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The Story of Julius Axelrod (1912-2004): A Testament to Commitment

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Abstract

The key research of Julius Axelrod focused on the release, reuptake and storage of the neurotransmitters norepinephrine and epinephrine. These discoveries provided a new model for understanding the metabolism and regulation of neurotransmitters. In elucidating how neurotransmitters transmit their specific messages, Axelrod not only revolutionized research in catecholamine metabolism, but ultimately fostered the development of therapies for mental illness and pain relief. In 1970 Julius Axelrod was awarded the Nobel Prize in Physiology or Medicine for discoveries related to the mechanisms involved in the storage, release, and inactivation of neurotransmitters.

Introduction

Early years and education

By possessing the best attributes in the broad area of science, Julius Axelrod was a compelling figure in biomedical research (Figure 1). As a former laboratory technician who became a pioneer in neurobiological research, his determination stands out as an example of anyone who is committed to realizing his/her ambitions. Raised by parents who were Jewish immigrants from Poland, his father was a basket maker who sold his wares from a horse-drawn wagon on the streets of lower Manhattan [1,2]. Despite his modest background, young Julius became interested in science, particularly in medicine, at an early age. However, these early years were met with a number of impediments and frustrations. He enrolled in New York University (NYU) in 1929; but had to transfer to the tuition-free College of the City of New York after one year, when he could no longer pay his tuition. He majored in Chemistry, but his best grades were in literature, philosophy, and history. Because Julius had to work after school, most of his studying was done on the subway ride to and from City College [3]. After graduating in 1933, Axelrod was denied admission to medical school because of religious quotas. In addition, because of the Depression, he found it difficult to obtain a position in a medical field. However, Axelrod was eventually employed at the Harriman Research Institute at NYU. He was paid only $25/month for assisting a biochemist in his research [4,5].

In 1935 Axelrod found more permanent employment in the Laboratory of Industrial Hygiene in the New York City Department of Health, where he modified methods for assaying vitamin supplements added to foods. Although young Axelrod found the work routine, the experience that he gained by working there until 1946 would ultimately prove valuable for his future research.

In 1941 Axelord lost his sight in one eye when a bottle of ammonia exploded in his face. As a result, he was declared unfit for military duty. He took advantage of this injury by attending NYU at nights to earn his Master's degree in Chemistry in 1942 [6].

Early career at Goldwater Memorial Hospital

In February 1946, Axelrod arranged a meeting with Bernard Brodie at the Goldwater Memorial Hospital to enhance his knowledge of analgesics. Brodie, a major figure in drug metabolism, was carrying out research at Goldwater and at the time was Professor of Pharmacology at New York University (NYU) (Figure 2). After discussing research strategy with Axelrod, Brodie offered him a position in his laboratory. Axelrod would work independently in Brodie's Laboratory for the next eight years, and Axelrod always considered Brodie a mentor who offered him the intellectual challenges he desired to become successful.

Brodie introduced Axelrod to the subject of drug metabolism when his laboratory was awarded a grant to study why individuals who used certain non-aspirin analgesics, such as acetanilide and phenacetin, were experiencing methemoglobinemia. After developing methods for analyzing acetanilide and its metabolites, Axelrod discovered that aniline was responsible for its toxic effects,

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while acetanilide, being a pro-drug, exerted its pharmacologic action by being metabolized to N-acetyl-p-aminophenol (acetaminophen).

Two papers co-authored by Brodie and Axelrod published in 1948 launched Axelrod's career [7,8]. Acetaminophen was subsequently marketed as Tylenol and became one of the most popular pain relievers in the world. Axelrod followed up this work by investigating the metabolic fate of other analgesics [9].

Career at the national institutes of health

When James Shannon, Director of the Goldwater Laboratories, was named Head of the recently established National Heart Institute at the National Institutes of Health in Bethesda Maryland in 1949, he recruited Bernard Brodie as Chief of the Laboratory of Clinical Pharmacology. Realizing Axelrod's value as a collaborator, Brodie invited Axelrod to accompany him. Initially, Axelrod decided to undertake studies on the disposition of caffeine, including its plasma half-life and tissue distribution [10]. However, because of the advent of new drugs to treat mental illness, such as chlorpromazine and meprobamate, Axelrod soon became interested in studying the sympathomimetic amines, ephedrine and amphetamine.

Sympathomimetic amines were a term coined by the eminent pharmacologist Sir Henry Dale to include drugs that mimic the effects of sympathetic nerve stimulation [11]. Aware that ephedrine and amphetamine, which produced varied behavioral actions, mimicked the effects of sympathetic nerve stimulation, Axelrod decided to investigate which enzymes were responsible for their metabolism. Initially provided with advice about enzymology by a colleague Gordon Tomkins, Axelrod determined that ephedrine was metabolized by two mechanisms, demethylation and hydroxylation [12]. Whereas amphetamine was found to be metabolized by a variety of metabolic pathways [13]. During this period, Axelrod was also involved in metabolic studies of various narcotics and psychoactive drugs [14,15].

By 1954, Axelrod had published 25 articles, despite the fact that he did not own a doctoral degree. However, he began to feel that he did not possess the intellectual freedom that he desired from Brodie. In addition, without an advanced degree, his chances of promotion would remain problematic. So, even though at the time the prospects of a career as an independent investigator were not promising, Axelrod did not possess the necessary inclination or the finances to implement the idea of obtaining a doctoral degree. But fate once again intervened, when in 1953 Axelrod discovered that drug-metabolizing activity was mediated by the cytochrome P-450 enzyme system, which was localized to the microsomal fraction of the liver and required NADPH [16,17]. Because other workers in Brodie's laboratory also demonstrated that the P-450 system metabolizes a wide variety of drugs, Brodie claimed credit for its discovery. Axelrod eventually received recognition for helping to provide the foundation for present-day drug metabolism. However, the controversy surrounding the discovery of the cytochrome system left Axelrod with negative feelings about his mentor, and in 1982 he authored a review on his version of the subject [18].

Because of the lingering resentment he harbored about the drug metabolism affair, Axelrod eventually took a leave of absence from the NIH to enroll as a student in the Department of Pharmacology at George Washington University. Because he had taken requisite courses for his Master's degree, his matriculation as a predoctoral student was rather brief. In addition, his thesis advisor George Mandel allowed him to include some of his recent publications in his thesis, which was entitled "The Fate of Phenylisopropyl-amines," however, he was required to take courses in biochemistry, physiology, and pharmacology and pass a language exam. Axelrod graduated with a Ph.D. in Pharmacology in 1955. He was now equipped with the necessary credentials to become an exceptional figure in the annals of science [19,20].

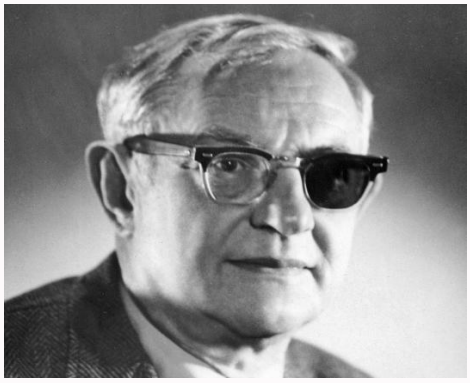

Figure 1: Dr. Julius Axelrod. Courtesy of the Famous People.com last updated October 2017.

Career as an independent investigator

About the time Axelrod began matriculating at George Washington University, He sent letters to the National Institute of Mental Health (NIMH) inquiring about a possible position. One of his letters crossed the desk of Seymour Kety, the new Institute Director (Figure 3). Impressed by Axelrod's publication record, Kety forwarded his application to Edward Evarts, Head of the section on Physiology in the new laboratory in Clinical Sciences. Evarts, who was recruited to the NIMH to study schizophrenia, named Axelrod to Head the new Section on Pharmacology. Evarts also had the foresight to allow Axelrod to develop his own ideas and objectives [21]. So, at the rather advanced age of 42, Julius Axelrod was now able to launch an independent research program. This move finally extricated Axelrod from Brodie's Laboratory and his influence. Moreover, the world-class and eminently successful research program established by Seymour Kety at the NIMH would enable Axelrod to flourish.

As a member of the NIMH, Axelrod felt obliged to undertake a study concerned with mental health. However, in the early 1950's, very little was known about the metabolism of brain catecholamines. Although Axelrod considered the possibility that abnormal metabolism of catecholamines might explain the biochemical basis of mental illness, he knew that he would have to gain knowledge of normal catecholamine metabolism before he would be able to determine any abnormal metabolism. So, Axelrod next focused on finding causal links between drug metabolism and mental health. Initially, Axelrod examined whether Monoamine Oxidase (MAO) inhibitors altered the function of adrenergic neurotransmitters without much success. However, the breakthrough came when Axelrod became aware of an abstract published in 1957 reporting the excretion of the O-methylated product VMA (3-methoxy-4-hydroxy-mandelic acid) in patients with a pheochromocytoma, a tumor of the adrenal medulla [22]. This brief report prompted Axelrod to initiate a study in 1961 to identify the enzyme that would prove that VMA was a metabolite of norepinephrine.

Axelrod found that rat liver produced S-adenosyl-methionine,

Figure 2: Dr. Bernard "Steve" Brodie (1909-1989). Courtesy of the office of NIH History. National Institutes of Health.

Figure 3: Dr. Seymour S. Kety (1915-2000). Taken from Holtzman PS, Sokoloff L, Obituary and Seymour S. Kety, MD (1915-2000). Arch Gen Psychiatry. 2001;58:604-6.

which then donated its methyl group to norepinephrine to form metanephrine, an O-methylated product [23,24]. He discovered that other catechols, including epinephrine and dopamine could also be converted to the O-methylated product and that circulating catecholamines were inactivated by an O-methylation reaction in liver and at certain postsynaptic sites. In 1959 Axelrod succeeded in isolating and purifying the enzyme, which was named catechol-O-methyltransferase [25,26]. This work led to the discovery of a number of methyltranferase enzymes, including one that was responsible for the enzymatic N-methylation of histamine [27]. So only two years after becoming an independent investigator, Axelrod made several fundamental discoveries concerned with the metabolism of catecholamines and drug-metabolizing activity. His later studies would demonstrate the dominance of the uptake system within the neuronal synapse (vide infra).

Reuptake of neurotransmitter: The success that Axelrod achieved with the COMT studies provided the catalyst to continue his work on the mechanisms involved in adrenergic neurotransmission. Although von Euler had demonstrated that the neurotransmitter released from adrenergic nerves was norepinephrine, the mechanisms involved in its inactivation were unknown [28,29]. Axelrod was cognizant of the fact that the actions of acetylcholine at cholinergic sites were rapidly degraded by the enzyme cholinesterase.

Although the prevailing view at the time was that the actions of other neurotransmitters were also annulled by enzymatic processes, the fact that the termination of adrenergic transmission was a slower event suggested to Axelrod that an alternate mechanism might be involved. In addition, he was aware of the fact that when COMT and MAO were inhibited *in vivo*, the effects of systemically administered epinephrine were still rapidly diminished. This prompted Axelrod to consider other explanations.

Because of the low endogenous levels of catecholamines in the urine and sympathetic nerves, Axelrod realized that his intent to elucidate the mechanism involved in catecholamine metabolism could not be fulfilled by existing methodology and that he would need to develop a method that identified very small amounts of radiolabeled catecholamine of high specific activity in order to examine its distribution and half-life in animals. Fortunately, Axelrod became aware of a supply of ^{3}H-epinephrine that had been obtained by Seymour Kety, who planned to investigate catecholamines in schizophrenics [30]. Although Kety was quite critical of Axelrod's idea, he provided Axelrod with a small supply; and Axelrod and Hans Weil-Malherbe were able to demonstrate that, in contrast to the enzymatic breakdown of acetylcholine, tissues innervated by sympathetic nerves, such as heart and salivary glands, sequestered large amounts of unmetabolized radioactive epinephrine in cats [31,32]. The amount of uptake was related to the density of the adrenergic innervation. Furthermore, Axelrod and Georg Hertting discovered that when an organ innervated by sympathetic nerves, such as the heart, was chronically denervated, the ability to take up catecholamine was substantially reduced [33].

Additional evidence verified the existence of the uptake mechanism. Cocaine, which was known to cause super sensitivity to catecholamine, presumably by interfering with its inactivation, markedly reduced the accumulation of radiolabeled catecholamine in tissues innervated by sympathetic nerves. This experiment indicated that cocaine blocked the uptake of catecholamine in sympathetic nerves and enabled the biogenic amine to accumulate in the synaptic cleft, causing an enhanced response of the effector [34]. A number of diverse drugs, including hypotensives and psychotropic drugs were also shown to block uptake [35-37].

Finally, Axelrod and his colleagues identified by electron microscopy the granular structures in nerve endings in which the catecholamines were concentrated. When the nerve endings were prelabeled with tritiated norepinephrine, enhanced radioactive catecholamine release was detected following nerve stimulation [38,39].

On the basis of these studies, an all-encompassing picture of catecholamine metabolism began to emerge. Axelrod proposed that following the interaction with its postsynaptic adrenergic receptor, norepinephrine was recaptured by the presynaptic neuron by an active uptake system, reincorporated into secretory vesicles and recycled for later neurotransmission. This work established reuptake as the physiologic mode of inactivation of catecholamines.

The focus of the next study turned to examining whether a similar mechanism was operative in the central nervous system. However,

because of the blood brain barrier, radiolabeled catecholamine was unable to enter the brain when injected systemically. However, capitalizing on the fact that Jacques Glowinski devised a method for injecting ^{3}H-epinephrine directly into the brain, a differential distribution of the unmetabolized compound was detected in various regions.

From these studies, Glowinski and Axelrod concluded that a similar mechanism for amine uptake existed in the brain [40,41]. In addition, they found that several psychoactive drugs blocked the uptake of ^{3}H-norepinephrine and epinephrine in brain [42]. This work laid the groundwork for the later development of selective uptake inhibitors such as Prozac and Sertraline (Zoloft), which block the reuptake of another neurotransmitter, serotonin [43,44].

The investigations carried out by Julius Axelrod and his colleagues revealed that drugs modulate the sympathetic nervous system in diverse ways. They may block neurotransmitter uptake, inhibit or enhance neurotransmitter activity; alternatively, they may inhibit MAO within the neuron and COMT outside of the neuron. These studies not only provided a new model for understanding the metabolism and regulation of neurotransmitters, but they facilitated the development of new drugs to treat mental illness. Julius Axelrod's outstanding contributions were acknowledged when he shared the 1970 Nobel Prize with Sir Bernard Katz of the United Kingdom and Ulf von Euler of Sweden "for their discoveries concerning the humeral transmitters in the nerve terminals and the mechanism for their storage, release, and inactivation" [45].

Beyond the prize

In his later years, Axelrod continued to make important advances in various areas, including the pineal gland and its key hormone melatonin [46]. He and his colleagues demonstrated that melatonin, like serotonin, was formed from tryptophan. He also found that melatonin had diverse effects on various areas of the central nervous system, but primarily acted as a biological clock to regulate the sleep-wake cycle [47,48]. In 1965 Axelrod and Richard Wurtman published a detailed study of the pineal gland for lay readers in *Scientific American* [49].

T*he Researcher and Educator* Julius Axelrod demonstrated exceptional skills as a researcher, as well as inordinate talents as a mentor [50,51]. His background as a technician enabled him to develop new methodologies; yet he had the vision to direct his attention to simple approaches to fundamental problems and to ask the right questions. In fact, because he disliked dealing with complex problems, Axelrod was rather disdainful of statistics. He remarked "to do good research one must be highly motivated, exercise good judgment, and have imagination and determination, plus a little luck".

Axelrod was also an ideal mentor, who was accessible to students, and used positive reinforcement for encouragement. Research Associate Programs at the NIH enabled recent PhD or MD graduates to spend two or three years working in Axelrod's Laboratory that became a training ground for future leaders in pharmacological research. Axelrod enjoyed working closely with his many colleagues, whom he considered in large part responsible for the success of his laboratory. More than 60 fellows carried out research in Axelrod's Laboratory and most of them went on to productive careers in research. After he received the Nobel Prize, Axelrod felt responsible for making concerted efforts to inform the layman about neuroscience; and in 1974, he published an article in *Scientific American* on the functions of neurotransmitters [52]. In addition, he gave interviews on recent advances in developments in psychopharmacology.

Axelrod also became increasingly involved in many political issues and was active in a number of controversial political causes. For example, Axelrod offered his name to several protest groups against the mistreatment of scientists in the Soviet Union.

Awards and honors

In his later years, Axelrod continued to garner many honorary degrees and professional awards. He served on the editorial boards of several journals, including the Journal of Pharmacology and Experimental Therapeutics, Journal of Neurochemistry, and the International Journal of Psychobiology. He was awarded the prestigious Gairdner Foundation International Award in 1967. In the early 1970's, he served as a member of the Psychopharmacology Study Section at the NIMH. In 1987 the Julius Axelrod Distinguished Lecture Series was established at his alma mater, the City University of New York. The NIH sponsored a scientific symposium in 1992 devoted to Axelrod's life and work and named him a *scientist emeritus* [53].

Conclusion

After his retirement, Axelrod did consulting and was a member of several boards. In addition, just prior to his death at the age of 92, he frequently visited the laboratory as an unpaid researcher. Julius Axelrod's influence extended far beyond his scientific contributions. In establishing fundamental information about how nerve cells interact in the sympathetic nervous system and brain, he provided a factual framework for future research on the biological basis of human behavior which led to the development of new and better modes of treatment of depression, anxiety, and other psychiatric disorders.

References

1. Iversen L. Julius Axelrod: 20 May 1912-29 December 2004. Biogr Mem Fellows R Soc. 2006;52:1-13.
2. Axelrod J. An unexpected life in research. Annual review of pharmacology and toxicology. 1988;28(1):1-24.
3. Snyder SH, Axelrod J. 1912-2004. Biographical Memoirs. National Academy of Sciences. 2005;87:3-5.
4. The Julius Axelrod Papers. Biographical Information. In: Profiles in Science; United States National Library of Medicine.
5. Julius Axelrod (1912-2004). Jewish Virtual Library-A Project of AICE.
6. Craver CF, Axelrod J. New Dictionary of Scientific Biography. 2008.118-23.
7. Brodie BB, Axelrod J. The estimation of acetanilide and its metabolic products, aniline, N-acetyl-p-aminophenol and p-aminophenol free and total conjugated in biological fluids and tissues. J Pharmacol Exp Ther. 1948;94(1):22-8.
8. Brodie BB, Axelrod J. The fate of acetanilide in man. J Pharmacol Exp Ther. 1948;94(1):29-38.
9. Brodie BB, Axelrod J. The fate of aminopyrine (pyramidon) in man and methods for the estimation of aminopyrine and its metabolites in biological fluids. J Pharmacol Exp Ther. 1950;99(2):171-84.
10. Axelrod J, Reichenthal J. The fate of caffeine in man and a method for its estimation in biological fluid. J Pharmacol Exp Ther. 1953;107(4):519-23.
11. Barger G, Dale HH. Chemical structure and sympathomimetic action of amines. J Physiol. 1910;41(1-2):19-59.

12. Axelrod J. Studies on sympathomimetic amines. I. The biotransformation and physiological disposition of l-ephedrine and l-norephedrine. J Pharmacol Exp Ther. 1953;109(1):62-73.

13. Axelrod J. Studies on sympathomimetic amines. II. The biotransformation and physiological disposition of d-amphetamine, d-p-hydroxyamphetamine and d-methamphetamine. J Pharmacol Exp Ther. 1954;110(3):315-26.

14. Axelrod J. The enzymatic N-demethylation of narcotic drugs. J Pharmacol Exp Ther. 1956;117(3):322-30.

15. Axelrod J, Brady RO, Witkop B, Evarts EV. The distribution and metabolism of lysergic acid diethylamide. Ann N Y Acad Sci. 1957;66(3):435-44.

16. Axelrod J. Journey of a late blooming biochemical neuroscientist. J Biol Chem. 2003;278(1):1-13.

17. Axelrod J. The Discovery of the Microsomal Drug Metabolizing Enzymes. The History of Neuroscience; Autobiography. 1996;1:57-60.

18. Axelrod J. The discovery of the microsomal drug-metabolizing enzymes. Trends in Pharmacological Sciences. 1982;3:383-6.

19. Snyder SH. Axelrod J. 1912-2004. Biographical Memoirs. National Academy of Sciences. 87:8.

20. Craver CF, Axelrod J. New Dictionary of Scientific Biography. 2008:120-1.

21. Kanigel R. Apprentice to Genius. The making of a scientific dynasty. The Johns Hopkins University Press. 1986;6.

22. Armstrong MD, McMillan A. Identification of a major urinary metabolite of norepinephrine. In Federation Proceedings. 1957;16(1):146.

23. Axelrod J. Noradrenaline: fate and control of its biosynthesis. Nobel Lecture. 1970:45-7.

24. Axelrod J. O-Methylation of epinephrine and other catechols *in vitro* and *in vivo*. Science. 1957;126(3270):400-1.

25. Axelrod J, Tomchick R. Enzymatic O-methylation of epinephrine and other catechols. J Biol Chem. 1958;233(3):702-5.

26. Axelrod J. Methylation reactions in the formation and metabolism of catecholamines and other biogenic amines. Pharmacol Rev. 1966;18(1):95-113.

27. Brown DD, Axelrod J, Tomchick R. Enzymatic N-methylation of histamine. Nature. 1959;183(4662):680.

28. Von Euler US. The presence of a substance with sympathin E properties in spleen extracts. Acta physiologica Scandinavia. 1946;11(2-3):168-86.

29. Von Euler US. The presence of a sympathomimetic substance in extracts of mammalian heart. J Physiol. 1946;105(1):38-44.

30. Kanigel R. Apprentice to Genius. The making of a scientific dynasty. The Johns Hopkins University Press. 1986:110-1.

31. Axelrod J, Weil-Malherbe H, Tomchick RJ. The physiological disposition of 3H-epinephrine and its metabolite metanephrine. J Pharmacol Exp Ther. 1959;127:251-6.

32. Whitby IG, Axelrod J, Weil-Malherbe HJ. The fate of H3-norepinephrine in animals. J Pharmacol Exp Ther. 1961;132:193-201.

33. Hertting G, Axelrod J, Kopin IJ, Whitby LG. Lack of uptake of catecholamines after chronic denervation of sympathetic nerves. Nature. 1961;189:66.

34. Whitby IG, Hertting G, Axelrod J. Effect of cocaine on the disposition of noradrenaline labelled with tritium. Nature. 1960;187:604-5.

35. Hertting G, Whitby IG, Axelrod J. Effect of drugs on the uptake and metabolism of 3H-norepinephrine. J Pharmacol Exp Ther. 1961;134:146-53.

36. Axelrod J, Whitby LG, Hertting G. Effect of psychotropic drugs on the uptake of 3H-norepinephrine by tissues. Science. 1961;133(3450):383-4.

37. Axelrod J. The uptake and release of catecholamines and the effect of drugs. Progress in Brain Research. 1964;8:81-9.

38. Hertting G, Axelrod J. Fate of tritiated noradrenaline at the sympathetic nerve-endings. Nature. 1961;192:172-3.

39. Axelrod J. Adrenergic Neurotransmission. Ciba Foundation Symposia; London. Churchill. 1968. Chapter 4.

40. Glowinski J, Kopin IJ, Axelrod J. Metabolism of (3H) norepinephrine in the rat brain. J Neurochem. 1965;12(1):25-30.

41. Glowinski J, Axelrod J. Effect of drugs on the disposition of 3H-norepinephrine in the rat brain. Pharmacol Rev. 1966;18(1):775-85.

42. Glowinski J, Axelrod J. Inhibition of uptake of tritiated-noradrenaline in the intact rat brain by imipramine and structurally related compounds. Nature. 1964;204:1318-9.

43. Fuller RW, Wong DT. Serotonin uptake and serotonin uptake inhibitors. Ann N Y Acad Sci. 1990;600:68-78.

44. Zweig M, Axelrod J. Relationship between catecholamines and serotonin in sympathetic nerves of the rat pineal gland. J Neurobiol. 1969;1(1):87-97.

45. Bernard K, Von Euler US, Axelrod J. The Nobel Prize in Physiology or Medicine 1970. Nobel Media AB. 2019.

46. Axelrod J, Wurtman RJ, Chu E. Melatonin, a pineal substance: Effect on the rat ovary. Science. 1963;141(3577):277-8.

47. Axelrod J, Wurtman RJ, Fischer JE. Melatonin synthesis in the pineal gland. Effect of light mediated by the sympathetic nervous system. Science. 1964;143(3612):1328-30.

48. Axelrod J, Snyder SH, Zweig M, Fischer JE. Control of the circadian rhythm on serotonin content of the rat pineal gland. Proc Natl Acad Sci U S A. 1965;53:301-5.

49. Wurtman RJ, Axelrod J. The pineal gland. Scientific American. 1965;213:50-60.

50. Iversen L. Julius Axelrod. 30 May 1912-29 December 2004. Biogr Mem Fellows R Soc. 2006;52:10-1.

51. Kanigel R. Apprentice to Genius. The making of a scientific dynasty. The Johns Hopkins University Press. 1986;7.

52. Axelrod J. Neurotransmitters. Scientific American. 1974;230:59-71.

53. Julius Axelrod- Biographical. Nobel Media AB 2019. 2018.