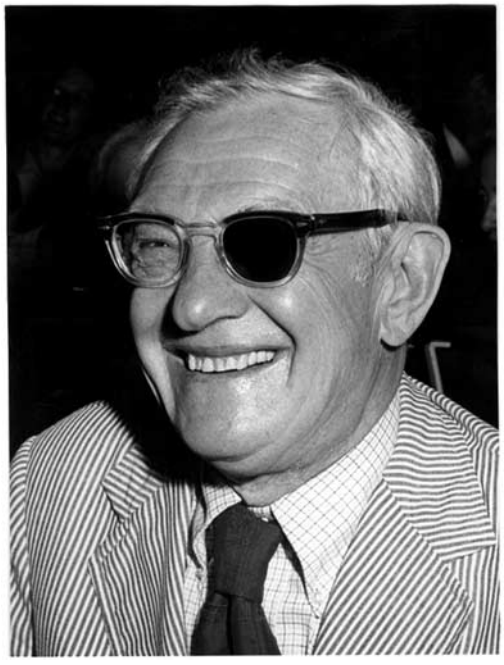
Neuropsychopharmacology (2005) 30, 1764–1766

www.neuropsychopharmacology.org

Obituary

Dr Julius Axelrod, 1912–2004

Neuropsychopharmacology (2005) **30,** 1764–1766. doi:10.1038/sj.npp.1300799



On December 29, 2004 Julius Axelrod, 92 years old, known to all his friends and colleagues as Julie, died suddenly. He had evidently awakened in the middle of the night, began to walk to the bathroom, and collapsed of a heart attack. Till the day of his death, Julie was alert and active, visiting the NIH several times a week to talk with colleagues and keep up with the literature. Julie had maintained a laboratory with a postdoctoral fellow until a few years ago and had visited his grandchildren in Wisconsin just a week before his death. In accordance with Julie's disdain for pomp and ceremony, his funeral lacked formal eulogies but was replete with personal reminiscences from a few long time friends. Such simplicity characterized Julie's life and scientific style.

Julie's parents emigrated to the United States from Polish Galicia and settled in the lower East Side of Manhattan where Julie was born May 30, 1912 in a tenement. His father Isadore was a basket maker who sold from a horse-drawn wagon to grocers and florists. Julie's high school, Seward Park, became renowned for its movie star graduates Zero Mostel, Walter Matthau, and Tony Curtis, but lacked serious intellectual tradition. Julie obtained his principal education from voracious reading in the public library. He attended the City College of New York, traveling each way to college on the subway and maintaining an almost full time job on the side. Julie would have liked to be a physician, but was rejected from several medical schools reflecting at least in part the Jewish quota of those days.

Graduating college in 1933, in the midst of the Great Depression, Julie had difficulty obtaining employment, but finally settled in the Laboratory of Industrial Hygiene, a New York City-operated portion of the Health Department that evaluated vitamin supplements. He worked there as a technician from 1935 to 1946, attending night school at New York University to obtain a Masters Degree.

In early 1946, Julie's laboratory was assigned the task of determining how the major nonaspirin analgesics, acetanilide and phenacetin, caused methemoglobinemia. Knowing nothing about drug metabolism, Julie was directed to a drug metabolism authority, Bernard Brodie, then at the Goldwater Memorial Hospital, a division of New York University. In their first meeting in February 1946, Julie and Brodie conversed for hours on how to solve the problem, and Brodie invited him into his laboratory. Examining the structure of acetanilide, they guessed that it might be metabolized to the dye aniline, already known to elicit methemoglobinemia. Julie developed a sensitive assay for aniline in urine and plasma and demonstrated a close correlation between its blood levels and those of methemoglobin. He then noted that a major metabolic product of acetanilide was *N*-acetyl-*p*-aminophenol, a substance which he showed to be analgesic and not cause methemoglobinemia. Thus, Julie's first publication concluded 'the results are compatible with the assumption that acetanilide exerts its action mainly through *N*-acetyl-*p*-aminophenol…that might have distinct advantages over acetanilide as an analgesic.' The two investigators similarly found that phenacetin, for years the most popular headache remedy in the United States in the combination APC (aspirin–phenacetin–caffeine), also acted through *N*-acetyl-*p*-aminophenol. This substance, better known as acetaminophen, was subsequently marketed as Tylenol with neither Brodie nor Axelrod receiving any royalties as it never occurred to them to patent their findings.

In 1949, James Shannon, Director of the Goldwater Memorial Laboratories, assumed leadership of the National Heart Institute in Bethesda and took Brodie as well as Julie with him. The two investigators continued their studies of drug metabolism. Although Julie still did not have a doctorate, he was allowed to publish some papers on his own and immersed himself in studies of amphetamine and ephedrine metabolism by intact rodents. He realized that major progress required finding the relevant drug-metabolizing enzymes. In early 1953, with the assistance of Gordon Tomkins, Julie discovered that drug-metabolizing activity was mediated via enzymes in the microsomal fractions of liver and required a soluble factor, which he showed to be NADPH. Thus, Julie discovered what is now known as the system of cytochrome *P*450 mono-oxygenases.

Over the years, Julie's friends urged him to get a PhD so that he could become an independent scientist. Paul K Smith, Chair of Pharmacology at George Washington University, agreed that Julie's published papers could constitute a thesis and that coursework could be minimal as he already had a Masters Degree. Absenting himself from the laboratory for a single year, Julie obtained his PhD in 1955 when he was 42 years old. About this time, Seymour Kety, Scientific Director of the National Institute of Mental Health, established the Laboratory of Clinical Science under Edward Everts, who in turn appointed Julie as head of the Section on Pharmacology. In 1956, Kety reported to the NIMH staff tantalizing reports by Abram Hoffer and Humphrey Osmond that epinephrine was selectively transformed in schizophrenic blood to adrenochrome. Julie tried unsuccessfully to find an enzyme that would convert epinephrine to adrenochrome, but, in the process, noticed an abstract in Federation Proceedings by Marvin Armstrong and Armand McMillan reporting the excretion of an *O*-methylated catecholamine metabolite, 3-methoxy-4-hydroxymandelic acid, also called vanillylmandelic acid (VMA), in the urine of patients with pheochromocytomas. Julie decided to seek the enzyme that might *O*-methylate the catechol ring, based on the recent finding by his NIMH colleague Giulio Cantoni that *S*-adenosylmethionine is the universal methyl donor. In short order, Julie identified catechol-*O*-methyltransferase (COMT). With the help of chemist colleagues, especially Bernhard Witkop, Siro Senoh, and John Daly, Julie was able to work out in detail the metabolic pathways of the catecholamines and, with Irv Kopin, he characterized their physiologic significance.

In 1970, Julie shared the Nobel Prize in Physiology or Medicine with Ulf von Euler and Sir Bernard Katz 'for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation.' Julie's portion of the prize was for his discovery that reuptake is a principal mechanism for neurotransmitter inactivation. Based on the paradigm of acetylcholinesterase, it was assumed that norepinephrine was inactivated enzymatically, either by COMT or monoamine oxidase, but inhibiting these enzymes did not terminate the effects of injected catecholamines. Julie did not begin by investigating neurotransmitter inactivation. Rather, Seymour Kety had obtained custom preparations of [^{3}H]epinephrine to investigate catecholamine metabolism in schizophrenics as a further test of the Hoffer–Osmond hypothesis, and provided Julie with samples. With Hans Weil-Malherbe, Julie investigated the disposition of [^{3}H]epinephrine and, with Gordon Witby, conducted similar studies with [^{3}H]norepinephrine. In both cases, the radiolabel concentrated in sympathetically innervated organs such as the heart, spleen, and salivary glands. George Hertting, a visiting scientist, lesioned sympathetic nerves unilaterally in the cat and observed a selective loss of norepinephrine accumulation into the salivary gland and eye muscles of the lesioned side. Based on these data, Julie proposed that reuptake by sympathetic nerves accounts for synaptic inactivation of norepinephrine. Julie's subsequent studies with drugs provided compelling support for this hypothesis. He showed that cocaine, amphetamine, and other sympathomimetic amines blocked norepinephrine reuptake, a process that presumably accounted for the ability of these drugs to potentiate the effects of sympathetic nerve stimulation, thereby establishing reuptake as the physiologic mode for neurotransmitter inactivation. With Jacques Glowinski and Leslie Iversen, Julie approached the brain utilizing Glowinski's technique for introducing [^{3}H]norepinephrine directly into the lateral ventricles. Glowinski showed that the capacity of tricyclic antidepressants to inhibit norepinephrine accumulation paralleled their antidepressant efficacy. Inhibition of norepinephrine (and serotonin) uptake to this day remains the accepted mechanism of action of these drugs.

The above are only limited highlights of Julie's manifold contributions such as his pineal gland research, which opened up a major field. The dermatologist Aaron Lerner had isolated the pineal gland hormone melatonin as 5-methoxy-*N*-acetylserotonin, leading to Julie's identification of the melatonin-generating methylating enzyme. With Richard Wurtman, Julie showed that melatonin possesses major endocrine actions.

His colleagues have speculated for many decades as to Julie's creative magic. A few themes emerge again and again. Julie had the vision to divine simple approaches to complex problems commenting to the historian Robert Kanigel, 'I am not a complicated person…Picasso makes a single line, but it takes a lot of time and thought.' His background as a technician led to Julie's focus upon methodology. His characteristic 'simple, sensitive and specific' assays enabled him to ask dozens of questions in the time that scientists utilizing tedious methodology might address only one or two. In biomedical research, scientists typically work through their students, and Julie was an ideal mentor. He provided gradations of positive reinforcement, encouraging even modestly successful results and becoming exuberantly ebullient when experiments worked out really well. Most of all, he conveyed that research is fun. As Lincoln Potter commented to Kanigel, 'It was that sense of wonder, magic, discovery and the life that we had when we were kids that Julie brings to science.' I recall a talk he gave soon after winning the Nobel Prize, which he opened by commenting 'It seems that all these speaking invitations are a conspiracy to get me out of the lab. I find it hard to imagine that I am paid a good salary for doing things that are so much fun that I'd work in the lab for no pay.'

Julie, quiet, mild-mannered, self-effacing, was rarely angered. Although his wife Sally and he did not socialize with students, Julie was ever mindful of our personal lives and helpful in our career plans. He and Sally (nee Taub) were wed in 1938. Sally, who also was born on the lower East Side, worked for years as a second grade school teacher and died in 1992 from complications of her diabetes. Their elder son Paul is a Professor of Anthropology at Rippon College in Wisconsin where he and his wife Michelle live with their children Sonya and Sander. His son Fred is a Forestry Consultant in Wisconsin where he resides with his wife Johanna. Their daughter Julia is a student at Bethel College in St Paul, Minnesota, while their son Nathan died in 2004. Julie was immensely devoted to his children and grandchildren and visited frequently in Wisconsin.

Julie himself best summed up his career, 'One of the most important qualities in doing research, I found, was to ask the right questions at the right time. I learned that it takes the same effort to work on an important problem as on a pedestrian or trivial one. When opportunities came, I made the right choices.'

Julie was a founding member of the ACNP and was promoted to Life Fellow Emeritus in 1998.

Solomon H Snyder[1]
[1]*Department of Neuroscience, Johns Hopkins University, School of Medicine, Baltimore, MD*