical school was founded, and he would joke with visitors about having a portrait while still being alive. But, he was a living legend and is it befitting that Nowell is remembered among the pioneers of American medicine, surrounded by other trail blazers whose contributions have advanced science and improved health for the world.

1 Nowell PC, Hungerford DA (1960) A minute chromosome in human chronic granulocytic leukemia. *Science* 132:1497.
2 Nowell PC (1976) The clonal evolution of tumor cell populations. *Science* 194:23–28.
3 Nowell PC (1960) Phytohemagglutinin: An initiator of mitosis in cultures of normal human leukocytes. *Cancer Res* 20:462–466.