

# Stanley Cohen (1922–2020)

Award-winning biochemist who shed light on cell growth

By **Graham Carpenter**<sup>1</sup> and **Robert Coffey**<sup>2</sup>

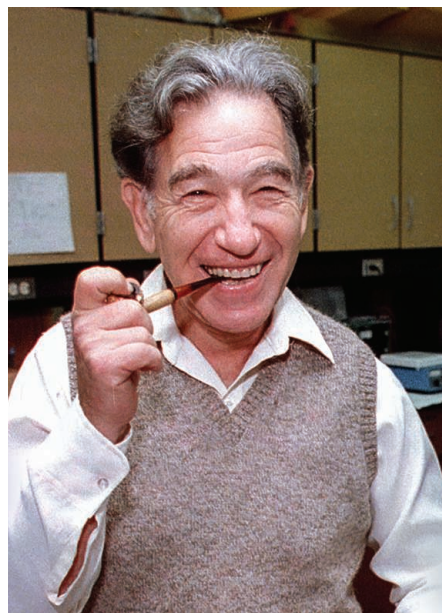
**S**tanley Cohen, biochemist and Nobel laureate, died on 5 February at age 97 in Nashville, Tennessee, where he had served on the faculty of Vanderbilt University since 1959. With neurobiologist Rita Levi-Montalcini, Cohen discovered the first growth factor, a hormone-like protein that regulates cell responses such as proliferation and differentiation.

Born to Russian immigrants in Brooklyn, New York, Cohen graduated from Brooklyn College in 1945 with majors in chemistry and zoology. He then received a master's degree in zoology from Oberlin College in Ohio and a Ph.D. in biochemistry from the University of Michigan in 1948. After a postdoctoral fellowship, he became a faculty member at Washington University in St. Louis in 1953. There, his collaboration with Levi-Montalcini resulted in the discovery of nerve growth factor (NGF). Levi-Montalcini had made the crucial observation that NGF's biological activity was due to a diffusible substance. Cohen then proved that a single protein was the responsible agent—a critical advance that made NGF a scientifically recognized agent. Both Levi-Montalcini and Cohen were creative thinkers and determined experimentalists. As Cohen once remarked, "On our own we were good and competent. Together we were marvelous."

In 1959, Cohen moved to Vanderbilt University as an assistant professor of biochemistry, where he discovered and purified epidermal growth factor (EGF) from mice. His bioassay for EGF was based on its capacity to induce precocious eyelid opening in newborn mice. It is difficult to imagine the time, coordination, patience, skill, and luck required for this to succeed. Years later, another group reported that in this assay, newborn female mice also exhibited precocious opening of the vagina. Stan's shy response was that he had also noticed this but was too embarrassed to report it.

In the following decades, Cohen relentlessly and productively pursued the mechanism of action underlying EGF. The

identification of the EGF cell surface receptor (EGFR) provided a starting point to elucidate the mechanism by which EGF provoked biological responses, such as cell proliferation, in target cells. By showing that EGF binding to the EGFR in membrane preparations activated a biochemical response, Cohen paved the way for the first analysis of a hormone's mechanism at the biochemical level. When investigators in the lab of biochemist Edward Krebs in Seattle called Cohen to say that they had success-



fully repeated his experiments, Cohen was enormously proud. He always took great care to delay publication of data in his lab until repeatability was assured.

Finally, Cohen's group demonstrated that the EGF:EGFR complex was trafficked from the cell surface to intracellular lysosomes. These studies upended the accepted view that bioactive molecules, bound to receptors, simply associated and dissociated at the cell surface. These seminal investigations have proven to be true for other bioactive proteins, including hormones, growth factors, viruses, and toxins.

Cohen's contributions served as a model that has led to the identification of nearly 100 other growth factors and at least 50 receptors, all with important biological activities in humans. His trailblazing leadership led to numerous scientific awards, culmi-

nating in the 1986 Nobel Prize in Medicine or Physiology. Cohen's EGFR studies later provided the basis for the development of clinically effective drugs used to combat cancer. This application was unanticipated when the Nobel Committee made its prescient decision, a decade before the advent of precision medicine.

Stan's productivity belied that fact that his lab group seldom included more than three other people: two dedicated research assistants and one postdoctoral fellow (students were very rare). With the exception of one 10-year period, the Cohen lab was continuously funded by one rather modest National Institutes of Health grant. Stan's relentless focus and thinking was the key to the group's success. Puffing on a corn cob pipe, he spent hours walking the hallways at Vanderbilt either devising the ideal experiment or stopping to test his ideas with colleagues (including the two of us). Inevitably, the pipe was left on a nearby refrigerator or stuffed in his pocket where it would burn a hole. This routine was well known by everyone and the mislaid pipes would be returned by professors, technicians, or janitorial staff. This intense experimental focus also made him an easy target for April Fools' jokes perpetrated by lab personnel.

Stan approached life with optimism and a smile. Always humble, he attributed his professional success to paying careful attention to the data and to luck. Colleagues were always impressed at how Stan logically identified the next question and then went to his lab to do the critical experiment himself. Stan had a driving need to be as close to the experiment as possible, which included the validity of reagents—he never accepted experiments conducted with "kits."

In addition to working intensely, Stan enjoyed listening to music, playing the clarinet (with local amateur musicians), whitewater canoeing, and hacking away at a tennis ball. Shortly after retirement, Stan moved for a few years to Arizona, where he discovered a passion for off-road driving. He also devoted much of his time to volunteering in a public junior high school as a science adviser.

Stan is survived by his devoted wife Jan, three sons, and two granddaughters. His stellar career serves as a reminder that basic observations in the lab, pursued doggedly, can have long-lasting, beneficial consequences for humankind. Today, Stan's discoveries help countless patients with advanced lung, colorectal, and head and neck cancer, for which pharmacological blockade of the EGFR is a mainstay of treatment. ■

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