The Clinical Diagnosis of Pinealoma*

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In spite of concerted efforts by many investigators, the function of the pineal gland remains an enigma. Certainly understanding has progressed since the observations of the philosopher Herophilus who thought that the pineal was a sphincter to control the flow of thought from the ventricles or Descartes' proclamation that the pineal was the "Seat of the Soul." Unfortunately, no investigator has yet identified a single hormone produced exclusively by the pineal gland that influences a distant target organ(s). Therefore, a review of pineal physiology is a prerequisite to understanding the difficulties encountered in the diagnosis of pineal gland tumors.

The Pineal Gland

The human pineal organ arises from the ependyma which lines the roof of the third ventricle, but there are no direct neural connections with the brain. The pineal gland lies beneath the posterior border of the corpus colossum, weighing approximately 100 to 180 mgm in the adult and being 5 to 9 mm long by 3 to 6 mm wide. The gland is divided into lobules by connective tissue septa which contain blood vessels and unmyelinated nerve fibers. Within each lobule are pinealocytes with long intertwining processes and glial cells that appear morphologically similar to astrocytes. Soon after birth, pinealocytes produce a ground substance matrix which calcifies intracellularly and extracellularly. These early calcifications are not visible by x-ray, but they can be demonstrated at autopsy prior to one year of age. X-ray evidence of pineal calcifications does not commonly occur in most normal individuals until after puberty.

Innervation of the pineal gland in mammals is by autonomic nerve fibers arising from the superior cervical ganglia. If the autonomic nerve fibers are surgically interrupted and/or the eyes are enucleated, there is a loss of a measurable biochemical response by the pineal gland to light exposure. In mammals, pineal endocrine response is also lost in the presence of β-adrenergic blockade, suggesting noradrenaline transmission for activation of the pineal biochemical systems. In birds and fish, the interruption of nerve connections or eye enucleation does not abate the biochemical response of the pineal gland, thus indicating a possible direct "third eye" function in these species which is not present in mammals.

The pineal gland and the appendix produce melatonin, an indoleamine which causes frog melanophores to contract and thereby blanch the skin. Melatonin is produced by the action of
the enzyme hydroxyindole-O-methyl transferase (HIOMT) on the substrate N-acetyl-5-hydroxytryptamine (figure 1). HIOMT activity is suppressed when mammals are exposed to light, returning to measurable levels after a period of darkness.\(^{17}\) Measurement of melatonin in human sera and cerebrospinal fluid parallels HIOMT activity, being highest during darkness and unmeasurable after light exposure.\(^{12}\) Mean blood levels of melatonin by radioimmunoassay at night in normal human volunteers is 102 pg per ml as compared to 54 pg per ml in cerebrospinal fluid (CSF) obtained by lumbar puncture.\(^{14}\) Other variables, such as the menstrual cycle, may also affect melatonin serum levels; melatonin rises markedly during menstruation and falls during ovulation.\(^{15}\) Unfortunately, urinary values

![Figure 1](image)

**Figure 1.** Melatonin is produced by the action of the enzyme hydroxyindole-O-methyl transferase (HIOMT) on the substrate N-acetyl-5-hydroxytryptamine.

...for melatonin are much more variable and more difficult to measure, but they are highest during darkness in normal individuals.\(^{17}\) In blind volunteers, melatonin levels in urine are cyclical but do not bear relationship to light or darkness.\(^{6}\)

The biological role of melatonin in man is not as well documented as are the levels in CSF and blood. For many years it was believed that melatonin was the "antigonadotropic" hormone (AGH) because pineal extracts retarded onset of sexual maturity in mammals, while pineal ablation was associated with early sexual maturation. Recently, investigators have questioned whether or not melatonin is the active AGH factor in pineal extracts. Benson\(^{2}\) has shown that melatonin-free pineal extracts have potent AGH activity in rats. A new protein, arginine vasotocin (AVT), had also been found in pineal extracts from mice, and it has a maturational inhibition effect on mouse ovaries.\(^{13}\) Small polypeptides from pineal extracts have been found to inhibit lutenizing hormone release from rat pituitaries with secondary infertility.\(^{8}\) Finally, researchers have recently found high levels of gonadotropin-releasing hormone and thyroid releasing hormone in procine, bovine and ovine pineal glands; these hormone levels were 10 to 20 times higher than levels in the hypothalamus,\(^{1}\) but their significance is not yet known.

The active components in pineal extracts, which account for antgonadotropic effects in man, continue to be elucidated, but presently all investigational data are consistent with the concept that the pineal gland produces a substance which inhibits the release of lutenizing hormone from the anterior pituitary without directly changing follicle stimulating hormone.\(^{8}\) Other target organs that may be under pineal influence are yet unknown, but it is possible that the pineal hormone also has a direct action on human gonadal tissue. Finally, the modulation of pineal melatonin release by light exposure is
Diagnosis of pinealoma is most commonly made by pneumoencephalography or computerized tomography. However, since the advent of RIA techniques for sensitive measurements of serum and CSF melatonin, it is expected that this test may be used in the future for diagnosis. Assays of two pineal tumors have revealed markedly increased HIOMT activity which would suggest increased melatonin production by the tumors. The applicability of melatonin assays is still unproven but data should be available soon from ongoing studies.

Therapy consists of radiation to the area or surgical removal, with the five year survival rate at 50 percent. Hopefully, this survival rate will be improved in the future with the development of a sensitive serum assay of one of the pineal extracts being investigated.

References

11. SHAW, K. M.: The pineal gland: A review of the biochemistry, physiology and pharmacological


