Axelrod, the Pineal and the Melatonin Hypothesis: Lessons of 50 years to shape chronodisruption research

Thomas C. Erren [1, 2], Russel J. Reiter [3]

1 Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research, University of Cologne, Lindenthal, Germany.
2 Temporary affiliation: Visiting scholar at the University of California, Berkeley, School of Public Health, Division of Epidemiology, 50 University Hall MC7360, Berkeley, CA 94720-7360.
3 Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio, TX, USA.

Correspondence to: Prof. Thomas C. Erren, MD, MPH.
Director of the Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research, University of Cologne, Lindenthal, Germany.
TEL.: +49-221-4784450; FAX: +49-221-4785119;
E-MAIL: tim.erren@uni-koeln.de; erren_tc@berkeley.edu

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Abstract

With key work in the 1950s and 1960s, the 1970 nobel laureate Julius Axelrod made major contributions to the development of pineal science. Looking back at some of his accomplishments in and for the field, we feel that lessons can be derived for future work regarding impairments of the pineal gland's and melatonin's many functions for promoting health and preventing disease in man.

COMMENTARY

Some 85 MEDLINE-listed papers and some 15 years of his productive lifetime Axelrod focused on the pineal's role and on facets of melatonin, respectively. Between 1960 and 1965, he conceived and conducted pioneer work which led to suggesting that the powerful neurotransmitter melatonin enabled the pineal gland to act as a biological clock (Axelrod and Wurtman 1966). Still in 1965, "The Melatonin Hypothesis" was formulated (Wurtman and Axelrod 1965). This hypothesis proposed causal links between melatonin as the pineal's principal hormone which is regulated by environmental lighting (Wurtman et al. 1963), on the one hand, and causal links between melatonin and a number of pineal-gonadal effects, on the other. This conceptualization made the mammalian pineal a "neuroendocrine or neurochemical transducer" (Wurtman and Anton-Tay 1969; Axelrod 1974) where the gland translates environmental light information into endocrine signals to many parts of the body via the time messenger melatonin. Importantly, the melatonin hypothesis provided a testable framework for studies into relationships between light, the pineal and melatonin and a host of endpoints, be they beneficial or detrimental.

With a view to main themes of Axelrod's studies (light, the pineal, melatonin, biological clocks, neuroendocrine effects), abundant experimental information and limited epidemiological information has been synthesized in recent years in the chronodisruption theory (Erren and Reiter 2008). Actually, this theory consolidates many facts documented over decades with what Pittendrigh has postulated 50 years ago (Pittendrigh 1960):

"…. circadian rhythms are inherent in and pervade the living system to an extent
that they are fundamental features of its organization; and to an extent that if deranged they impair it".

In this vein, chronodisruption was defined (Erren and Reiter 2009) "as being a breakdown of phasing internal biological systems appropriately relative to the external, i.e., environmental changes, which leads to chronobiological disorders". Now, since a cascade of chronodisruption studies – both experimentally and epidemiologically – can be expected, a closer look back to Axelrod's research and to scientific perspectives he provided seems warranted.

Axelrod's prolific research may be organized into – at least – three phases with some overlap: the analgesic research, the catecholamine research and the pineal gland research. His work on pain-killers (Brodie and Axelrod 1948) in the 1940s ultimately contributed to the development of paracetamol (Tylenol). Highest scientific and public visibility he earned by elucidating how noradrenaline is released, reuptaken and stored in the brain; after all, it won him – together with Bernard Katz and Ulf von Euler – the shared Nobel Prize in Physiology or Medicine in 1970. His awarded work ultimately paved the road to subsequent selective serotonin reuptake inhibitors, known to many for instance as Prozac. Remarkably, his nobel prize neurotransmitter work had significant interfaces with his major contributions to understanding the pineal's and melatonin's physiological roles and how they are regulated by light and during the sleep-wake-cycles. This is, for instance, evinced by Axelrod's 1970 Nobel Lecture (Axelrod 1970) in which he repeatedly points to the pineal's role in his research of the fate and control of the biosynthesis of noradrenaline. In fact, "The pineal gland was chosen [for localization of noradrenaline retention] because of its rich sympathetic innervation" (Axelrod 1970: pages 448-449) and by studying the pineal gland, Axelrod and his colleagues gained many insights into how effector organs were regulated by sympathetic nerves. The heading of the penultimate paragraph of the nobel lecture is "Noradrenaline as a neurochemical transducer in the pineal gland" (Axelrod 1970: pages 462-463). There, Axelrod described that a year before melatonin was discovered by Lerner (Lerner et al. 1959), he had found an O-methylating enzyme, COMT (Axelrod 1957). In the search for the enzyme that O-methylates indoles to generate melatonin, Axelrod and Weissbach identified such an enzyme which they named hydroxyindole-O-methyltransferase, HIOMT (Axelrod and Weissbach 1961). Still in 1961, N-acetyltransferase (NAT) which acetylates serotonin to N-acetylserotonin which – when O-methylated by hydroxyindole-O-methyltransferase – is formed into melatonin, was also described by researchers around Axelrod (Weissbach et al. 1961).

The 1970 nobel prize has been awarded to Axelrod for elucidating the fate and control of the transmitter substance noradrenaline. The melatonin hypothesis, formulated in the aforementioned contribution to *Scientific American* (Wurtman and Axelrod 1965), is about control as well: this time, though, it is about pineal control via melatonin of "the neurendocrine apparatus" (Wurtman and Axelrod 1965). One such link, fitting well into the principal framework of the melatonin hypothesis, namely control of reproductive physiology in photoperiodic mammals by the pineal gland was unequivocally shown in 1965 and 1966 (Hoffman and Reiter 1965; Reiter and Hester 1966).

Axelrod's opposition in the early 1970s to the reductionist focus to cure one disease endpoint by the Nixon-founded *Conquest of Cancer Agency* on the expense of research into other medical problems could provide lessons for research into the wealth of functions of the pineal and the wide-ranging effects of melatonin as well. With reference to the original 1965 melatonin hypothesis (Wurtman and Axelrod 1965), allowing numerous predictions for rigorous testing, we advocate not to focus prematurely on the development of cancers alone when researching adverse health effects that may stem from or be related to chronodisruption. Indeed, the original melatonin hypothesis leaves room for broadly-based chronodisruption studies, including research into chronic processes beyond cancer, such as ageing, neurodegenerative disease and sleep and reproductive disorders. The last sentence from the 1965 *Scientific American* article proposing "The Melatonin Hypothesis" may therefore be quoted verbatim:

"One is tempted to argue teleogically that
any control mechanism
as complicated and sensitive as that found in the mammalian pineal gland
must have some place in the economy of the body".

In conjunction with the earlier Pittendrigh quote, the deranged organization of circadian rhythms, conceptualized as chronodisruption, can certainly be expected to compromise the economy of physiologically effective processes in our bodies, and thus impair health at different organizational levels. In conclusion, we suggest that universal – rather than reductionist – research into chronodisruption holds promise to understand numerous adverse health effects related to the pineal and to melatonin.

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