

OBITUARY - Julius Axelrod

Julius Axelrod a Nobel-Prize winning scientist internationally known for his research on brain chemistry and pharmacology died on Wednesday December 29th at his home in Rockville, Maryland near the National Institute of Mental Health, where he worked for most of his career. He was 92.

Dr Axelrod shared the 1970 Nobel Prize in Physiology or Medicine with Bernard Katz and Ulf von Euler for fundamental discoveries on neurotransmitters, the chemical messengers used as signals in the nervous system. When such chemicals are released from nerve cells they must be rapidly inactivated and it was widely assumed that this involved their degradation to other inert substances. But Axelrod discovered a completely novel mechanism for the inactivation of neurotransmitters, involving their recapture by the nerves from which they were released. He studied the catecholamine neurotransmitter noradrenaline, present in the peripheral sympathetic nervous system and in the brain. Experiments with radiolabelled noradrenaline showed that when it was injected into experimental animals some was metabolised as expected, but a substantial part of the injected material was taken up and retained unchanged in sympathetic nerves from which it could be released on nerve stimulation. Together with a visiting Austrian scientist, George Hertting, Axelrod in 1961 proposed that the inactivation of noradrenaline involved an uptake system that recaptured much of the neurotransmitter into the same nerves from which it was released. A French visitor, Jacques Glowinski, and Axelrod found that antidepressant drugs acted as powerful inhibitors of this uptake mechanism in brain – and thus acted to prolong the effects of the released neurotransmitter. This discovery had a profound impact on the development of improved antidepressant drugs. Work in other laboratories subsequently showed that the reuptake concept had wide applicability to several neurotransmitter mechanisms, with the discovery of similar uptake mechanisms involved in inactivating the neurotransmitters serotonin, dopamine, glutamate and GABA. The serotonin uptake system proved particularly important, as it became the target of today's generation of antidepressant drugs, the so-called "serotonin-selective reuptake inhibitors" (SSRI's), exemplified by Prozac. Despite the poor image that these drugs have gained recently, they have benefited many millions of depressed patients.

Although these advances were of fundamental importance, they were by no means the only major discoveries made during an extraordinary scientific career. Julius Axelrod was a classic example of the "late starter" –his first significant scientific publications were not made until he was in his late thirties and he did not gain his PhD until he was 43.

His parents were Jewish immigrants from Galician Poland and he was born in a poor neighbourhood in New York in 1912, where he grew up and attended public schools. He was unable to afford College fees, but like many other bright children from poor families in New York his education was rescued by being able to attend the tuition-free City College of New York, from which he graduated in 1933 with a degree in biology. He married Sally, a teacher, in 1935 and they had two sons - Paul and Alfred (1946, 1949) who survive him. Sally died in 1992.

Having made unsuccessful attempts to obtain a place to study medicine, he took a job as a laboratory technician, initially at New York University and subsequently at the New York City Public Health Department, where he devised methods for measuring the vitamin content of various foods. By attending night school, he obtained a Masters degree in Chemistry at New York University in 1942. He held the laboratory job for some ten years, and might have stayed there for the rest of his working life. But in 1946 he met Bernard Brodie, a charismatic scientist who was to change Axelrod's career dramatically.

For the first time Axelrod had met someone who could supply the intellectual and scientific challenges that had so far been lacking in his career. Brodie was a brilliant scientist and a pioneer of the application of chemical and biochemical techniques to the study of drug actions. He introduced Axelrod to the study of drug metabolism and they started to work on a problem concerning the then widely used painkiller acetanilide. After taking high doses of this drug some people developed a severe blood toxicity known as methaemoglobinaemia. Brodie and Axelrod showed that the drug was partly degraded in the body to form aniline, a known blood toxin which was the likely cause of the problem. But they also found unexpectedly that another major product of the metabolism of acetanilide was the hydroxylated product acetaminophen. Brodie and Axelrod discussed in their 1948 paper the idea that acetaminophen might represent a safer drug than acetanilide, as it did not carry the risk of methaemoglobinaemia. This indeed proved true, and acetaminophen (known more commonly in the US as "Tylenol" or in Europe as "Paracetamol") became the most widely used painkiller in the world – although Axelrod received no share of the commercial gains and little recognition for his scientific discovery.

Axelrod continued to work with Brodie for nearly ten years, but he grew increasingly impatient for a more independent role, free from the somewhat overpowering influence of his mentor. In 1955 he was able to complete his PhD studies at George Washington University and he was recruited to the National Institute of Mental Health where he had his own independent laboratory. Here he was introduced to neuroscience for the first time, and was able to apply his chemical skills to the new subject of neurochemistry. He discovered a novel enzyme, catechol-O-methyl transferase (COMT) involved in the metabolism of adrenaline and noradrenaline, and later discovered the reuptake mechanism described previously. Subsequent work produced a series of discoveries on other methyl transferase enzymes and a detailed analysis of the biochemical mechanisms underlying the daily rhythm of biosynthesis of the pineal hormone melatonin – a pioneering model of understanding the molecular details of rapid changes in gene expression.

Julie Axelrod was an unassuming and modest man, with a wry sense of humour, who took a simple and almost naive approach to science. He did not indulge in deep intellectual or mathematical analysis, but instead had a knack of being able to understand and define a problem and to describe a creative experimental solution. As he put it: *"I soon learned that it did not require a great brain to do original research. One must be highly motivated, exercise good judgement, have intelligence, imagination, determination, and a little luck. One of the most important qualities in doing research, I found, was to ask the right questions at the right time."*

The Axelrod lab drew visiting scientists from all over the world - I was privileged to be among the early visitors in the 1960's. The experience of working with Julie proved to be a starting point for a generation of scientists working in the then new fields of neurochemistry and neuropharmacology. The important influence that mentors of genius have is graphically described by Robert Kanigel in his book *"Apprentice to Genius: The Making of a Scientific Dynasty"* (1993, Johns Hopkins Univ Press) which describes in more detail the influence that Brodie had on Julie Axelrod, and that Julie in turn had on his "apprentices". Julie's students all over the world continue to share a common affection for their mentor. He was constantly interested and solicitous of the members of his extended scientific family, and we will all sorely miss him.

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