RETROSPECTIVE

Peter C. Nowell (1928–2016)

Tumor biologist who set the stage for precision medicine

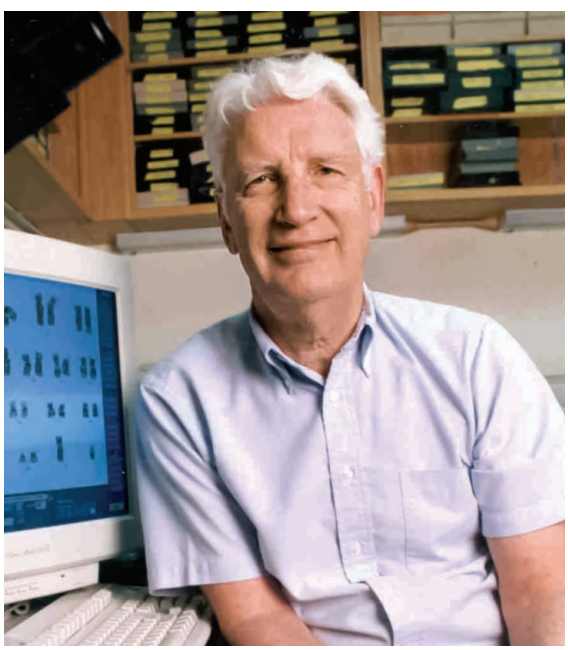
By **Mark I. Greene** *and* **Jonni S. Moore**

Peter C. Nowell, a cancer researcher whose contributions to the field of tumor biology formed the basis of much of today's precision medicine, died in the early hours of 26 December 2016. He was 88 years old. With his passing, the scientific community lost a gifted scholar, a dedicated teacher and mentor, a true gentleman, and a good friend.

Nowell was born and spent virtually his entire life near Philadelphia, Pennsylvania. He studied biology and chemistry, earning his bachelor's degree from Wesleyan University in 1948 and his medical degree from the University of Pennsylvania in 1952. After a residency in pathology at Presbyterian Hospital in Philadelphia, Nowell spent 2 years at the U.S. Naval Radiological Defense Laboratory in San Francisco, California. In 1956, he returned to the University of Pennsylvania, where he remained until his retirement. We had the privilege of working closely with Nowell as a colleague (M.I.G.) and as a student and colleague (J.S.M.) for more than 25 years.

Nowell is best known for his co-discovery of the Philadelphia chromosome in 1960 with David Hungerford, a graduate student at the Institute for Cancer Research at Fox Chase in Philadelphia. At the time, Nowell was exploring the role of chromosomes in tumors, an area filled with speculation, but little evidence. Nowell and Hungerford observed the frequent occurrence of a minute chromosome in patients with chronic myelogenous leukemia. Early studies could not identify whether it was a translocation or a deletion. The true nature of the Philadelphia chromosome was demonstrated in the 1970s, with the evolution of chromosomal banding techniques, by Janet Rowley of the University of Chicago, who identified it as a translocation of genetic material between chromosomes 22 and 9. The translocation essentially leads to unregulated cell proliferation and defective DNA repair. This translocation is often referred to as the first genetic link to cancer. Later, Brian Druker of Oregon Health and Science University demonstrated that a targeted inhibitor could effectively inhibit the translocation's effect. This was the basis of Gleevec (marketed by Novartis), one of the first of this new class of targeted cancer therapeutics. Nowell and Hungerford's work, along with Rowley's later analysis, served as the precursor to today's expanding field of cancer genomics, and it earned them the Lasker Award in 1998, often referred to as "America's Nobel Prize."

One of Nowell's most important contributions was his proposal that cancer evolved through multiple genetic stages, indicating that tumor heterogeneity may ultimately require individualized therapy. In a 1976 Review in *Science*, he described evidence to support the clonal evolution model of tumor progression, which was at odds with the prevailing idea that tumors evolved through somatic mutation. His ideas were met with some skepticism at the time, but sequential changes in tumors are now understood to result from genetic instability, which is a part of the neoplastic process. This observation has become increasingly appreciated as we understand the critical importance of personalized genomic diagnostics as the basis for precision therapy for malignancies.



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Clearly he was a forward thinker and a brilliant scientist, but Nowell cited his role as a mentor and teacher as the most rewarding aspect of his career. On a weekly basis, his lab would fill with students ranging from elementary school children to visiting scientists. His door was always open to discuss any late-breaking scientific finding (he always knew the current topics). Physicians from many specialties in the Hospital of the University of Pennsylvania would drop by to explore ideas and to learn, but his favorite time was spent with young scientists. At a time when the scientiftic community is devising programs to encourage STEM interest, Nowell's enthusiastic sharing of his knowledge with budding scientists should serve as a model.

Nowell was an icon in science, but to many, he was a cherished mentor and dear friend. He often reminded those of us who worked closely with him that "we made the boxes; biology did not." Trainees in his lab were always pushed to think outside of the boxes of current scientific dogma, and no hypothesis was too outrageous as long as you could devise an approach to test it. His lab meetings often resembled think tank sessions rather than detailed presentations of data. His laboratory was his scientific family, embraced as both friends and colleagues. He understood early on the importance of work-life balance and encouraged those of us who trained with him to be more than a "lab rat." Home and family always came first to Nowell, and he encouraged that in all who shared the journey with him.

A true "renaissance scientist," Nowell had the rare ability to see the big picture. A visionary for the future of oncology research, he recognized the importance of genomic alterations in tumorigenesis and as a target for therapy, predicted how biological processes such as tumor clonal evolution and regulation of lymphocyte proliferation would function, and devised approaches to prove his hypotheses, even to the point of creating new technology. Today's world of very focused research, necessitated by the current funding environment, is difficult terrain for broad-thinking scientists made in the mold of Nowell. The biomedical community owes much to him for his scientific achievements, especially his role as one of the fathers of precision diagnostics, but his most important contribution is serving as a role model for future generations. It is scientists like Nowell who will ensure the future of biomedical scientific advancement. ■

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