Neoplasia in the Parakeet

I. Spontaneous Chromophobe Pituitary Tumors*

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Tumors of the pituitary make up approximately 7 per cent of the intracranial neoplasms of man (61). As isolated cases they have been found in the horse (41, 48), dog (29, 37), cow (1), deer (53), Indian buffalo (16), baboon (25), and mouse (25, 54). Following the description by Olga Fischer of large hypophyseal adenomas in two old rats (15), several investigators have reported a high incidence of these tumors in rats of advanced age (18, 40, 46, 47, 59, 60). Only two instances of reported pituitary tumors in animals other than mammals are known to the writer. One was seen in an African parakeet Agapornis pullaria by Slye (54); the second, a chromophobe adenoma in an aquarium fish Lebistes reticulatus, was recently described by Stolk (55). The absence of additional reported cases in the lower vertebrates is particularly striking among the birds where thousands of chickens, ducks, turkeys, and geese are autopsied yearly by veterinary pathologists (27).

This report is based on a study of 50 parakeets with pituitary tumors. The investigation was undertaken after a bird brought to the writer by Dr. Jerome Rini proved to have such a lesion and when a cursory examination of several flocks had revealed the prevalence of the tumor (50). The cases presented are unselected and represent the first 50 pituitary neoplasms examined in this laboratory.

MATERIALS AND METHODS

The parakeet under study is Melopsittacus undulatus, a member of the parrot family (Psittacinae). It is known in this country by a variety of names, such as shell parakeet, grass parakeet, undulate parakeet, and budgerigar. The latter term is derived from the name given the bird by the natives of Australia, where it lives on the grassy plains and in shrubbed semi-desert regions. The name "lovebird," though occasionally used, should be reserved for an African bird of a different genus.

Shell parakeets were first brought to Europe about 1880; their ready acclimatization, frequent color mutations, and ability to learn to talk made them popular cage birds. During the early 1920's parakeets became sought-after pets in this country, but following epidemics of psittacosis traceable to them their number declined sharply after 1929. Since World War II there has been renewed public interest, innumerable small aviaries are now scattered throughout the country, and the parakeet population has risen enormously.

To obtain birds with tumors, advertisements were placed in a popular pet magazine and in monthly bulletins of the two national budgerigar societies. The great majority of birds are received alive and are kept under observation in the laboratory aviary for days or weeks. Feeding and care of the birds is similar to that employed by most breeders (18). A useful guide to the more common diseases of the parakeet has been recently published (14).

PHYSICAL SIGNS OF PITUITARY NEOPLASIA

The most striking sign of a pituitary tumor in the parakeet is uni- or bilateral ocular proptosis (Fig. 1). This was observed in nine of the 50 cases (18 per cent) and is due to invasion of the retro-ocular tissue by the tumor which pushes the eye outward. Despite this evidence of a large rapidly growing tumor, birds so afflicted often survive for several weeks. In one instance (No. 29) proptosis of the left eye was observed for 6 months prior to death; at autopsy the retro-ocular tumor was found to be a papillary adenoma of the Harderian gland wholly unrelated to the pituitary which, however, was enlarged to 3 times normal size. This is the only instance in which proptosis was not attributable to the pituitary neoplasm.

Impaired vision is the most frequently occurring symptom of a pituitary tumor in man (61); the same is true of the parakeet. In this series nineteen of 50 birds (38 per cent) became totally blind or showed evidence of serious visual disturbance. One of the earliest signs was frequent blinking, suggesting increased light sensitivity, and photophobia. Blindness was indicated by failure of the bird to fly about the cage; instead it walked on the bottom or climbed up the sides. When the observer's hand was suddenly brought close to its head the bird did not startle or blink. To insure
adequate feeding it was often necessary to place food and water on the floor of the cage so that the bird would literally stumble upon it. An unsteady gait was occasionally manifested, but whether this should be attributed to impaired vision and/or involvement of other cerebral centers is difficult to determine. The cerebellum was never invaded by the tumor nor was a marked degree of imbalance like that observed in parakeets with primary cerebellar or middle-ear lesions encountered.

The sequence of events that characterizes progressive involvement of the optic nerves is exhibited by No. 13, in which there may also have been damage to the vestibular nerve. The bird hatched November 15, 1950; impaired vision was first noted early in December, 1952. By the middle of that month he was blind; proptosis became apparent on January 1, 1953. A few days later his gait became unsteady, and by February 1 he could not raise his head which was twisted to one side. The bird remained in this condition for 2 weeks, when he lapsed into coma and died.

Cerebral involvement is indicated by somnolence and the occurrence of convulsive seizures. Although a terminal convulsion is often seen in birds dying of various causes, the convulsions observed in birds with a pituitary tumor have their onset several days before death. The seizures are accompanied by an incoordinated beating of the wings on the floor of the cage associated with clonic twitching of the legs and occasional piercing cries. The convolution lasts for about 30 seconds followed by a 2-3-minute period of unconsciousness during which the bird appears to be dead. Recovery is usually abrupt, and the bird may subsequently climb back on its perch. Five or six seizures may occur before death.

It is difficult to assess the effect of the tumor on the bird’s intellect; nevertheless, in the case of a pet an evaluation is occasionally possible. Thus, one owner wrote that her bird (No. 7) wanted as much attention from her mistress during the 2 weeks he was obviously ill as he did formerly. He was less active than before and would fly to his favorite perch and sleep. He was a good talker and exercised this ability until the day he died.

Diarrhea is very frequently observed in birds with pituitary tumors, but it is a common symptom of many minor ills of the parakeet and its cause is difficult to determine. However, in birds the normally semi-solid urine is mixed with the feces in the cloaca; therefore, polyuria would give rise to signs simulating those of diarrhea. An associated polydypsia noted in three cases suggests that at least in several instances the diarrhea was actually a manifestation of polyuria resulting from dysfunction of the neurohypophysis. In the bird the neurohypophysis appears as the infundibular process (43) and possesses antidiuretic as well as oxytocic and pressor properties (9). The destruction or distortion of this structure by the pituitary tumor may account for the symptoms described.

The significance of obesity or emaciation in the affected birds also poses a problem. Obesity could be attributed to the diminished activity often observed in these birds, and the emaciation might be readily explained by assuming that visual disturbances affect the birds’ ability to feed. However, several of the obese birds showed no difference in activity when compared to their normal cage mates, and many of the emaciated birds had no visual impairment. In normal parakeet hens 2-4 years old there is often a pronounced deposition of fat beneath the skin of the breast and abdomen, as well as in the peritoneum, mesentery, and liver. Such obesity is uncommon in the normal male; yet of the seventeen obese birds with pituitary tumors, seven were males. The possible mechanism of obesity and emaciation in these parakeets will be considered in the discussion.

Several of the physical signs observed in birds with pituitary tumors characterize similar lesions in man. Jefferson (32) has listed somnolence, thirst, and polyuria among the outstanding features in patients with pituitary adenomas that have extended into the hypothalamus.

**GROSS MORPHOLOGY**

The pituitary body of birds occupies the same relative position as it does in mammals, viz., the pituitary fossa of the basi-sphenoid directly behind the optic chiasm. In the avian pituitary the pars anterior or glandular hypophysis greatly exceeds the posterior in bulk; there is no pars intermedia (44). The average weight of the pituitary of a young adult parakeet is 0.65 mg., its diameter is 1.0 mm., and its shape is that of a flattened sphere.

**Group I: Diffuse enlargement of the pituitary (Table 1).**—In twenty birds (40 per cent) the pituitary was diffusely enlarged, measuring 2-5 mm. in diameter (Fig. 2). However, the weight of these glands was up to 10 times that of the normal gland. The capsule was intact, but occasionally the surface was nodular and the gland firmer than normal. Only one of the birds (No. 38) showed evidence of visual impairment; this was attributable to compression of the optic chiasm. Diarrhea and polydypsia were occasionally encountered; seven of the birds were obese. In none was a diagnosis of pituitary tumor made before death.

**Group II: Locally invasive tumors (Table 2).**—Of the 50 birds in the series, 28 (56 per cent) showed
extension of the neoplasm beyond the confines of the sella, but the lesion had not metastasized. The tumor had grown into one or both orbits in nine cases (Fig. 3). Careful examination of the orbital bones, however, rarely showed evidence of destruction; the tumor had grown along the optic nerves and passed through the optic foramen into the retro-orbital tissue. Gross evidence of optic nerve involvement characterized by the presence of tumor nodules (Fig. 4) was only seen in five instances. In an equal number the cancellous bone of the basi-sphenoid was invaded; in four of these

### TABLE 1

**NONINVASIVE PITUITARY TUMORS (GROUP I)**

<table>
<thead>
<tr>
<th>Bird no.</th>
<th>State</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Large</th>
<th>Impaired</th>
<th>Associated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Ohio</td>
<td>2½</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>A 2X3 mm. diffuse enlargement of gland</td>
</tr>
<tr>
<td>7</td>
<td>Mich.</td>
<td>4</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>History of drinking much water</td>
</tr>
<tr>
<td>8</td>
<td>Texas</td>
<td>1½</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>Compression of normal pituitary by tumor cells</td>
</tr>
<tr>
<td>20</td>
<td>Ohio</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Subjected to artificial light 3 hours daily</td>
</tr>
<tr>
<td>21</td>
<td>N.Y.</td>
<td>1½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Had young previous year; during past year laid no eggs</td>
</tr>
<tr>
<td>24</td>
<td>Texas</td>
<td>1½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>A 5X5.5 mm. firm gray tumor at pituitary site</td>
</tr>
<tr>
<td>25</td>
<td>Texas</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Fatty dystrophy of the liver</td>
</tr>
<tr>
<td>28</td>
<td>Ohio</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Retained egg with yolk peritonitis</td>
</tr>
<tr>
<td>27</td>
<td>Wis.</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Egg incarcerated in oviduct</td>
</tr>
<tr>
<td>29</td>
<td>Ohio</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Fatty liver</td>
</tr>
<tr>
<td>30</td>
<td>Ohio</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Fatty liver produced abdominal swelling</td>
</tr>
</tbody>
</table>

* The pituitary tumors in this group ranged in size from 1 to 3.5 mm. in diameter.

### TABLE 2

**LOCALLY INVASIVE PITUITARY TUMORS (GROUP II)**

<table>
<thead>
<tr>
<th>Bird no.</th>
<th>State</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Large</th>
<th>Impaired</th>
<th>Associated</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ohio</td>
<td>4</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Left retro-ocular tumor with exophthalmos</td>
</tr>
<tr>
<td>4</td>
<td>Calif.</td>
<td>3½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>A 7-mm. tumor mass extends into mid-brain</td>
</tr>
<tr>
<td>5</td>
<td>Texas</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Bilat. retro-ocular and mid-brain extension</td>
</tr>
<tr>
<td>6</td>
<td>Ill.</td>
<td>3½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Invaded brain stem, bone, and oopharynx</td>
</tr>
<tr>
<td>9</td>
<td>Texas</td>
<td>1½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>An 8-mm. tumor that invaded brain stem</td>
</tr>
<tr>
<td>10</td>
<td>Wis.</td>
<td>4½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>A 6-mm. nodular tumor; 4 hrs. artificial light daily</td>
</tr>
<tr>
<td>11</td>
<td>N.J.</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>A 5-mm. tumor, invaded bone; pap. adenoc. left kidney</td>
</tr>
<tr>
<td>12</td>
<td>Kan.</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Invaded bone, brain and extra-ocular muscle</td>
</tr>
<tr>
<td>14</td>
<td>Ill.</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Invaded rt. orbit, bone and oopharynx</td>
</tr>
<tr>
<td>15</td>
<td>Ill.</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Invaded left orbit, bone and oopharynx</td>
</tr>
<tr>
<td>16</td>
<td>Texas</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Invaded rt. optic nerve; low intensity artificial light all night</td>
</tr>
<tr>
<td>17</td>
<td>Texas</td>
<td>3½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Small tumor invaded optic chiasm</td>
</tr>
<tr>
<td>18</td>
<td>Maine</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Left retro-ocular tumor with exophthalmos</td>
</tr>
<tr>
<td>19</td>
<td>Texas</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>A 3-mm. pituitary tumor invading brain stem</td>
</tr>
<tr>
<td>22</td>
<td>Texas</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Tumor invading base of skull</td>
</tr>
<tr>
<td>23</td>
<td>Texas</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Bilateral retro-ocular invasion</td>
</tr>
<tr>
<td>28</td>
<td>Calif.</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>A 5X5 mm. tumor invaded brain to depth of 2 mm.</td>
</tr>
<tr>
<td>30</td>
<td>Mich.</td>
<td>4½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>A 3-mm. tumor invading bone</td>
</tr>
<tr>
<td>32</td>
<td>Pa.</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>A 5-mm. tumor invading floor of sella</td>
</tr>
<tr>
<td>35</td>
<td>N.Y.</td>
<td>2½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>Massive tumor with retro-ocular and pharyngeal invasion</td>
</tr>
<tr>
<td>36</td>
<td>Calif.</td>
<td>3½</td>
<td>M</td>
<td>+</td>
<td></td>
<td></td>
<td>A 4X5-mm. tumor invading brain</td>
</tr>
<tr>
<td>37</td>
<td>Calif.</td>
<td>3½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>A 5-mm. tumor invading bone; exposed to artificial light</td>
</tr>
<tr>
<td>38</td>
<td>N.C.</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>A 6-mm. tumor invading brain and bone</td>
</tr>
<tr>
<td>44</td>
<td>Calif.</td>
<td>1½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Tumor invaded left retro-ocular tissue. First became very obese, later emaciated</td>
</tr>
<tr>
<td>46</td>
<td>Ind.</td>
<td>1½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Tumor invaded left retro-ocular tissue and oopharynx. A fibrosarcoma in spleen; adenocarcinoma in kidney</td>
</tr>
<tr>
<td>47</td>
<td>La.</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>Deep extension of tumor into brain</td>
</tr>
<tr>
<td>49</td>
<td>Fla.</td>
<td>2½</td>
<td>F</td>
<td>+</td>
<td></td>
<td></td>
<td>A 5-mm. tumor invading infundibulum</td>
</tr>
</tbody>
</table>
the tumor protruded into the oropharynx (Fig. 6). No evidence could be found for an origin of these tumors from embryonic rests within the sphenoid bone, the so-called pharyngeal pituitary gland.

Compression and/or invasion of the adjacent brain tissue was apparent in eleven of these birds (Fig. 5). In several instances the intracerebral extension of the tumor was much larger than the portion occupying the region of the pituitary (Figs. 7 and 8).

In keeping with the anatomical evidence of optic nerve and brain involvement in this group of 28 birds is the finding that in fourteen (50 per cent) there was serious impairment of vision often ending in blindness. Obesity was notable in nine birds; only four of these had shown signs of visual disturbance.

In man invasion of retro-ocular tissue has not been reported, although erosion of the sella with penetration of the sphenoid sinus and even of the nasopharynx are described (2, 33, 56). Most authors have classified such tumors as adenomas, reserving a diagnosis of malignancy for those instances in which there was an accompanying vascular invasion, e.g., of the cavernous sinus.

Group III: Metastasizing tumors—In only two birds (4 per cent) was there evidence of metastasis from the pituitary tumor. One of these was No. 3, a male bird bred in Ohio, which had a pituitary tumor that had deeply invaded the overlying brain and produced a large retro-ocular extension. On histological examination a small metastatic nodule was found in the kidney. The second case with metastasis was a bird bred in South Carolina; here, too, the secondary tumor was associated with a large pituitary neoplasm (No. 19). The primary tumor had extended through both optic foramina and appeared as a $5 \times 5$ mm. mass in each retro-ocular space. The liver was small, and approximately two-thirds of it was replaced by nodules of firm grayish-pink tumor tissue (Fig. 9).

Both of these birds were males; the age of the first was unknown, that of the second was 2$\frac{1}{2}$ years. The first bird was well nourished at the time of death, the second was emaciated; both were blind.

Metastasis of human pituitary tumors is apparently very rare. Vasiliu (57) reviewed the literature in 1930 and found only four cases. In two of these the metastases were limited to the central nervous system; in the other two the lungs were involved. In his own case there were metastases to several bones as well as to the dura. Dott, Bailey, and Cushing (11) reported a case in which the pituitary tumor had metastasized to the liver; and Gilmour (24) described one in which metastases were found in both the liver and kidneys.

**Microscopic Morphology**

The cellular composition of the avian pituitary resembles that of the mammalian gland in that the characteristic acidophils, basophils, and chromophobes are present (44). Differential staining of the bird hypophysis is often difficult (49), and even with the technic of Severinghaus (52) the granules in the parakeet pituitary lack the brilliance of those found in the human gland. The most thoroughly studied avian pituitaries are those of the pigeon (51) and of the chicken (42). In their study of the pituitary in eighteen species of birds, Rahn and Painter (43) noted a regional restriction of cell types which they identified as the “avian pituitary pattern.” This agrees with the findings of Schooley in the pigeon (51), in which the posterio-central area of the pituitary shows a preponderance of basophils, the anterior-peripheral area a majority of acidophils. A similar distribution is seen in the parakeet pituitary. Investigations of the bird pituitary are largely in agreement that the granular acidophils and basophils develop from the non-granular chromophobes.

The predominant cell type in the pituitary tumors of parakeets is the chromophage, a cell which is also the chief component of most mammalian pituitary neoplasms. A cytological distinction between hyperplasia and neoplasia in the pituitaries of Group I, and between the localized tumors of Group I, the invasive tumors of Group II, and the metastasizing carcinomas in Group III is difficult. Gardner (22) has noted a similar difficulty in distinguishing sharply between chromophobe hyperplasias and chromophobe adenomas in the pituitary glands of rats and mice.

The diffusely enlarged pituitary that has not invaded the surrounding structures and that is only two to four times the size of the normal pituitary usually shows almost complete replacement of the granular by the chromophobe cells (Fig. 10). Occasionally, small nests and interlacing strands of acidophils are present among the chromophobes; less often, normal chromophobes and acidophils are compressed by the neoplastic chromophobe cells to form a peripheral zone about the tumor (Fig. 11). In these cases the adenomatous character of the lesion is easily recognized. The distinction between hyperplasia and neoplasia in the pituitaries of Group I cannot be made with any certainty when based on histological or cytological criteria. Occasionally, careful scrutiny of the slides shows that some of the cells have escaped from the pituitary and have invaded the peri-
vascular spaces of the arachnoid. In such cases a
diagnosis of neoplasia rather than of hyperplasia
can be made with some assurance.

The typical cell of all these tumors, whether the
latter are localized, invading, or metastasizing, has
a rather scanty pale pink or colorless cytoplasm in
which there are often a few faintly staining acidoph-
philic or basophilic granules. The spherical nucleus
is often dense and hyperchromatic (Fig. 12); in
other instances the chromatin is clumped, and the
nuclei appear vesicular. With special fixatives and
stains the chromatin may be finely dispersed,
while one or two prominent nucleoli make their
appearance (Fig. 13). In the more malignant tu-
mors there is a somewhat greater variation in the
size and chromatin content of the nuclei than is
found in the benign neoplasms.

Tumor giant cells are found in all three groups.
Occasionally, the cytoplasm of these cells is rather
c scant (Fig. 12), but usually it is abundant and
stains pink. The nuclei are single, occasionally
vesicular with prominent nucleoli (Fig. 14). Often
they are large, hyperchromatic, and irregular in
outline (Fig. 15).

A specific histological pattern, characteristic of
these tumors, is the grouping of the cells in cords or
trabeculae between parallel capillaries (Fig. 16).
Occasionally, the cells assume a columnar shape
and are arranged about the capillaries in the form
of pseudorosettes (Fig. 17). These patterns, how-
ever, are not characteristic of most of the tumors
in which sheets of cells with no special relation to
the capillaries make up the bulk of the neoplasm.

The malignant character of the locally invasive
tumors (Group II) is clearly indicated by their in-
filtration of adjacent structures. Although the
hypothalamus may be simply displaced by the
expanding neoplasm, invasion by groups of tumor
cells often occurs. Most striking is the frequent
invasion of the optic chiasm and optic nerves
(Fig. 18). Occasionally, the extraocular muscles are
involved (Fig. 19), and instances of perineural
infiltration have been seen (Fig. 20). The cance-
llous bone beneath the floor of the sella turcica is
often the site of direct extension from the primary
tumor.

Distant metastases (Group III) were seen only
twice. In both cases the cells in the primary neo-
plasm were similar to those in the metastases. In
the first (No. 3) the cells of the pituitary tumor
and of the renal metastasis were small with scanty
cytoplasm (Fig. 21). In the second (No. 13) the
cells of the primary tumor were elongate and ar-
ranged in a pseudo-papillary manner; those in
the liver metastasis were similar in appearance (Fig.
22).

Changes in Other Endocrine Glands
No constant or significant change in the size,
weight, or histology of the parathyroids or adre-
nals could be established in birds with pituitary
tumors. The parathyroids are easily recognized as
single yellow nodules 0.5 mm. in diameter at the
lower pole of each thyroid. The combined weight
of the adrenals ranged from 6 to 9 mg.; this is the
same as that found in normal birds. No consistent
histological changes could be identified, although,
following hypophysectomy of young chicks, Nal-
bandov and Cord (38) found complete disappear-
ance of the adrenal cortex and degeneration of the
medulla.

The thyroids, which are bilateral in the para-
keet and have a combined weight of 5–10 mg.,
were 2–3 times normal size in nine of the 50 birds
(18 per cent). Histologically, this was due more to
colloid storage than to hyperplasia of the epi-
thelium. These changes in the thyroid are of
interest in view of the thyroid hyperplasia and
neoplasia, respectively, reported by Fischer (15) in
two rats with spontaneous pituitary tumors. The
thyroid plays the leading role in several of the
methods employed to induce pituitary neoplasia
in mice (19, 26, 36). Furth et al. (18) have shown
that normal mice bearing grafts of the autonomous
pituitary tumors have tremendously enlarged
thyroids due to the production of thyroid-stimu-
lating hormone (TSH) by the tumor. There were
no demonstrable changes in the pituitaries of six-
teen parakeets with large goiters that weighed 10–
25 times more than did the normal gland.

The pituitary tumors occurred with approxi-
mately equal frequency in the two sexes: 23 were
males, 27 females. There was always a marked de.
cline in the sexual activity of these birds. Females
ceseed egg laying or on rare occasions failed to
care for their young. Males failed to mate. In all
cases the gonads were in a state of rest, spermat-
ogenesis was absent in the testes, and maturing
follicles were not seen in the ovaries. Nevertheless,
fibrosis of the gonads and degeneration of the germ
cells, as described in the fowl following
hypophysectomy of young birds (38), were not
present. This arrest of gonadal function in para-
keets bearing pituitary tumors suggests that the
gonadotropic hormone is not elaborated by the
neoplastic cells.

Associated Neoplasms
In seven of the 50 cases of pituitary tumor (14
per cent) there were neoplasms in other organs. In
one instance (Case 29) this was a papillary ade-
noma of the Harderian gland that produced a
proptosis of one eye suggestive of retro-ocular in-

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vasion by the pituitary neoplasm. However, the hypophyseal tumor had produced only a diffuse enlargement of the gland without any evidence of local invasion.

In another case (No. 46) there was a 3-mm. papillary adenocarcinoma in the left kidney and a 1-cm. fibrosarcoma in the spleen of a bird with a large pituitary tumor that had invaded the retroocular tissue. The remaining five cases (Nos. 11, 31, 40, 42, 45) all bore single large papillary renal adenocarcinomas.

Of the seven cases with associated tumors five were males. The pituitary tumors in five of the seven were noninvasive (Group I); in two the neoplasm in the pituitary showed evidence of local invasion (Group II). The coincidence of papillary adenocarcinoma of the kidney in six birds with pituitary tumors is worthy of note, for Haddow and Horning (28) have observed the simultaneous occurrence of pituitary adenomas and renal carcinomas in male hamsters receiving stilbestrol. Nevertheless, in a series of sixteen parakeets (twelve males, four females) with renal adenocarcinomas careful examination showed no changes in the pituitary.

**Transplantation Experiments**

Fragments of the pituitary tumors from seven birds (Nos. 6, 9, 12, 15, 18, 24, 34) classified as Group II were inoculated into the brains of 30 parakeets and 81 fowl chicks; the latter were 24—36 hours old. No growth of the transplants was observed; survival of the tissue for 1—2 weeks was obtained in both parakeets and fowl chicks (Fig. 23). Operative mortality was very low; one chick died of hemorrhage, and in another the cerebral wound was infected.

One of the tumors (No. 28) was also inoculated into the yolk sac and allantoic membrane, respectively, of 24 fowl embryos. Only three embryos died; however, no tumor could be found in the remaining 21 eggs 12 days after inoculation.

Transplantation could not be carried out with material from the two cases in which the tumor had acquired a considerable degree of autonomy as evidenced by the presence of metastases. The pituitary tumors used in the transplantation studies were probably still dependent upon subtle changes in their hormonal environment in the manner of the conditioned neoplasms recently discussed by Furth (17).

**DISCUSSION**

For many years the role of the pituitary in obesity has been debated, and to many investigators it appeared probable that interference with pituitary function could lead to increased storage of fat. However, recent studies have indicated that the hypothalamus rather than the pituitary is most directly concerned with food intake and obesity in mammals (6, 7). Electrolytic lesions in the ventromedial hypothalamic nuclei of the rat lead to marked hyperphagia and a doubling of body weight (30, 31). In six of seventeen obese parakeets in this series the obesity was found associated with a pituitary tumor that had invaded or severely compressed the adjacent hypothalamus. In one case (No. 12) the bird, a male, was noted to be gaining weight while caring for the last nest of young. Shortly thereafter he became blind and 6 weeks later died. At autopsy the pituitary was found to be completely replaced by a tumor that invaded the optic nerves and hypothalamus.

These findings in the parakeet coincide well with the experimental evidence obtained with the rat. However, in eleven of the seventeen obese birds the pituitary neoplasm was small; neither gross nor microscopic study of the adjacent structures showed signs of pressure distortion or invasion by the tumor. Bird No. 21, a male with a large tumor-like accumulation of fat tissue beneath the skin of the breast, may serve as an example. It had been used in a laboratory feeding test by a commercial food firm; the subcutaneous fat was first noted about 20 days after conclusion of the study. At that time the bird weighed 60 gm.; 6 days later the weight was 63.3 gm., as compared to the 35—40-gm. weight of other birds in the aviary that were of the same age and had received the same feedings. However, except for this marked degree of obesity the bird appeared to be as normal and as active as its fellows. After several days under observation in our laboratory it was sacrificed, and in addition to extreme obesity the only abnormality found was an enlargement of the pituitary to 3 times its normal size. Histologically, there was complete replacement of the normal tissue by a chromophobe adenoma but no evidence of invasion of surrounding tissue.

The effect of hypophysectomy in birds is still not entirely clear. In adult hens Rothchild (45) found that hypophysectomy led to a sharp weight loss followed by a slow return, with stabilization of the body weight at about 11 per cent greater than the pre-operative weight. Using young growing fowl 60 days old and weighing 500 gm., Nalbandov and Cord (38) found that increase in body weight continues after complete removal of the hypophysis and is due to the abnormal deposition of fat rather than to true growth. Carcasses of hypophysectomized chickens contain 5—7 times more fat than do their controls. Whether these operative procedures in chickens were accompanied by any
damage to the hypothalamus is not recorded.

Excessive amounts of pituitary adrenocortico-
trophic hormone (ACTH) acting upon the adrenal
may lead to obesity. Recently, Furth et al. (20)
found that a pituitary tumor which developed in
a mouse following ionizing irradiation was trans-
plantable to normal untreated mice. Among
the changes produced in the recipients were obesity
and polyuria. The authors concluded on the basis
of these and other findings that the tumor trans-
plants secreted ACTH. In the light of these find-
ings in mice, it seems possible that the sporadic
obesity found among the parakeets may be due to
the secretion of ACTH by some of the pituitary
tumors.

The emaciation which is more often a late mani-
festation of a pituitary tumor than is obesity may
be explained by the bird's progressive inability to
get about and feed. However, loss of appetite and
emaciation have also been produced in rats by
sharply localized electrolytic lesions in the hypo-
thalamus. Its role in the parakeet cannot be de-
termined from the data at hand.

On the basis of the material examined it appears
that in the parakeet pituitary there is a gradual
transition from hyperplasia to neoplasia. A dis-
cussion of etiology may therefore concern itself
primarily with a consideration of factors known
to produce pituitary hyperplasia; the immediate
cause for the change from hyperplasia to neo-
plasia is unknown in the bird, as it is in other
animals.

Adenomatous hyperplasia and neoplasia of the
pituitary have been produced experimentally in
several rodents, viz., mice, rats, and hamsters.
The method employed produced a disturbance of
dermatine relationships involving either the pitui-
tary and the gonads (10, 21, 28, 39) or the pitui-
tary and the thyroid (19, 26, 36). The problem has
been reviewed by Gardner (32).

The incidence of pituitary tumors is approxi-
mately equal among male and female parakeets.
This suggests that, if a pituitary-gonadal imbal-
ance exists, it is not due to over-secretion of a single hormone, e.g., estrogen. However, the effect of stilbestrol on the pituitary of both the male and female parakeet is being investigated.

The normal life span of the parakeet is about 9
years. Birds with pituitary tumors are relatively
young—the average age is 2.5 years, which repre-
sents a period of great sexual activity. Most of the
birds in whom an adequate history could be ob-
tained were good breeders until signs of a pituitary
tumor became manifest. Because of the current
great demand for parakeets, many owners of
aviaries are breeding them when the birds are less
than a year old. In addition, some of the birds are
allowed to rear more than three clutches of young
annually. Such intensive breeding, including feed-
ing and caring for the young which is carried out
by both male and female, may lead to overstimu-
lation of the pituitary followed by hyperplasia and,
evitably, neoplasia of that organ.

No definite relationship between the thyroid
and pituitary tumors in the parakeet could be
demonstrated. The condition of the thyroid in
these birds has been discussed in the section on
changes in endocrine glands other than the pitui-
tary.

The effect of light on sexual activity, so-called
“sexual photoperiodicity,” has been extensively
investigated in birds (5, 8). It is of considerable
commercial importance in the poultry industry,
where artificial light is used to prolong the day-
light hours for egg laying (58). This custom is also
widespread among parakeet breeders. The con-
sensus is that light may stimulate the hypophysis
indirectly through visual perception or excitation
of deeply situated nerve centers, or directly after
it has penetrated the overlying tissues (3). The re-
sultant stimulation leads to an increased produc-
tion of gonadotrophins.

The possibility that prolonged or more intense
light may lead to hyperplasia and neoplasia of the
pituitary is under experimental investigation. Data derived from the birds received with sponta-
aneous tumors are inadequate to permit any con-
clusions. Many breeders when questioned replied
that the birds were exposed to varying amounts of
artificial light. Of interest is the fact that the larg-
est number of birds with tumors (14) were received
from Texas where the intensity of solar radiation
is well known to cause an unusually high incidence
of skin cancer in man. In that state most avia-
 ries are outdoors. Nevertheless, there are so many
variables, e.g., a larger bird population, interested
breeders willing to send their birds, etc., which
might account for such a high incidence that the
significance of geographical distribution must re-
main speculative.

No evidence that a genetic factor plays a part
in the induction of these tumors has been ob-
tained. In most instances the relationship of sev-
eral birds received from the same aviary was un-
known. The absence of records was particularly
distressing when four or even six birds with pitui-
tary tumors were received from a single breeder
over a period of several months. The majority of
birds were obtained from such widely separate
parts of the country that kinship seems unlikely.
Offspring of birds that subsequently died with
pituitary tumors have been obtained in an effort to establish inbred strains of these birds.

SUMMARY

Spontaneous chromophobe pituitary tumors are not uncommon in the parakeet, Melopsittacus undulatus. The incidence is approximately equal in the two sexes.

Fifty cases have been examined and the tumors classified into three groups: (I) diffuse enlargement of the pituitary (40 per cent); (II) locally invasive tumors (60 per cent); and (III) metastasizing tumors (4 per cent).

Signs of a pituitary neoplasm in the parakeet include unilateral or bilateral exophthalmos, blindness, somnolence, polyuria, polydypsia, and obesity. The parakeet has a normal life span of about 9 years. The average age of birds with a pituitary tumor was 2.5 years.

The gross and microscopic morphology of the tumors is described; it differs little from that of mammalian pituitary neoplasms.

In six birds (10 per cent) there was an associated renal adenocarcinoma. Goiter occurred in nine of the parakeets (18 per cent); no changes were observed in the adrenals. The gonads were always in the resting state, but advanced atrophic changes were not encountered.

Transplants of tumor tissue from seven different birds into a total of 30 parakeets and 81 fowl chicks failed to grow. Most of the transplants were intracerebral.

Factors relating to the probable etiology of these tumors are discussed.

ACKNOWLEDGMENTS

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REFERENCES


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Fig. 7.—Ventral view of head after removal of jaw showing enlarged pituitary immediately behind optic chiasm. See also Figures 8 and 17. Bird No. 4. Mag. ×3.

Fig. 8.—Sagittal section of brain shown in Figure 7. A large darkly staining circular tumor is seen occupying the entire region of the mid-brain and infiltrating the meninges over the brain stem. The neoplastic pituitary appears as a more lightly staining ventral projection; the cross section of the optic chiasm is indicated by an arrow. Bird No. 4. Mag. ×10. Hematoxylin and eosin stain.

Fig. 9.—Section through liver showing pale gray tumor metastases from primary neoplasm in pituitary. For histologic structure see Figure 92. Bird No. 13.

Fig. 10.—Histological section through an entire pituitary that was grossly 3 times normal size. There is diffuse replacement of normal tissue by chromophobe cells. Infiltration of the adjacent meninges by the chromophobes had occurred. Bird No. 21. Mag. ×20. H. and E. stain.

Fig. 11.—Section of pituitary that was twice normal size. A chromophobe adenoma is seen compressing the adjacent normal tissue. Bird No. 45. Mag. ×135. H. and E. stain.
FIG. 1.—Section from primary tumor that had invaded the retro-ocular tissue. Its malignant character is indicated by the variability in the size of the cell nuclei, some of which may be classified as giant forms. However, the majority of cells with their hyperchromatic nuclei and scant cytoplasm are typical of those found in both the benign and malignant chromophobe tumors. See also Figures 20 and 21. Bird No. 3. Mag. ×700. H. and E. stain.

FIG. 13.—The epithelial character of the cells in a 6-mm. pituitary tumor that was invading the brain and underlying bone is apparent. The nucleoli stain sharply; no cytoplasmic granules are present. Bird No. 39. Mag. ×700. Severinghaus technic.

FIG. 14.—Giant cell in a tumor that invaded both orbits. See also Figure 23. Bird No. 18. Mag. ×700. H. and E. stain.

FIG. 15.—Giant cells in a pituitary adenoma; there is some variability in size of the chromophobe cell nuclei, but no evidence of invasion—note compression of adjacent normal tissue. For gross appearance see Figure 2. Bird No. 8. Mag. ×180. H. and E. stain.

FIG. 16.—Trabecular pattern of cells in a pituitary tumor that had penetrated the basi-sphenoid bone. There is moderate nuclear irregularity. Bird No. 6. Mag. ×550. H. and E. stain.

FIG. 17.—Perivascular and pseudo-papillary pattern of the large intracerebral tumor shown in Figures 7 and 8. Bird No. 4. Mag. ×400. H. and E. stain.
Fig. 18.—Infiltration of optic nerve by tumor cells. For gross appearance see Figure 4. Bird No. 1. Mag. X105. H. and E. stain.

Fig. 19.—Invasion of extra-ocular muscle by tumor. Bird No. 12. Mag. X175. H. and E. stain.

Fig. 20.—Perineural infiltration of tumor cells. For histologic structure of primary see Figure 12. Bird No. 3. Mag. X175. H. and E. stain.

Fig. 21.—Section of kidney from same case as Figures 12 and 20, showing renal metastasis. Bird No. 3. Mag. X175. H. and E. stain.

Fig. 22.—Metastatic tumor in liver. For gross appearance see Figure 9. Bird No. 13. Mag. X350. H. and E. stain.

Fig. 23.—Viable tumor transplant in brain of fowl chick 13 days after inoculation of tumor from Bird No. 18. See also Figure 14. Mag. X175. H. and E. stain.


Neoplasia in the Parakeet: I. Spontaneous Chromophobe Pituitary Tumors

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