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The Human Pineal Gland in Malignancy

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With 6 Figures

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Summary

The weight and degree of calcification of 500 pineal glands has been measured. The degree of cellularity, the size of the pineocyte nuclei and the extent of degeneration has been estimated in histological examinations of the glands.

There are some differences in the weight of the gland in males and females of different ages and part of this is due to variations in the amount of calcium in the glands. There is only a minor decrease in the cellularity of the glands with increasing age, and this is accompanied in females by a slight increase in fibrosis and gliosis. The weight of the gland is high in patients dying from trauma and burns.

No statistical differences are found in the weight of the pineal glands from patients dying of malignant and non-malignant conditions, although in most age-groups the glands tend to be smaller in patients dying of malignancy. On the other hand patients dying from carcinoma of the breast and from melanoma have much larger glands than those dying from sarcoma.

Key words: Human pineal gland, malignancy.

Introduction

In general the pineal gland is the organ most neglected when autopsies are carried out on humans. As a result of this very inadequate information is available in the literature as to the normal range of variations in the size, weight and histological appearances of the gland.

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Although there are reports in the literature on variations in the weight, degree of calcification and histological appearances of the pineal gland in malignancy, these are, on the whole, poorly controlled as far as comparisons with the normal gland are concerned (*Kutcherenko*, 1941; *Hajdu, Porro, Lieberman*, and *Foote*, 1972).

Material and Methods

A survey has been carried out on a series of 500 pineal glands from patients coming to autopsy in a single hospital during a two-year period. Of these glands 154 were from patients dying of malignant conditions. The glands were fixed in formol saline for one to two weeks and then blotted dry and weighed to the nearest milligram. Decalcification was then carried out in a formic acid-formaldehyde solution and when this was completed the glands were re-weighed. The difference in weight before and after decalcification has been accepted as the weight of the calcium contained within the gland.

Histological sections cut at 5μ were then prepared from the decalcified glands and stained with haematoxylin and eosin (H & E). Measurements of the degree of cellularity, the size of the nuclei and extent of degeneration were carried out on H and E sections in the following ways. The degree of cellularity was determined by projecting a medial histological section of the gland at a magnification of $\times 315$, on paper divided into 1 cm squares. The outlines of the whole section together with those of the parts occupied by parenchymal cells were then drawn on the paper. The number of squares within the lines demarcating the cellular areas were counted and expressed as a percentage of the total number of squares within the gland outline. The mean diameter of the parenchymal-cell nuclei in the central part of the gland was calculated from 20 nuclei measured in two axes at right-angles. The extent of fibrosis, gliosis and lobulation together with the amount of pigment in the parenchymal cells was estimated subjectively and a score of 0—3 given for each feature. The mean score was then calculated for each age-group in both males and females.

Results and Discussion

Table 1 shows the weight of non-malignant gland in males and females of different ages. In males there is a gradual increase in the weight up to old age, whilst in females by far the highest weights are in the 30—59-year age-groups. The difference between males and females is statistically highly significant in the 45—59-year age-group. These findings certainly indicate that differences in the weight of the gland in males and females must be taken into account in comparisons of the gland from patients dying of different diseases.

Table 1. *Weight of pineal glands (non-malignant cases)*

Age (years)	Males	Females
14—29	108	136
30—44	125	194*
45—59	130	185**
60—74	166	149
75—95	158	140

* $p < 0.05$.
** $p < 0.001$.

Part of the increase in weight of the gland in females in the 30—59-year age-group, but clearly not all of it, is due to the presence of increased amounts of calcium (Fig. 1). When the percentage calcification is analysed in five-year-stages it is clear that some glands, particularly in the 46—50-year age-groups, contain quite large amounts of calcium (Fig. 2). The graph also shows that the degree of calcification of the pineal in males remains fairly constant during adult life.

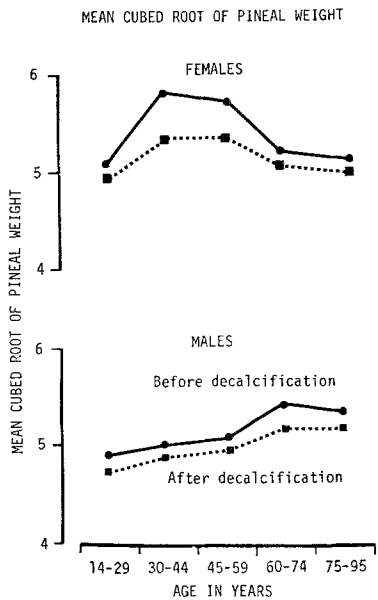

Fig. 1. Mean cubed root weight of pineal gland in normal males and females at different ages before and after decalcification

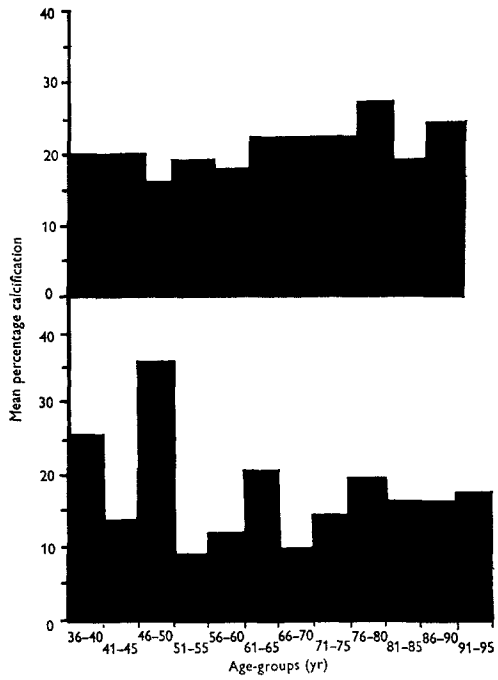

Fig. 2. Mean percentage calcification in normal males (upper graph) and females (lower graph) according to age-groups

The percentage of the gland taken up by pinealocytes is seen in Fig. 3. There is possibly some fall in the pinealocyte cellularity in males with age, but in females this is not as well marked. It is an

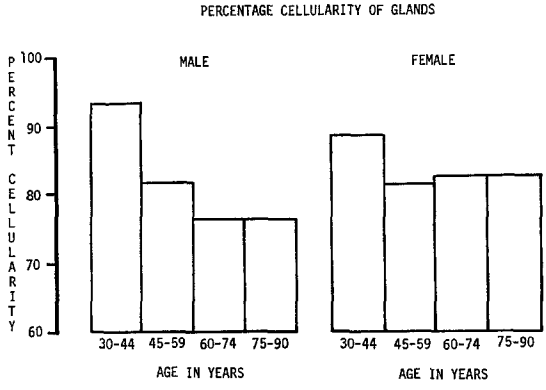

Fig. 3. Percentage cellularity of pineal glands at different ages in normal males and females

interesting fact that the greater bulk of the gland is still composed of pinealocytes even in old age. Moreover, the pinealocyte nuclei remained constant in diameter at all ages.

These findings are certainly in keeping with modern thinking that the activity of the gland extends into old age. There is, of course, support for this from other studies, the most important probably being the finding of high enzyme activity in the gland at all ages (*Wurtman, Axelrod,* and *Barchas,* 1964).

The extent of lobulation, fibrosis and gliosis in the gland are seen in Figs. 4 and 5. The amount of fibrosis follows the degree of lobulation in the gland closely. These features show a progressive but slight increase in females whilst they are much more variable in males. On the other hand, gliosis is fairly constant in amount in males whilst

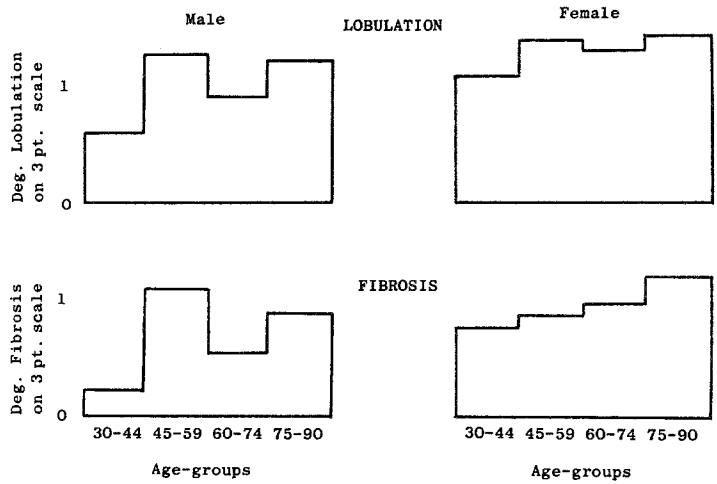

Fig. 4. Lobulation and fibrosis in the pineal gland in normal males and females according to age-groups

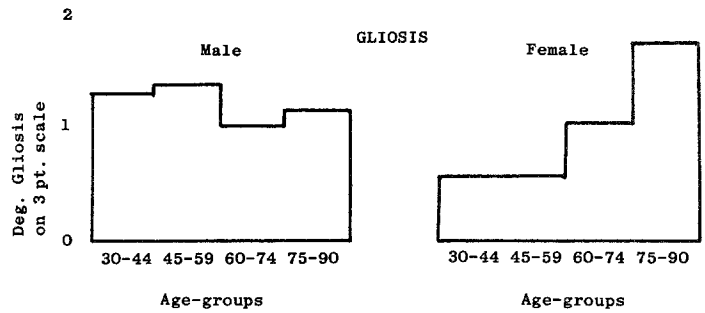

Fig. 5. Gliosis in the pineal gland at different ages in normal males and females according to age-groups

again it increases with age in females. It is of interest to note that the amount of gliosis in females in the 30—59-year age-group is small, whilst the weight of the gland is highest in females in this age-group.

Table 2 shows the weight of the glands in males and females classified according to the system in which the fatal disease occurred. No striking differences are seen except in the group dying of burns or trauma. In this group the weight of the gland is significantly higher and this is particularly so in females.

Table 2. *The mean cubed root of the pineal weight of males and females dying of non-malignant disease*

	Mean cubed root of pineal weight	
Type of disease	Male	Female
Cardiovascular system	5.1 (63)	5.3 (57)
Respiratory system	5.3 (46)	5.3 (32)
Central nervous system	5.3 (22)	5.3 (36)
Digestive system	5.3 (11)	5.3 (8)
Urinary system	4.9 (11)	5.5 (8)
Burns and trauma	5.5 (16)	5.9 (19)

Number of cases between brackets.

As most of the patients dying from trauma or burns did so soon after admission to hospital, a group of 20 pineals from males and 20 from females who died within two days of the onset of the final illness were compared with similar groups matched for age who died after a more prolonged illness. Table 3 shows that the weight of the gland from females dying of an acute illness is significantly greater than those dying of a more prolonged illness. These findings are certainly in keeping with the finding of high pineal weights in females dying of burns and trauma but are probably not the whole explanation. It may however, be speculated that the marked differences in weight between the glands of the patients dying after illnesses of varying lengths and of trauma compared with other diseases is related to stress.

Table 3. *Mean cubed root of the pineal weight acute and chronic illness*

	Males	Females
Acute illness	5.3 (20)	5.6 (20)
Chronic illness	5.3 (20)	5.2 (20)

Turning now to the pineal gland in malignancy, in most age-groups the pineal tends to be smaller (Fig. 6), although in females in the 45—59-year age-group in which the pineal weights are particularly high, the weight of the gland in malignancy appears to be even higher. However, these differences are not statistically significant.

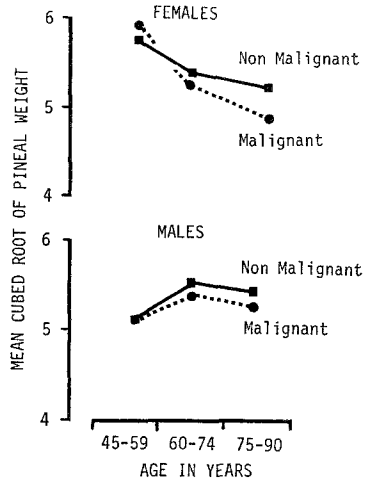

Fig. 6. Mean cubed root weight of the pineal gland in malignant and non-malignant male and female patients according to same age-groups

This absence of demonstrably significant differences in the weight of the gland from malignant and non-malignant groups when large numbers are examined and split into male and female groups is in contradistinction to previous reports on much smaller numbers of glands by *Tapp* and *Blumfield* (1970) and by *Rodin* and *Overall* (1967). The latter authors stated, on the basis of a computer analysis of a number of variables, that sex need not be considered as a control variable in analyses concerned with changes in pineal weight associated with age and malignancy. It is clear on the basis of the present work that this is not so.

Smaller pineals in cases of malignancy have also been described by *Kutcherenko* (1941) but this result was based on only a small group of pineals and was badly controlled, normal pineals from another series being used.

No significant differences were found in the amount of calcium in the pineal glands of patients with and without malignancy. This has been a subject of interest in the past, *Kutcherenko* (1941) considering that increased amounts of calcium were present in his

investigation of pineals from tumour-bearing patients, whilst *Drexler* and his co-workers (1957) also found a significantly greater incidence of calcification, as determined from radiographs of the skull in women with mammary carcinoma.

Histologically the difference in the number of cysts in the pineal glands of patients with malignancy was particularly striking, cysts being present in 18 % of pineals in patients with benign conditions and in 45 % of pineals from patients with malignancy. This finding is of interest in view of the recent report of multiple cystic cavities in the enlarged glands of patients dying with malignancy (*Hajdu, Porro, Lieberman,* and *Foote,* 1972). This, however, was an unusual study in that only 31 enlarged glands were selected for study out of a group of 275 pineals from patients with malignancy. The changes were particularly noticeable in 24 of the 31 patients who had acute leukaemia.

In an attempt to explain both the presence of degenerative changes such as cyst formation and calcification in the pineals of patients with malignancy, and the variation in the weight of the pineal gland in malignancy, *Relkin* (1976) suggested that degenerative changes are the end result in glands which have been chronically hyperactive (and thus increased in size) in secreting substances which are capable to some extent of controlling neoplasia. If this were true, pineals in malignancy might either be heavier or lighter than normal glands depending on the stage reached by the reactive process in the degenerative gland.

Table 4 gives the weight of the pineal gland in different kinds of malignancy. Considerable differences are present, particularly between carcinomas and sarcomas. These differences in weight will clearly give rise to substantial variations in the weight of the gland as examined by research centres dealing predominantly with one type of malignancy only. They are also interesting in view of the fact that experimentally and in human therapy the effect of pineal gland extracts and melatonin varies according to the type of tumour being treated (*Starr,* 1970; *Lapin* and *Ebels,* 1976).

Table 4

Histological type of malignancy	Mean cubed root of pineal weight
Undifferentiated carcinoma	5.4
Adenocarcinoma	5.3
Squamous carcinoma	5.2
Sarcoma and reticulosis	4.7

An analysis of the pineal weights according to the cell or tissue of origin is given in Table 5. Patients with carcinoma of the breast have the largest pineal glands. Some of these will be women in the 45—59-year age-group who normally have large pineal glands, but in this respect it is interesting to remember that the pineal glands from women in this age-group with malignancy were the only ones in which the pineal weight was greater than that in the glands of patients dying of non-malignant conditions.

Table 5

Origin of malignancy	Mean cubed root of pineal weight
Breast	6.0
Melanoma	5.8
Colon	5.4
Bronchus	5.2
Reticulosis	4.8
Sarcoma	4.5

Moreover, it is interesting to bear in mind that many breast tumours are hormone dependent and consequently, as there is now good evidence that pineal substances have inhibitory effects on the gonads either directly or through the hypothalamo-hypophyseal axis it may well be that the pineal plays a part in the control of breast cancer through these mechanisms (*Tapp*, 1978). In addition, prolactin may also be important in the genesis of breast carcinoma. Melatonin has been shown to increase the release of prolactin (*Lu* and *Meites*, 1972) and consequently may well influence breast carcinoma in this way.

It is also worthwhile recalling *Hamilton*'s (1969) finding that experimentally (DMBA) induced tumours of the breast in rats behaved considerably more malignantly when melatonin was administered. This author also found that continuous daylight and probably in particular the presumed suppression of glandular activity which goes with this, resulted in a diminution in the incidence of malignancy in these tumours. As it is known that the growth of these tumours is also increased by hyperprolactinaemia (*Welsch, Louks, Fox,* and *Brooks*, 1975) it is possible that the melatonin in Hamilton's experiments promoted growth by increasing the release of prolactin from the pituitary.

Melanomas were also found to be associated with high pineal weights. This is interesting in view of the fact that melanomas may

be stimulated by MSH and that there is work to indicate inter-relationships between MSH, MIF and melatonin (*Relkin,* 1976).

Finally, it is worth noting some work reported a few years ago by *Starr* (1970) in New South Wales. This author found low serum growth hormone (GH) levels in patients suffering from certain tumours, particularly carcinoma of the breast and melanomas, whilst high GH levels were present in patients with reticulosis and sarcomas. It should be noted that the GH levels are inversely proportional to the pineal weights. Moreover, *Starr* (1970) found that patients suffering from tumours associated with high GH levels (such as sarcomas) respond best to melatonin treatment whilst melanomas and carcinomas of the breast respond very poorly.

The significance of these findings and the inter-relationships of GH and the pineal in these cases remains to be investigated, but it could be suggested that in patients with low GH levels the pineal gland is already exerting its maximum effect on the tumours, whilst patients with high GH levels benefit from melatonin by its inhibitory effects on the hypothalamus and pituitary. Now that melatonin may be measured in the serum by radioimmunoassay it will be important to correlate measurements of GH and the other pituitary hormones with those of melatonin in the serum in people suffering from different types of tumour. Work on this has already begun and it is hoped that this will eventually give a better understanding of the part played by the pineal gland in patients suffering from malignancy.

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