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# The Pineal Gland

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**Abstract**
Although the pineal gland (epiphysis cerebri) has been noted in medical writings for at least 2,000 years its possible physiological role remains unresolved. Early Greek anatomists, including Herophilus and his disciples, believed that the cerebral ventricles were the seat of the mind and that the pineal body or conarium had a sphincteric function to regulate the flow of thought. This concept was refuted by Galen who concluded that the pineal was probably a gland, similar to the lymph glands. Belief in a thought sphincter persisted and Galen ascribed this function to the cerebellar vermis.

In the seventeenth century Descartes established the idea that this organ was the seat of the soul. It is an awe-inspiring reflection of the power of Cartesian authority that, three centuries later, this is still the first association in the minds of many when the pineal gland is mentioned. His opinions were not accepted by everyone. Thomas Gibson, for example, in his descriptions of the anatomy of the brain in 1763 returned to the genital analogies of the early anatomists with respect to the pineal body.

"The first is Glandula pinealis, or Penis; because it representeth the Pine-nut, or a Man's Yard. It is seated in the beginning of that Pipe, by which the third and fourth Ventricles are united . . . This Gland *des Cartes* thinks to be the primary seat of the Soul, and that all animal operations draw their origine from it. But *Bartholin* has sufficiently confuted that opinion; for it seems to be but of the same use as other glands, and particularly the GlanduIa pituitaria placed near to it, viz. to separate the *Lympha* from the Arterial blood; which Lympha is resorbed by the Veins . . . Near to this on both sides of this third ventricle four round bodies appear. The two upper are lesser and are called Testes: the two greater are lower, and are called Nates. The chink between the Nates is called Anus" .



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# THE PINEAL GLAND


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Although the pineal gland (epiphysis cerebri) has been noted in medical writings for at least 2,000 years its possible physiological rôle remains unresolved. Early Greek anatomists, including Herophilus and his disciples, believed that the cerebral ventricles were the seat of the mind and that the pineal body or conarium had a sphincteric function to regulate the flow of thought. This concept was refuted by Galen who concluded that the pineal was probably a gland, similar to the lymph glands. Belief in a thought sphincter persisted and Galen ascribed this function to the cerebellar vermis.

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In the twentieth century these philosophic postulates of sphincter of the mind and repository of the soul have been supplanted by ascribing a neuro-endocrine function to the pineal. Initially this idea developed from the observation of clinical relationships. In 1898 Heubner reported that a boy who had been observed to have precocious somatic and sexual development died with a tumour of the pineal gland. Associated changes in sexual development have been noted in about one third of case reports. Sexual precocity is a particular feature of pineal tumours in boys. It is a matter for debate whether the effects upon the gonads result from disturbance of pineal endocrine activity, from associated pituitary dysfunction or from the effects of pressure upon the hypothalmus. Kitay and Altschule in their review of the literature up to 1954, concluded that precocious puberty resulted from reduced pineal activity, whereas true pineal tumours with increased activity caused delayed sexual development in children.

Such observations from the field of clinical medicine have naturally led to a renewal of interest in the pineal body from time to time and investigations have been extended to the experimental laboratory. A number of these studies indicate that the pineal gland and its secretions may have an important rôle in the modification of endocrine function by environmental influences.

ment cells. Subsequent chemical analysis identified the active principle as N-acetyl-5-methoxytryptamine or melatonin. Within the next few years Bagnara had conducted some elegant experiments on tadpole melanocytes. He concluded that melatonin (or a similar amine) was secreted by the pineal in response to darkness and that, in conjunction with pituitary melanocyte-stimulating-hormone (MSH),

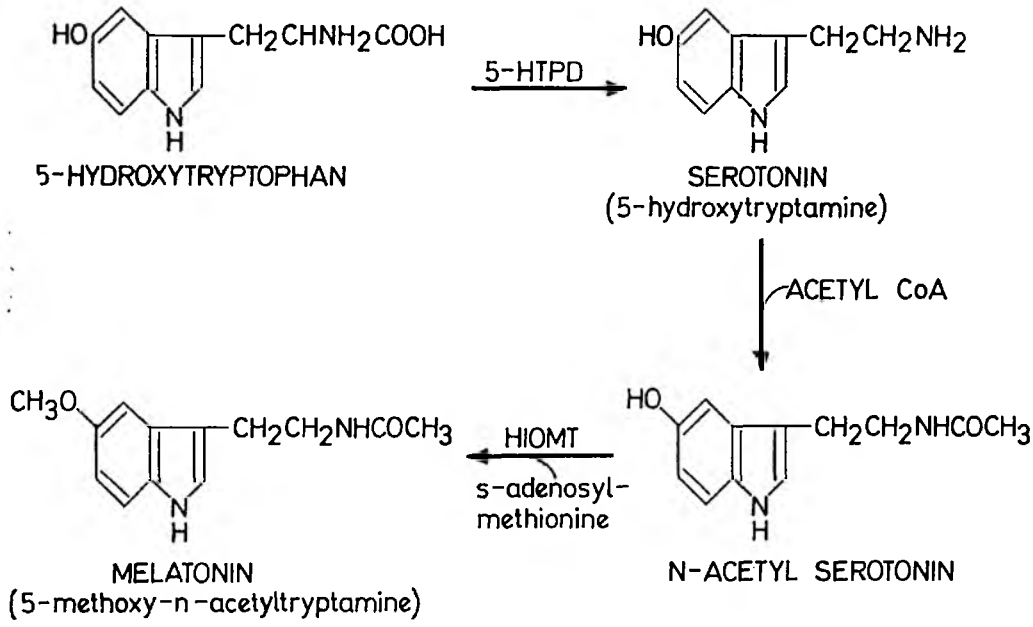


FIGURE 1

*Metabolism of 5-hydroxytryptophan to melatonin in rat pineal gland as suggested by Wurtman. The enzymes 5-HTPD (5-hydroxytryptophan decarboxylase) and HIOMT (hydroxyindole-O-methyl transferase) are under photoperiodic control, the activity of the former increasing during illumination and of the latter during the hours of darkness.*

## PINEAL HORMONE

A significant contribution to knowledge of pineal function was made by Lerner and his colleagues in 1958. From bovine pineal glands they extracted a substance with the remarkable property of blanching frog's skin. This is the most powerful agent known to cause aggregation of melanin granules in amphibian pig-

it was concerned with the adaptive responses to changes in environmental illumination.

The biosynthetic pathways from tryptophan to melatonin have been established by Axelrod and his collaborators (Fig. 1). The essential final step from N-acetylserotonin is effected by the enzyme hydroxy-indole-O-methyl-transferase (HIOMT) with co-factor S-adenosyl-methionine as a methyl donor. This

enzyme and the capacity to synthesize melatonin has been restricted to the pineal glands of all mammalian organs so far investigated. Relatively small amounts of melatonin can, however, be manufactured by the brain and eye of some birds and amphibia.

The stage was now set for the collation of these findings with earlier and concurrent observations on the biological effects of excision of the pineal gland, administration of pineal extracts and the suppression of pineal "activity" by manipulation of the environment.

#### EFFECTS OF LIGHT ON THE PINEAL GLAND

The most striking effect of exposure to continuous illumination in rats, the species most frequently studied, is the induction of a state of persistent oestrus in females. In association with this there is a marked decrease in the size and weight of the pineal gland. Melatonin content and HIOMT activity are depressed.

Quay has found that serotonin levels in the pineal are greatest at mid-day and lower at night. In contrast melatonin content is low by day with peaks after darkness.

#### ANATOMY OF THE PINEAL

The Dutch neuro-anatomist Ariëns Kappers has made a particular study of the anatomy of the pineal gland. Although the epiphysis is embryologically of diencephalic origin it loses all nerve connections with the brain soon after birth. The pineal gland of the adult is richly served by sympathetic fibres deriving their origin from the superior cervical ganglion in the neck and entering the skull in association with cerebral blood vessels. Electron-microscopic studies have revealed sympathetic nerve endings terminating directly on pineal parenchymal cells.

During its evolutionary development the pineal has become modified from the light-sensitive structure of amphibia — the "third eye" — to an organ in which the morphological characteristics of its cellular elements are more suggestive of a glandular, secretory nature. Recent studies have confirmed the opinion expressed by P. T. Herring of St. Andrews in his monograph of 1927 that "the mammalian pineal body cannot be regarded morphologically or histologically as a vestigial structure. It is not a remnant of the parietal eye of reptiles, but an organ which persists throughout the vertebrate series and attains a high degree of specialisation in higher members of the series".

#### THE PINEAL AND THE GONADS

The effects upon the gonads of excision of the pineal gland are similar to those resulting from exposure to continuous light. These include hypertrophy of the gonads, acceleration of vaginal opening and prolongation of oestrus. It has been shown further that these effects can be reversed or blocked by the administration of pineal extracts or melatonin. The fact that the changes induced by light or by excision of the pineal are not additive is suggestive of the gland being concerned in the mechanism of light-induced alterations of gonadal function.

By the use of suitable radioactive tracers melatonin is found to be concentrated not only in ovaries but also in the pituitary. Further evidence that the pituitary is involved in the pineo-gonadal relationship is derived from the observation that pinealectomy increases pituitary gonadotrophins but the administration of pineal extract reduces the gonadotrophin content of the pituitary and the level of circulating gonadotrophins.

The nervous pathways integrating retina, superior cervical ganglion and the pineal gland have not been established. Their existence is indicated by the blockage of light-induced changes in the gonads which results from both enucleation of the eyes and bilateral superior cervical ganglionectomy.

From these and other observations a plausible theory of possible pineal function has been put forward by Wurtman, Axelrod and their colleagues. The pineal gland seems to operate as a "biological clock" by converting into hormonal terms the cyclical nervous activity induced by changes in environmental lighting thus influencing target organs of which the gonads are pre-eminent.

#### THE PINEAL AND OTHER ENDOCRINE ORGANS

A relationship to other endocrine organs has not been so clearly established. There are suggestions that the thyroid gland is affected by excision of the pineal; and that, conversely, suppression of thyroid function results in alter-

ations in pineal constituents. The evidence is so far inconclusive.

The pineal gland does seem to influence the adrenal glands. Attention has focussed mainly on aldosterone production. Although conflicting results have been obtained most studies indicate that the pineal, and extracts from it, stimulate aldosterone secretion.

#### ENDOCRINE RHYTHMS

In 1943 Pincus demonstrated that an increase in urinary ketosteroid excretion occurred in the evening. Since that time a variety of endocrine products and their physiological consequences have been shown to fluctuate in an approximately 24-hour or circadian rhythm. These include the secretion of corticosteroids, the number of circulating eosinophils, ascorbic acid levels in the ovary, prolactin content of the pituitary, the level of thyroid-stimulating hormone in the blood and many others. Such rhythms have been observed in several species from birds to man and some can be influenced by suitable manipulation of environmental lighting. Many of these phenomena, however, revert to what appears to be intrinsic rhythmic activity after an initial response to environmental changes. Others appear to depend more directly upon environmental lighting for their cyclical behaviour and it has been suggested that even endogenous rhythms may be governed by natural illumination acting as a "Zeitgeber". The possibility that the circadian rhythm of pineal amines is concerned in this mechanism awaits confirmation.

In many species photoperiodic influences govern seasonal behaviour which is under endocrine control. For example, many birds respond to the "long days" of spring by sexual maturation. Dutch and Japanese farmers have traditionally exposed song-birds to extra illumination in the autumn to induce singing in the winter — a phenomenon dependent upon testicular function. Other species, like the sheep, come into oestrus during the "short days" of autumn in the northern hemisphere, and the timing of oestrus can be set by suitable alteration of environmental illumination.

The complex nature of these behavioural phenomena is demonstrated by the ferret. Premature oestrus can be induced by the addition of an extra hour of lighting at midnight in winter or by increase in the artificial day-length to 14 hours. However, the totally unnatural schedule of 2 hours light, 10 hours darkness. 2 hours light, 10 hours darkness in the day achieves the same effect.

That man is not spared from such influences is indicated by Zacharias and Wurtman who found that the onset of the menarche occurs more than a year earlier than in normal adolescents in those girls blinded at birth by retrolental fibroplasia. It is also of interest that the phenomenon of "furore sexualis" in the Esquimaux after the long winter days may be an example of man's seasonal behaviour in response to environmental factors.

#### THE PINEAL GLAND AND MALIGNANT TUMOURS

In the Department of Clinical Surgery we have found that the induction of either simple or malignant mammary tumours in the rat by carcinogenic hydrocarbons can be modified by environmental illumination. Exposure to continuous light results in predominantly fibroadenomatous tumours. There are associated changes in the pituitary, ovaries and pineal gland. The administration of melatonin has resulted in a significant increase in the number of mammary adenocarcinomas induced by the carcinogen.

An interesting association between the pineal gland and cancer in man has been reported by Rodin and Overall. In their autopsy series the size and weight of the pineal was significantly increased in patients who had died from a variety of malignant diseases compared with those in whom death was caused by non-malignant conditions. The pineal gland was shown to be enlarged in the middle-aged and elderly. This is not, as might be anticipated, solely the result of increasing calcification. Functional parenchymal tissue remains and enzymic activity is high even in the elderly. There is obviously a need for more careful study of the pineal gland which is rarely considered during routine post-mortem examination.

#### CONCLUSION

For centuries the pineal gland has been one of the enigmas of the central nervous system. The evidence from recent investigations suggest a physiological rôle as a neuro-endocrine transducer by which environmental information modifies the function of the gonads and related endocrine organs. Its main clinical value remains as a useful landmark in neuroradiology but it can no longer be regarded as a functionless vestigium.

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