Obituary

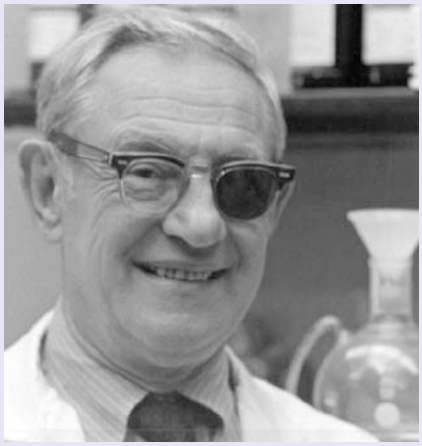
Julius Axelrod (1912–2004)

Julius Axelrod, known to friends and colleagues affectionately as 'Julie', died on 29 December 2004, following a career that was highlighted by so many extraordinary discoveries about how drugs act that his place among the twentieth century's greatest biochemical pharmacologists is secure. The research for which he shared the Nobel Prize in Physiology or Medicine in 1970 was only a small, and perhaps not even the most important, part of his opus.

Axelrod's life story is an inspiration to those who care about science but lack elaborate academic credentials. The son of a poor basket-maker in New York City, he graduated from the City College of New York and applied to numerous medical schools but was rejected by all of them. For 11 years he worked as a technician in a New York City health laboratory, where he was assigned the task of monitoring the vitamin content of foods. Here he honed his skills in developing simple, sensitive and specific methods for measuring drugs.

A turning point was his department's assignment to clarify why phenacetin and acetanilide — the principal ingredients, along with aspirin, in major headache remedies of the day — led to dangerously high levels of methaemoglobin, a product of haemoglobin metabolism, in patients' blood. In 1946, he sought the assistance of Bernard Brodie, then at the Goldwater Memorial Hospital, thus commencing a career-transforming collaboration. With Brodie he showed that acetanilide and phenacetin are respectively metabolized to aniline and *p*-phenetidin — the toxic culprits. Another metabolite, *N*-acetyl-*p*-aminophenol or acetaminophen (paracetamol), is probably responsible for the analgesic effects. This discovery, never patented, made up Axelrod's first two publications, and led to the marketing of this metabolite as Tylenol, the world's most widely used analgesic.

In 1950, Axelrod moved to the newly formed National Institutes of Health (NIH) in Bethesda. He continued working in Brodie's laboratory but with increasing independence, elucidating the metabolism of caffeine, ephedrine and amphetamine in animals. Although he had never worked with enzymes, he wanted to understand in greater detail how drugs are metabolized, and so incubated various subcellular fractions with amphetamine and ephedrine. Using membrane fractions from the liver, he discovered a previously unknown group of enzymes that require NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) and



NIH

From pharmacologist to neuroscientist

molecular oxygen. This is the cytochrome P450 family of drug-metabolizing enzymes, and their discovery represents a classic advance in pharmacology.

All of these discoveries were made while Axelrod was only a technician. Responding to pressure from friends, he took a year's leave of absence, enrolled at George Washington University and, at the age of 42, received his PhD. With a doctorate in hand, Axelrod was made head of pharmacology in the laboratory of clinical science at the National Institute of Mental Health.

Seymour Kety, the laboratory director, was intrigued by reports that implicated the abnormal metabolism of adrenaline (also known as epinephrine, a neurotransmitter) in schizophrenia. To understand how adrenaline is normally metabolized, Axelrod exploited a brief abstract reporting that adrenaline-producing tumours metabolize adrenaline to a product that is methylated on one of the two hydroxyl groups of its catechol ring. Axelrod soon discovered an enzyme that uses *S*-adenosylmethionine to methylate catechols; he dubbed it catechol-*O*-methyltransferase. Using radiolabelled *S*-adenosylmethionine, Axelrod went on to identify several other methyltransferases. These include the adrenal enzyme that generates adrenaline from noradrenaline, and one that forms melatonin, a substance unique to the pineal gland.

Kety had set up research wards to compare the metabolism of radiolabelled adrenaline in schizophrenics and normal controls, and provided Axelrod with samples of [^{3}H]adrenaline for metabolic studies. When [^{3}H]adrenaline or [^{3}H]noradrenaline was injected into rats and cats, the radiolabel concentrated in tissues enriched in sympathetic-nerve endings. But lesions of the sympathetic nerves abolished the accumulation. So Axelrod postulated that noradrenaline, the neurotransmitter used by sympathetic nerves, is inactivated by a 're-uptake' system that involves the transmitter being pumped back into the nerve ending that had released it. Adrenaline, released from the adrenal gland, is also taken up into sympathetic nerves.

Neurotransmitter inactivation had previously been thought to be primarily enzymatic, because the first known transmitter, acetylcholine, is inactivated by an enzyme. But it soon became evident that re-uptake inactivation is the rule rather than the exception for most neurotransmitters. Axelrod also found major drugs that inhibit re-uptake, and his discovery that antidepressants work in this way spawned the modern generation of antidepressants, exemplified by fluoxetine (Prozac). For this research he shared the Nobel prize with Ulf van Euler, who established that noradrenaline is a neurotransmitter, and Bernard Katz, who showed that neurotransmitters are stored in synaptic vesicles in nerve endings.

Axelrod's gifts as a creative scientist were matched by his gifts as a mentor. His extraordinary discoveries emerged from a tiny laboratory of only three or four scientists. Although he carefully structured concrete projects for new students, he soon weaned them, encouraging independent thinking by the "unconditional positive regard" (to quote psychologist Carl Rogers) that he lavished on every student's efforts. He maintained an active laboratory at the NIH until a few years ago, and subsequently visited his small office there regularly. His wife Sally died in 1992; he is survived by his sons Paul and Fred and three grandchildren.

Like almost all of Axelrod's trainees, my entire scientific career was predicated upon the lessons learned in my two years (1963–65) with him. Many of us have tried to divine Julie's gift for recognizing important questions that can be addressed by simple means, and for devising experiments so elegantly efficient that, with just 25 test tubes, he could answer four or five important scientific questions. We all have our own ideas about Julie's magic formula, but I suspect he has taken the real answer with him to the grave.

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