Spontaneous pineal body tumours (pinealomas) in Wistar rats; a histological and ultrastructural study

A. J. AL ZUBAIDY* & W. MALINOWSKI

Department of Pathology, Life Science Research, Stock, Essex, CM9 9PE

Summary
The pathology of 5 cases of pinealomas in Wistar rats used in long-term toxicological studies is described both grossly, microscopically and ultrastructurally, together with a review of the related literature.

Review of the literature shows that a marked strain difference as to the type and incidence of neoplasia, as well as of non-neoplastic diseases, exists in rats. Spontaneous neoplasms of the nervous system of the rat are rare (Billups, 1976) and tumours of the pineal gland have been uncommonly reported in animals (Benirschke, Garner & Jones, 1978). In a survey of 1100 albino Wistar rats, Bots et al. (1968) reported 3 brain tumours in the test animals, which they considered were unrelated to experimental treatment; 2 tumours were diagnosed as oligodendrogliomas and 1 as a malignant neuroectodermal tumour.

Thompson et al. (1961) reported 4 CNS tumours among 62 spontaneous neoplasms in 125 albino Sprague-Dawley rats, one of which was a pinealoma in a 16-month-old rat. The largest study on CNS tumours was reported by Newman & Maudesley-Thomas (1974), who described 38 tumours in 3500 Sprague-Dawley rats of more than 1 year old and from both those receiving compounds and control groups.

The present study reports 5 pineal body tumours in a survey of 1800 Wistar rats used in long-term toxicity studies; the brain of each was examined grossly and microscopically.

Case 1
A male Wistar rat from a control group was killed in extremis at 112 weeks of age. It had a history of piloerection, lacrimal discharge with conjunctivitis, shallow irregular respiration and tremors. At necropsy the thymus was haemorrhagic, and pancreatic blood vessels were thickened and polyarteritic. The kidneys showed irregular subcapsular surfaces with occasional raised cysts and slight hydronephrosis indicating geriatric nephropathy. Parathyroids were prominent, but there was no grossly detected abnormality in the brain. Microscopic examination of the brain revealed an infiltrating tumour of the pineal body, a malignant pinealoma. It consisted of large pale-staining parenchymal cells and smaller dark-staining cells, with numerous mitotic figures and pseudorosettes around areas of necrosis (Figs 1–3). The neoplasm encroached upon adjacent brain tissue with local invasion but not metastasis.

Case 2
A female Wistar rat from a control group, killed in extremis after 109 weeks, had a history of respiratory irregularity, convolution and ocular and nasal discharge staining the ventral surface of forelegs. It also had hypothermia, piloerection and pallor. It showed bodyweight loss of 113 g from week 108. At necropsy, the lungs were congested with pale, raised foci, there were bursal ovarian cysts and subcutaneous mammary tumours. Microscopical examination of the brain revealed a pinealoma.

Case 3
A female Wistar rat from a test group, killed after 2 years (week 109) had a history of hair loss on the fore limbs, there were also piloerection, laboured respiration, facial and dorsal staining and some loss of weight. Necropsy revealed multiple thoracic fibrous adhesions. The stomach showed twisting involving an area adjacent to the oesophagus and a congested fundic mucosa with multiple dark ulcerated areas (12 × 10 mm). No gross brain abnormality was recorded at necropsy. Microscopic examination of the brain revealed a pinealoma.

Case 4
A female Wistar rat from a test group, killed after 2 years of a chronic toxicity study, exhibited no clinical signs before death. At necropsy the lungs were congested, with occasional petechiae and pale subpleural areas (7 × 5 mm) on all lobes. The cervix had a large firm pale mass (15 × 10 × 10 mm). The brain showed a large, congested pineal body (5 × 4 × 3 mm), which on histological examination was a
Spontaneous pineal body tumours in Wistar rats

Figs 1-3. Pinealoma from a male Wistar rat. Microscopically a malignant tumour of the pineal body, consists of large pale-staining parenchymal cells, with numerous mitotic figures. The cells are arranged in pseudorosettes around areas of necrosis (Figs 1, 2). Fig. 2 is high power of Fig. 1. Note 'endocrine' arrangement of the tumour cells with sinus dilation and blood-filled spaces. Fig. 3 demonstrates a high power of tumour cells with active mitotic activity. [(1) H&E x 90; (2) H&E x 120; (3) H&E x 180]

Fig. 4. Pinealoma from female Wistar rat. The tumour is seen in the correct neuroanatomical area for the pineal gland. It is located between the posterior position of the 2 cerebral hemispheres just anterior to the sagittal sinus. (H&E x 45)

Fig. 5. High power of Fig. 4. The neoplasm consisted of a mosaic of ill-defined pale-staining parenchymal cells with fine stromal tissue containing smooth muscle fibres. (H&E x 120)

Fig. 6. Higher power of Fig. 5. A mosaic of ill-defined large round cells (pinealocytes) with a few small darker cells present. The cells are arranged in an 'endocrine' fashion with a tiny capillary in the middle. Note also a smooth muscle fibre (left). (H&E x 360).
pinealoma (Fig. 4). This neoplasm was located between the posterior position of the 2 cerebral hemispheres just anterior to the sagittal sinus. The neoplasm was made up of large, pale-staining parenchymal cells interspersed with smaller, round dark-staining cells. The cells were pocketed in groups of pseudoacinar pattern separated by fine stromal tissue containing smooth muscle fibres (Figs 5 & 6).

Case 5
A female Wistar rat from a test group was killed after 81 weeks of a long-term toxicity study. It had a history of respiratory irregularity, with rapid weight loss, and was anaemic. The abdomen was hard and swollen, with pallor of the extremities. At necropsy the brain showed a haemorrhagic cyst (5 × 5 mm) at the junction of the cerebral hemispheres and cerebellum. Microscopic examination of the lesion showed it to be a pinealoma.

Electron microscopy was performed on Araldite-embedded formalin-fixed pineal tissues from cases 1 and 4. Despite suboptimal fixation, the majority of organelles were well preserved (Figs 7 & 8). However, some cells showed evidence of degeneration, with the formation of myelin figures and distortion of the rough endoplasmic reticulum, coupled with mitochondrial swelling and disintegration of their cristae. Degenerative changes were also noted in the axons. Most cells were in the early stages of differentiation, having large numbers of free ribosomes, monosomes and polysomes present in the cytoplasm. Poorly developed Golgi zones were seen and early stages of desmosome formation were evident.

Discussion
The term tumour is used here in its specific sense (Willis, 1960) to denote neoplasia. All the tumours examined were pinealomas: 4 of the 5 cases were benign, while the 5th case showed features of malignancy. Histologically, all the neoplasms were made up of large, pale-staining parenchymal cells, and smaller round, dark-staining cells. They were thus similar to the human pinealoma (Russell & Rubinstein, 1971). Mitoses were very numerous in 1 case. The ultrastructural morphology was compatible with that previously described for pinealocytes (De Martino, Toriretti and Accini, 1964). Opinion on the lipid arrays needs to be reserved until microscopy has been carried out on non-neoplastic pineal gland fixed in formalin. Further investigation is also required to identify the nature of the dark cells.

Although very little is known of the specific function of the pineal body, it is presently believed (based on observations mostly in rodents) that this organ serves as a neuroendocrine transducer in many species (Rhodin, 1974). Melatonin was first identified in the pineal gland of cattle (Wurtman & Moskowitz, 1977), and the hormone appears to mediate in the functions of the pineal body relating to time and light cycles (Binkley, 1978). The clinical signs noted in this series — gasping respiration, hypothermia, weight loss — may have some cause-and-effect relationship with the pineal lesion, as indeed also with the change of the dark-light cycle. The differentiation of the neoplasm from focal hyperplasia of pinealocytes resulting in enlarged pineal bodies must, to some degree, lie in the eye of the beholder. A small number of potential pinealomas has been dismissed from our series as more likely to be focal hyperplasia.

The question of the incidence of nervous system neoplasms in small laboratory animals has been addressed by a number of authors (Benirschke et al., 1971). These workers feel that the time incidence in a given animal species cannot be determined until many series of animals of all age groups have been carefully studied. Obviously, species, breed, and strain differences in the frequency of neoplasia are encountered, but definitive data for many of the small laboratory animals and non-human primates are not available.

Spontaneous neoplasms of the pineal body of the rat are extremely rare, and in many of the earlier studies no mention was made of such tumours. Burek (1978) did not report any pinealomas in an older population of Wistar rats, nor did Newman & Maudesley-Thomas (1974) in a larger study which presented microscopic evaluation of 38 CNS tumours of Sprague-Dawley rats of greater than 1 year of age. Whether this is a true reflection of disparity in the incidence of such lesions among different laboratory species is not known though one reason for utilizing rodents, especially mice, for experimental brain tumour research originally was the rarity of such lesions in the natural state (Zimmerman, 1971).

Acknowledgements
We wish to thank Dr N. G. Read of the Electron Microscopy Unit, Department of Toxicology, Wellcome Research Laboratories, for his constructive criticism, and Mrs E. Turner for typing the manuscript.
Fig. 7. The cytoplasm contains numerous ribosomes, either as monosomes or polysomes, and rough endoplasmic reticulum cisternae. Golgi zones are not well-differentiated. Note multivesicular bodies (encircled) and myelin figures; the latter may be due to suboptimal fixation (× 6500).
Fig. 8. This electron photomicrograph shows vast numbers of long profiles of rough endoplasmic reticulum, with primary and secondary lysosomes. Note the myelin figures (top right corner) and a vascular capillary with RBS in the immediate proximity (lower right corner). (× 15000)

References


Zusammenfassung
Es wird die Pathologie von 5 Pinealoma-Fällen bei Wistarratten beschrieben, die in toxikologischen Langzeituntersuchungen waren. Makro- und mikroskopische sowie ultrastrukturelle Befunde werden zusammen mit einer Literaturübersicht verwandter Fälle gegeben. (G)