

## Spontaneous Adenomata of the Hypophyseal Anterior Lobe in Aged Pinealectomized Rats<sup>1</sup>

The spontaneous occurrence of adenomata in the anterior lobe of the pituitary gland of old laboratory rats has been known and studied for many years<sup>2-4</sup>. The incidence of these tumors appears to depend upon genetic strain, sex, and age of the animals<sup>4-6</sup>. Furthermore, most investigators seem to concur that persistence of some sort of hormonal disequilibrium is involved in the pathogenesis and growth of these pituitary tumors in mammals<sup>8-10</sup>.

The possible relevance of the pineal organ or gland to activity and tumorigenesis in the anterior lobe of the hypophysis stems from two lines of evidence, both of which continue to be subject to disagreement. One line of evidence has to do with tumor growth in pinealectomized rats, some investigators claiming accelerated growth<sup>11-13</sup>, others denying it<sup>14</sup>. The other line of evidence concerns a postulated specific regulatory effect of the pineal on the hypophysis, some authors claiming increased hypophyseal weight, basophil hyperplasia, or other signs of activity, after pinealectomy<sup>15-18</sup>, others claiming no significant changes in hypophyseal weight or signs of activity<sup>19-22</sup>. Little has been presented, however, on the status of the hypophysis after long-term pinealectomy of a mammal.

Sibling groups of Long-Evans female rats, consisting of unoperated, sham-operated and pinealectomized<sup>23</sup> individuals, were kept from the time of operation (at 17-24 weeks of age) to an age of 20-24 months. The animals were in individual cages of wire mesh in close proximity to each other. They received the same standard diet and tap water ad libitum, and a uniform photoperiod of 14 h of light per day. 10 animals were killed when about 20 months old and 27 when approximately 2 years old. The animals were perfused and the brains fixed and treated according to the methods of CAMMERMEYER<sup>24</sup>. Serial transverse paraffin sections of brain and hypophysis in situ, and 7 microns in thickness, were stained in part by a periodic acid-Schiff technique<sup>25</sup> and in part by HALMI's aldehyde fuchsin method<sup>26</sup>.

Hypophyseal tumors were not observed in the rats that had died due to natural causes during the course of the

post-operative period, nor in those killed at 20 months of age. But of the 27 (9 unoperated, 9 sham-operated and 9 pinealectomized) carried to 2 years of age, 4 (2 unoperated and 2 pinealectomized) had hypophyseal tumors. The 3 of these that were satisfactorily preserved were massive adenomata of the anterior lobe, compressing and distort-

<sup>1</sup> This investigation was supported in part by PHS research grant No. GM-05219 from the National Institute of General Medical Sciences, NIH, Public Health Service, USA, and the Miller Institute for Basic Research in Science, University of California, Berkeley (California).

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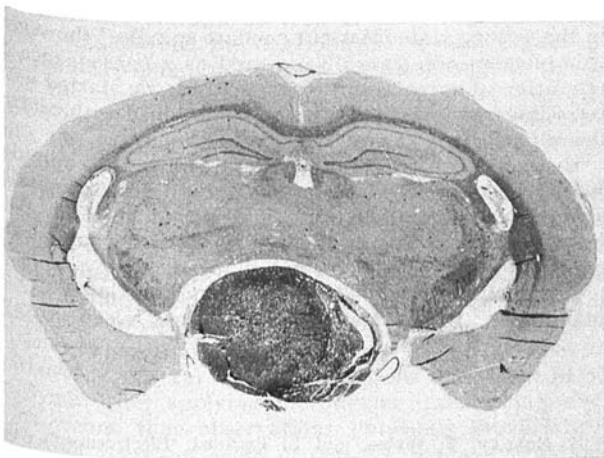


Fig. 1. Hypophyseal chromophilic adenoma in transverse section of entire brain of a pinealectomized rat. The neurohypophysis and pars intermedia have been compressed to one side by the tumor. Note also the distortion of the thalamus and the dilation of the ventricles. The tumor measures  $5\frac{1}{2}$  mm wide by  $3\frac{1}{2}$  mm high.

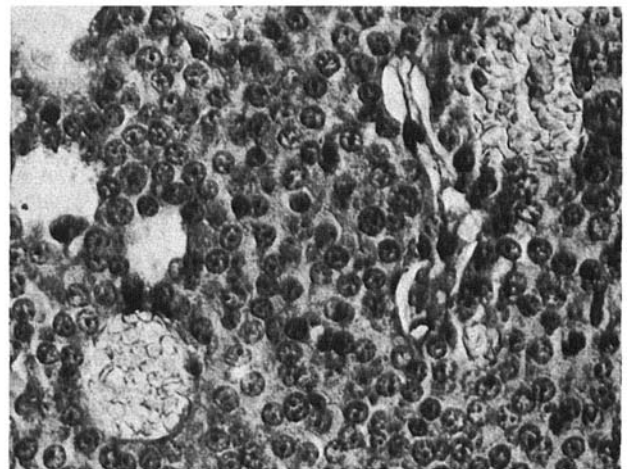


Fig. 2. Typical area in chromophobic hypophyseal adenoma of an unoperated rat. Note the dense and thick masses of parenchymal cells without much evidence of differentiation. Periodic acid-Schiff and hematoxylin.

ing other portions of the hypophysis as well as the hypothalamus and more dorsal brain regions (Figure 1). Although the animals bearing hypophyseal tumors did not have apparent tumors in other organs, 2 of the animals lacking hypophyseal hyperplasia had mammary tumors (1 unoperated and 1 pinealectomized), and a third had an ovarian tumor (pinealectomized). The sole well-preserved hypophyseal tumor of an unoperated rat was a chromophobe adenoma consisting of relatively solid masses and cords of small parenchymal cells (Figure 2). The hypophyseal tumors of the pinealectomized rats were

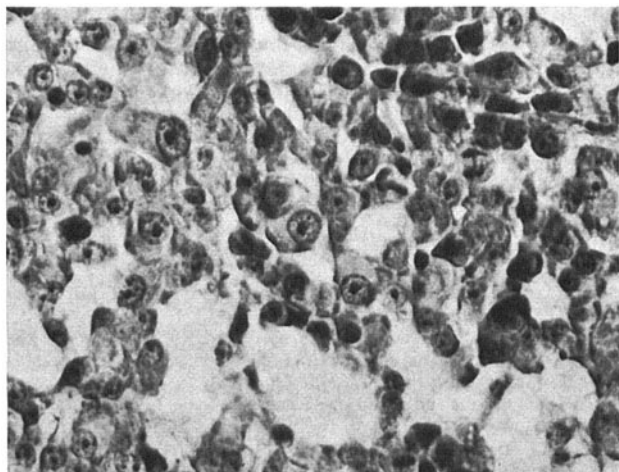


Fig. 3. Typical area in chromophilic hypophyseal adenoma of a pinealectomized rat. Note the slender strands of parenchymal cells between the vascular channels. Compare with Figure 2. Both Figures are from the same magnification. Periodic acid-Schiff and hematoxylin.

at least partly chromophilic, having scattered or regional masses of larger parenchymal cells with more cytoplasm which sometimes stained weakly to moderately with the periodic acid-Schiff technique (Figure 3). No aldehyde fuchsin-positive cells were found in these tumors, although small numbers of them were seen in anterior lobes of non-tumorous animals. These chromophilic adenomata were characterized also by having a greater blood content, localized in large and irregular channels between the usually slender strands of parenchymal cells. These features of the tumors in the pinealectomized rats are not necessarily referable to the absence of the pineal, since such features of apparently similar tumors have been noted in normal old female rats by other investigators. Nevertheless, further investigation of the effect of pinealectomy on the cytology of hypophyseal tumors is needed, particularly with the use of a large number of animals and quantitative examination of a tendency to develop tumor parenchymal cells of a more chromophilic and differentiated type. With the available results neither the incidence nor the characteristics of the hypophyseal tumors appear to be distinguished significantly or certainly in the pinealectomized animals.

*Zusammenfassung.* Es wurden Vorkommen und Eigenschaften des Hypophysenadenoma bei altersschwachen Ratten nach Pinealektomie beschrieben. Trotzdem in Tumoren zirkeldrüsenloser Tiere grössere Parenchymbildung und grösserer Blutgehalt erscheinen, können die vorliegenden Ergebnisse keinen entscheidenden Unterschied bestätigen.

W. B. QUAY

Department of Zoology, University of California, Berkeley (California 94720, USA),  
September 14, 1966.

### Influence of Long-Lasting Stimulation of the Caudate Nuclei on Sleep Cycle in Rats

It was shown previously, that before the onset of the rhombencephalic sleep phase (RP) a gradual decrease in the excitability of the reticular activating system (RAS) develops<sup>1</sup> and that the onset of RP may be delayed by subthreshold stimulation of the mesencephalic reticular formation during the telencephalic sleep phase (TP)<sup>2</sup>. The question solved in this paper is whether stimulation having an inhibitory effect on the brain (mainly on RAS)<sup>3</sup> may shorten the duration of the TP.

Bipolar electrodes were implanted in the frontal cortex, dorsal hippocampus, and caudate nucleus bilaterally in 8 rats. The length of different parts of the sleep cycles (Figure) was measured from 22 all-day (0900–1600) recordings in freely moving animals placed in a dimly illuminated sound-proof chamber. The recording was performed repeatedly 2 or 3 times on every rat either with or without all-day synchronous stimulation of both caudate nuclei with single rectangular pulses (duration 0.5 msec, repetition rate once every 2 or 3 sec). The amplitude of the pulses was chosen individually; they

were capable of evoking at the beginning of stimulation in the waking state clear-cut caudate spindles<sup>3</sup> (however, this phenomenon soon disappeared as a consequence of repetition of stimulation). In some cases we started with recordings during stimulation and continued with control recordings the next day, in others vice versa.

Evaluation of the results (Figure) shows that stimulation of the caudate nuclei evokes a slight but statistically significant decrease in the duration of the TP. The length of RP and arousal reaction occurring in rodents regularly after the RP was not changed.

The cyclic nature of sleep is a characteristic feature of mammals<sup>4</sup>. In physiological conditions sleep always

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