

Nobel Laureate, Neuroscience Pioneer Axelrod Mourned

By Jennifer Loukissas

Nobel laureate Dr. Julius Axelrod, an NIH veteran of over 50 years, died in his sleep Dec. 29, 2004. He is probably best known for his work on brain chemistry in the early 1960's that led to modern-day treatments for depression and anxiety disorders. In 1970, he shared the Nobel Prize for Physiology or Medicine for discovering how brain cells communicate with each other.

Axelrod, known to his colleagues as "Julie," came to NIH in 1949 to the then National Heart Institute (now NHLBI). In 1954, before moving to NIMH to begin a new career in neuroscience, he returned to school to complete his Ph.D. in pharmacology; he needed the credential in order to open his own lab where he continued to work for over 40 years. In 1996, NIH awarded him the title scientist emeritus.

"Dr. Axelrod made contributions to the fields of neuroscience and pharmacology that did much to improve the lives of countless millions of individuals who benefit daily from the medications that his



Dr. Julius Axelrod enjoys lunch at a 1987 event in honor of NIH's 100th anniversary.

insights made possible," said Dr. Elias Zerhouni, NIH director. "Our understanding of the biological basis of human behavior owes much to the work of this gifted and dedicated scientist who will be greatly missed by his friends and colleagues at NIH."

NIH deputy director for intramural research Dr. Michael Gottesman said of Axelrod, "He was an NIH icon—the model of a brilliant and compassionate scientist whose work on neurotransmission revolutionized modern neurobiology and medicine. His intellectual independence and courage have inspired generations of NIH trainees and scientists and he will be much missed on the campus."

Axelrod's Nobel Prize-winning research explained how neurotransmitters operate in the brain, forever altering the design of modern antidepressant drugs. His work laid the foundation for the treatment of anxiety and depression. He coined the phrase "re-uptake" inhibitors, referring to the "re-uptake" mechanism in brain cells that regulates the level of neurotransmitters available, influencing how neurons communicate. This revolutionary understanding of the brain's chemistry led to the modern generation of antidepressant medications—selective serotonin reuptake inhibitors (SSRIs).

"Dr. Axelrod was one of the giants. His contributions to the fields of mental health and neuroscience make possible current breakthroughs on mood and anxiety disorders, and many other areas of re-

Axelrod in an interview with the NIH Record on how he chose research over a postal career (Feb. 19, 1991 issue)



search," said Dr. Thomas Insel, NIMH director. "He will be greatly missed, but his legacy lives on in the work of others."

Colleagues say Axelrod had a remarkable approach to discovery, not only because of the breadth and depth of his interests, but also his attitude in the lab. He mentored and trained more than 70 scientists, many of whom went on to become leaders in brain research. Axelrod was a founding member of the now 40-year-old NIGMS Pharmacology Research Associate program (PRAT) to support post-doctoral fellowships in the pharmacological sciences at NIH and FDA.

"Axelrod's laboratory was an active training program for many of today's leaders in pharmacological research," said colleague and friend Dr. Ruth Kirschstein, senior advisor to the NIH director. "He was one of the key people responsible for its success and the perennial first choice mentor for students coming in to the program. There wasn't a year when he didn't have a fellow through the PRAT program."

One of his most distinguished protégés, Dr. Solomon Snyder of Johns Hopkins Medical School and co-discoverer of the brain's opiate receptor, called Axelrod "a humble giant of neuroscience and pharmacology. Most will agree that his contributions to our understanding of how drugs act in the brain was greater than any other scientist of the last half of the 20th century. Julie never tooted his own horn, preferring the lab to the lecture circuit. Indeed, at a banquet honoring Julie following his receipt of the Nobel Prize, he quipped, 'It seems these honors are a conspiracy to keep me out of the lab.'"

Axelrod's studies of brain chemicals were far from his only laudable success in science. Before coming to NIH, he helped discover the pain-relieving properties of acetaminophen, better known by its brand name, Tylenol.

Axelrod took a circuitous route through science, initially hoping to be a physician. But he was rejected from all the medical schools to which he

applied; there were strict quotas on the number of Jewish applicants, he told the *Record* in 1991. Refusing to accept defeat, Axelrod began his career by using his degree in biology to test vitamin supplements for the New York City department of health's laboratory of industrial hygiene. While at that lab, he took courses towards his master of science degree in chemistry. He wrote his master's thesis on the chemical breakdown of enzymes in cancerous tumor tissues.

In 1949, Axelrod arrived at the National Heart Institute, where he studied the tissue distribution and metabolism of caffeine, amphetamines, ephedrine and narcotic drugs. In 1953, he delved into diabetes research where he described a new class of enzymes in liver microsomes that metabolized drugs by a variety of pathways—all before receiving his Ph.D.

Following the completion of his doctoral studies, he promptly set out to direct research in a lab of his own at NIMH. His early work there focused on the metabolism of lysergic acid diethylamide (LSD) and other psychoactive drugs. He went on to revolutionize the field of pineal gland research, discovering melatonin as the gland's key hormone. Axelrod and his collaborators from NIDDK described the mechanism for glucocorticoid formation and showed that congenital non-hemolytic jaundice is due to a defect in glucocorticoid synthesis.

Until his retirement in 1984, Axelrod worked on research projects that sought to elucidate the relationship between drugs and behavior. His research suggested that mental states were the result of complicated physiology and brain chemistry, rather than the sole result of psychological or environmental factors. For years after his official retirement, Axelrod continued to have an active research program as an unpaid guest researcher; he was still coming to his lab regularly in mid-December 2004. He conducted research on transduction of neurotransmitter signals in cells, and more recently, he had been involved in studies on the natural ligand of the cannabinoid receptor anandamide. His many contributions still influence the work of his colleagues.

Reflecting about his mentor and friend, long-time NIMH co-worker Dr. Michael Brownstein says Axelrod was special: "It wasn't only that he had a capacity to enjoy other people's novel findings, he had a special appreciation for data and biology. He showed me that science could and should be fun. There was nobody who was more genuinely buoyant about the scientific enterprise than Julie. He loved to read and think about science, and talk about data. His magic was not in doing experiments that required lots of technical finesse; it was in doing work that anyone could have done—if they'd had the ideas. What separates the giants from the rest is the capacity to ask great questions." **E**