Effect of Pheochromocytoma and Hypophysectomy on Blood Pressure and Catecholamines in NEDH Rats

WILLIAM M. MANGER, M.D., PH.D., MILDRED C. HULSE, M.A., MARGARET S. FORSYTH, ROANNA N. CHUTE, M.A., CLARK E. BROWN, M.D., KIRWAN WEBB, RICHARD SUSSMAN, AND SHIELD WARREN, M.D.*

SUMMARY The New England Deaconess Hospital (NEDH) rat provides a ratable model with which to study pheochromocytoma (P). 59% of male rats 700 to 900 days old and 81% of those 900 days or older developed spontaneous P. One transplantable P (P259), when implanted into other NEDH rats, markedly increased plasma norepinephrine and dopamine as well as blood pressure, and usually caused death within 4 weeks. Even without P, about 83% of NEDH rats became hypertensive by 13/4 weeks of age and remained moderately hypertensive until 2 years of age when some animals developed spontaneous P and hypertension became severe. Whether a common mechanism is responsible for early appearance of hypertension and later development of P remains to be determined. Hypophysectomized NEDH rats remained normotensive or slightly hypotensive despite marked elevations of plasma norepinephrine and dopamine caused by P259 implantation; furthermore, survival was prolonged to 3 months. Catecholamine concentrations in plasma and RBC were usually quite similar, indicating that red blood cells play a significant role in inactivating circulating catecholamines. Unlike the normal adrenal, P259 in NEDH rats contains mainly norepinephrine and dopamine with little epinephrine; it appears that P259 is deficient in the enzyme phenylethanolamine-N-methyltransferase (PNMT), which converts norepinephrine to epinephrine. Why hypophysectomy prevents hypertension and prolongs life in rats with P259 implants is unclear; adrenal cortical and thyroid deficiency may play a role. Preliminary observations indicate that hypophysectomy can prevent spontaneous development of P in NEDH rats.

(KEY WORDS • pheochromocytoma • hypophysectomy • hypertension • NEDH rats • plasma catecholamines • red blood cell catecholamines • tumor transplantation)

THE New England Deaconess Hospital (NEDH) rat (Wistar related) provides a valuable model for studying pheochromocytoma (P). Spontaneous P occurs in NEDH rats especially with aging. P almost always arises in the adrenal medulla and about 50% occur bilaterally; very rarely it occurs in the organ of Zuckerkandl. Others1,2 have reported an increased incidence of P in Wistar rats, up to 85% in old males.2 Warren and Chute5 established a transplantable P (P259) from a spontaneous P. When implanted in NEDH rats (other strains reject P259) it will grow rapidly and secrete catecholamines; it causes hypertension, cardiovascular lesions, weight loss, and death usually within 1 month.5 If stored appropriately in liquid nitrogen, P259 retains its viability and can be used for tumor transplantation. Biochemical characterization3,4 and the influence of nerve growth factor on cytochemical and growth characteristics of experimental P5,6 (initially derived from P259) have been reported by others.

The purpose of this investigation was to study the effects of P259 transplantation and hypophysectomy in NEDH rats on the blood pressure (BP) and catecholamine concentrations in plasma and red blood cells (RBC). Further, we wished to observe the effect of hypophysectomy on the growth of implanted tumors and the occurrence of spontaneous P and other tumors, since chronic growth hormone administration to rats had been reported to cause P.11-12

Materials and Methods

Except where indicated, only male NEDH rats were used to study the effects of: 1) aging on BP; 2) P259 implantation on the life span, BP, plasma, RBC, and tissue catecholamines in normal and hypophysectom-
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ized rats; and 3) hypophysectomy on spontaneous development of P. Rats were housed in conventional animal facilities (temperature 22° to 26° C) and given Purina rat chow (containing 1% NaCl) and water ad libitum; no special provisions or endocrine replacement therapy were required for hypophysectomized rats to survive a normal life span. Hypophysectomy was performed on 2- to 3-month-old rats (under ether anesthesia) by a modified parapharyngeal approach.14 Completeness of hypophysectomy was evident by inhibition of growth; the weight of 17-month-old hypophysectomized rats (14 months posthypophysectomy) was 330 ± 10 g and that of control rats, 553 ± 15 g, a 40% weight difference (p < 0.001). Completeness of hypophysectomy was also evident by marked atrophy of gonads and adrenal glands, the appearance of fine fur and thin skin, and the absence of the pituitary at autopsy.

Systolic BPs were measured in unanesthetized rats by a tail cuff (2.5 cm width) method using a programmed electrosphygmomanometer PE-300 (Narco-Bio-Systems, Houston, Texas) and a pneumatic pulse transducer (E and M Instrument Company, Houston, Texas) to detect tail artery pulsations, which were recorded on a Grass polygraph (Grass Instrument Company, Quincy, Massachusetts); heart rates were determined from pulsations/min.

Several segments (diameter, 2 or 3 cu mm) of P259 were inserted into the needle end of a 16-gauge trochar which was then passed into subcutaneous tissue through a small incision in the back; tumor tissue was ejected from the needle into subcutaneous tissue by a stylet. Blood samples, transplanted P, and adrenals were usually removed, and the rats were sacrificed 3 weeks after implantation, when BP was markedly elevated by excess circulating catecholamines secreted from P tumors that had developed at the sites of implant.

Blood (2 ml) from the inferior vena cava below the level of the renal veins was rapidly collected through an abdinal incision in anesthetized (pentobarbital 40 mg/kg i.p.) rats and placed in ice-cold tubes containing 20 μl of 6% glutathione and 9% EGTA (pH 6.0 to 7.4) for each 1 ml of blood. (This anesthesia and blood sampling technique did not appear to significantly activate the adrenergic system.) Following centrifugation (350 × g), plasma was separated and frozen. RBC were washed 3 times with isotonic saline to remove residual plasma. Packed cell volume of RBC in the remaining saline was determined by hematocrit to permit calculation of catecholamines of undiluted RBC. 0.5 ml aliquots of RBC were lysed with deionized glass distilled water and lysates stored at −20° C (microscopic examination revealed complete RBC lysis). Plasma and RBC catecholamine concentrations were quantitated by radioenzyme assay.15

Tissues for catecholamine determinations were homogenized in ice-cold 0.4 N perchloric acid (containing 5 mM glutathione) and centrifuged to produce a protein-free supernatant which was separated and stored at −20° C. Glass-distilled deionized water was used for further dilution, and the pH adjusted to 7 to 8 at the time of radioenzyme analysis.

Twenty-four-hour urine samples were collected (with 1 to 1.5 ml of 2 N HCl) in metabolic cages from normal and hypophysectomized NEDH rats and from a group of NEDH rats implanted with P259. Urinary catecholamines, metanephrines, and vanilmandelic acid (VMA) were analyzed by modified fluorometric or spectrophotometric methods. Occasionally, serum sodium and potassium were determined by flame photometer, and blood counts by Coulter counter on blood removed from the tail artery of conscious or ether-anesthetized rats.

For histological studies, autopsies were performed and samples taken of almost all tissues, including tumors grossly visible. Tissues were fixed in Zenker-formol, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Absence of P was established by evidence of normal histologic examination of adrenal glands and normal concentrations of plasma and urine catecholamines and metabolites. Data was statistically analyzed by the Student’s t test.

Results

Figure 1 reveals mean systolic BP (mm Hg ± SEM), heart rate, and weights of NEDH rats observed for 113 weeks. Weights increased rapidly until 10 weeks of age and more gradually thereafter; heart rates, slightly greater in young rats, initially declined but between age 8 and 113 weeks did not change significantly. By 13½ weeks of age, mean BP was 159 ± 4 mm Hg and all but two of 12 rats were hypertensive (BP > 140 mm Hg). BPs thereafter increased slightly until 104 weeks of age when the surviving three rats became markedly hypertensive (223 ± 48 mm Hg). (One had a BP of about 320 mm Hg and, at death 1 week later, an adrenal P weighing 1.2 g was discovered.) The BP of both surviving rats at 113 weeks of age was 250 and both were losing weight; autopsy shortly thereafter revealed an adrenal P (weights, 0.35 and 0.22 g) in each rat.

Table 1 reveals mean catecholamine concentrations in the plasma and RBC of NEDH rats without and with P259 implants, and in normal adrenal glands. Rats with P implants generally survived 3 to 4 weeks. In rats without P259, plasma concentration of norepinephrine (NE) (440 ± 39 pg/ml) was about three times greater than that of epinephrine (E) (145 ± 15 pg/ml) whereas dopamine (D) was barely detectable (60 ± 6 pg/ml). RBC concentrations of NE and E were similar to plasma levels; however, D (225 ± 49 pg/ml) was significantly greater in RBC. Plasma concentrations of D and NE in rats with P259 were respectively about 100 times and 15 times that in control rats, whereas E was only 3 times greater. In rats with P259, RBC catecholamine concentrations were not significantly different from those in plasma. Tumor implants (av. wt., 0.55 g) contained 72% NE (115 ± 7 μg/g), 26% D (42 ± 5 μg/g) and only 2% E (3.4 ± 0.5 μg/g) whereas adrenal glands (av. wt., 0.02
**Figure 1.** Mean systolic blood pressure, weight, and heart rate of New England Deaconess Hospital (NEDH) male rats observed for 2 years.

**Table 1.** Catecholamine Levels (Means ± SEM) in Control NEDH Rats Without and With Pheochromocytoma Implants

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Rats without tumors</th>
<th>Rats with tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma (n = 9)</td>
<td>Adrenal glands (wt = 0.02 ± 0.001 g) (n = 5)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>RBCs (n = 9)</td>
<td>Adrenal glands (pg/ml)</td>
</tr>
<tr>
<td></td>
<td>(pg/ml)</td>
<td>(µg/g) (%)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>60 ± 6</td>
<td>225 ± 49 p</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>440 ± 39</td>
<td>440 ± 47 p</td>
</tr>
</tbody>
</table>

*p < 0.01 compared with levels in rats without tumors.
†p < 0.025 compared with levels in rats without tumors.
‡p < 0.005 compared with levels in rats without tumors.
§p < 0.001 compared with levels in rats without tumors.
\(\ll\)p < 0.005 compared with plasma dopamine in rats without tumors.
Table 2. Catecholamine Levels (Means ± SEM) in Hypophysectomized NEDH Rats Without and With Pheochromocytoma Implants

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Rate without tumors</th>
<th>Rate with tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma (n = 4) (pg/ml)</td>
<td>RBCs (n = 4) (pg/ml)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>120 ± 50</td>
<td>205 ± 66</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>910 ± 244</td>
<td>1390 ± 140</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>400 ± 154</td>
<td>380 ± 174</td>
</tr>
</tbody>
</table>

* *p < 0.05 compared with levels in hypophysectomized rats without tumors.
† *p < 0.005 compared with levels in hypophysectomized rats without tumors.

Adrenals from hypophysectomized rats weighed about one-third those of control rats. Although catecholamine concentrations tended to be less and the percent of NE greater than in controls, differences were not significant.

The effect of P259 implantation on the BP of normal and hypophysectomized NEDH rats is indicated in Table 3. Average BP in male and female rats (4 to 9 months old) without P259 were 149 ± 2 and 141 ± 3 mm Hg respectively. At 3 to 4 weeks after P259 implantation, BPs in males and females averaged 178 ± 3 and 173 ± 3 mm Hg respectively. In contrast, BPs of hypophysectomized male and female rats (2 to 3 months old) averaged 109 ± 2 and 98 ± 7 mm Hg; none was hypertensive (at this age about 83% of intact NEDH rats are hypertensive). At 6 to 8 weeks after P implantation in hypophysectomized rats, the BPs of male (110 ± 2 mm Hg) and female (105 ± 5 mm Hg) remained normal.

Table 4 reveals 24-hour urine volumes and concentrations of total catecholamines, total metanephrines, and VMA in control and hypophysectomized rats and rats with P259 implantation. Urine volumes were significantly greater in rats with P259 than in control rats of the same age. Urine volumes and concentrations of catecholamines and metabolites were significantly higher in P259 rats than in control rats. Although catecholamine concentrations tended to be less and the percent of NE greater than in controls, differences were not significant.
greater in older (≥1 year) than in young (10 weeks) controls. Catecholamine and metanephrine concentrations were significantly elevated in rats harboring P259, whereas VMA was elevated in only two of eight rats. Concentrations of VMA, metanephrines, and catecholamines in hypophysectomized rats were less than in old controls, but urine volumes were similar. In hypophysectomized rats, however, when compared with young controls of similar weight, the urine volume was significantly increased (p < 0.02) and VMA significantly decreased (p < 0.05).

Table 5 reports the percent of male rats found to have P and other tumors at various ages. The youngest single control rat discovered with P was 477 days old. Effect of hypophysectomy on spontaneous tumor development is also indicated. Incidence of P and other tumors increased with aging. Of rats >900 days old, 81% had P and 52% had other tumors. Of 18 rats (mean age 721 ± 42 days; 78% were 2 years or older) in which hypophysectomy was thought to be complete, only one P was found; since no gonadal atrophy occurred, however, and since a tiny cluster of pituitary cells was discovered at autopsy, it is probable that some anterior pituitary function persisted in this rat. Of eight rats with residual pituitary tissue, three (38%) developed P; the latter three had the largest residual pituitary tissue (25% to 50% of pituitary remaining). Serum sodium (137 ± 0.5 mEq/liter) and potassium (4.3 ± 0.1 mEq/liter) concentrations and blood counts of rats determined 39 days after hypophysectomy were not remarkably different from those of control rats. However, moderate anemia (RBC 5.86 ± 0.02 × 10¹² mm⁻³; Hgb 11.9 ± 0.1 g/dl; HCT 27.6% ± 0.2%) was observed in some rats within 2 years after hypophysectomy. RBC (8.56 ± 0.05 × 10¹² mm⁻³), Hgb (17.3 ± 0.2), and HCT (42.1 ± 0.9) were similar in young (3-month) and older (20-month) control NEDH rats.

### Table 4. 24-Hour Urine Volume and Concentrations of Catecholamines and Metabolites (Means ± SEM) in NEDH Rats Without and With Pheochromocytoma Implants

<table>
<thead>
<tr>
<th>Rat group</th>
<th>24-hr vol (ml)</th>
<th>VMA (µg/24 hr)</th>
<th>Metanephrines (µg/24 hr)</th>
<th>Total catecholamines (µg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 10 wks (females = 9)</td>
<td>9.4 ± 0.2</td>
<td>24.7 ± 1.7</td>
<td>2.3 ± 0.3</td>
<td>0.56 ± 0.03</td>
</tr>
<tr>
<td>≥ 1 yr (males = 5)</td>
<td>15.9 ± 2.4*</td>
<td>44.4 ± 7.0*</td>
<td>4.2 ± 1.0</td>
<td>1.36 ± 0.29*</td>
</tr>
<tr>
<td>With tumors (implanted for 1 mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 11 wks (females = 6)</td>
<td>15.8 ± 1.2†</td>
<td>28.0 ± 1.2</td>
<td>10.7 ± 1.7*</td>
<td>11.15 ± 1.46†</td>
</tr>
<tr>
<td>11 wks (males = 2)</td>
<td>20.0</td>
<td>55.0</td>
<td>47.6</td>
<td>41.69</td>
</tr>
<tr>
<td>Hypophysectomized (17 mos after hypophysectomy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 20 mos (males = 4)</td>
<td>15.9 ± 2.1</td>
<td>7.3 ± 6.3†</td>
<td>2.2 ± 0.4§</td>
<td>0.84 ± 0.20</td>
</tr>
</tbody>
</table>

VMA = Vanilmandelic acid.

* p < 0.025 compared with values for 10 wk old control rats.
† p < 0.001 compared with values for 10 wk old control rats.
‡ p < 0.01 compared with values for ≥1 yr old control rats.
§ p < 0.005 compared with values for ≥1 yr old control rats.

### Table 5. Percent of NEDH Male Rats with Pheochromocytoma and Other Tumors: Effect of Hypophysectomy

<table>
<thead>
<tr>
<th>Rat group</th>
<th>No. of rats</th>
<th>Age range (days)</th>
<th>With pheochromocytoma</th>
<th>With other tumors*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>163</td>
<td>300-699</td>
<td>34 21</td>
<td>38 23</td>
</tr>
<tr>
<td>Control</td>
<td>213</td>
<td>700-899</td>
<td>126 59</td>
<td>89 42</td>
</tr>
<tr>
<td>Control</td>
<td>211</td>
<td>&gt;900</td>
<td>17 81</td>
<td>11 52</td>
</tr>
<tr>
<td>Hypophysectomized</td>
<td>18</td>
<td>316-995</td>
<td>1† 5.5</td>
<td>2 11</td>
</tr>
<tr>
<td>Incompletely hypophysectomized</td>
<td>8</td>
<td>672-1000</td>
<td>3 38</td>
<td>1 13</td>
</tr>
</tbody>
</table>

*Mainly tumors of skin and subcutaneous tissue, blood-forming tissues, pituitary, fat, thyroid, breast, brain, kidney, and muscle (in descending order of frequency).
† Hypophysectomy probably incomplete.
Discussion

The NEDH rat is a particularly valuable model since it permits the study of the development and effects of spontaneous P as well as a conveniently transplanted P (P259). The latter secretes NE and D but little E, since it is deficient in PNMT enzyme.4

The finding that about 83% of NEDH rats developed hypertension by 13½ weeks of age, i.e., in the absence of P, is intriguing since it raises the question of whether a common mechanism is responsible for the early development of hypertension and subsequent development of P. It is noteworthy that, despite numerous histologic and biochemical studies, we have never demonstrated P or adrenomedullary hypertension in NEDH rats under 68 weeks of age.

Plasma and RBC catecholamine concentrations were quite similar in control NEDH rats and also in rats with elevated concentrations due to P259. It appears that RBC play a role in inactivating circulating catecholamines, a role especially significant in patients with P. Blood cell uptake of circulating catecholamines can occur by an energy-requiring mechanism as well as simple or facilitated diffusion.16-20 In addition to the ability of RBC to bind and transport circulating biogenic amines, recent evidence suggests that N may be catabolized inside RBC.16-20

Why plasma catecholamine concentrations tended to be greater in hypophysectomized rats with P259 than in unhypophysectomized rats with P259 is unclear. Although catecholamine concentrations in P implants from unhypophysectomized rats were greater than those in P from hypophysectomized rats, the latter tumors were about 4 times larger and may have released greater amounts of catecholamines into the circulation than P in unhypophysectomized rats. Hypophysectomized rats were also younger and significantly smaller than those unhypophysectomized; catecholamines released by P would be less diluted by smaller blood volumes in hypophysectomized rats. Reduced catecholamine catabolism in hypophysectomized rats might also have contributed to higher plasma catecholamines in these rats.

In rats with P implants, urinary catecholamines and metanephrines were always elevated, but only two of eight rats had increased VMA. The fact that catecholamines are readily metabolized to VMA in man but much less so in rats11 may explain normal VMA levels in some rats with P.

Hypophysectomized rats had significantly lower urinary concentrations of catecholamines and their metabolites than adult controls. Although smaller size of hypophysectomized rats may partly account for these lower concentrations, VMA was significantly less than levels in young rats of similar size. Others have reported increased VMA excretion following hypophysectomy.25 Hypophysectomy is known to markedly reduce activities of tyrosine hydroxylase, dopamine-B-hydroxylase, and PNMT,26 whether it also influences enzymatic conversion of catecholamines to VMA is uncertain. The fact that urinary catecholamines and their metabolites in hypophysectomized rats were not increased in the presence of elevated plasma catecholamines remains unexplained but suggests their renal clearance was reduced.

As expected, adult rats excreted larger volumes of urine and greater concentrations of catecholamines and metabolites than young rats. Elevated urine volumes in rats with P may have resulted from increased renal blood flow and/or a possible natriuretic and diuretic effect caused by high concentration of circulating D.24 25

Urine volumes of hypophysectomized rats were significantly greater than in young rats of similar size. Conceivably, antidiuretic hormone (ADH) deficiency could explain this finding although overt diabetes insipidus did not occur.

Why hypophysectomy prevented development of hypertension in rats without or with P (despite marked elevations of circulating catecholamines) is unclear. Prolongation of survival of hypophysectomized rats implanted with P may have been due to absence of hypertension; cause of their weight loss and death in 3 to 4 months probably was related to the effects of excess circulating catecholamines and perhaps cardiac complications.

Aoki26 reported that removal of the pituitary or adrenals, or suppression of thyroid function, prevented the development of hypertension in prehypertensive spontaneously hypertensive rats and normalized BP in those already hypertensive; gonadectomy had no effect on development or maintenance of hypertension. Administration of adrenocorticotropin (ACTH), thyroid powder, or cortisone to rats made normotensive by hypophysectomy increased BP to hypertensive levels but levels less than before hypophysectomy; vasopressin had no effect on BP.27 Aoki concluded that ACTH and thyroid-stimulating hormone (TSH) were the pituitary hypertensive factors and that thyroid and adrenal hypofunction inhibited development of hypertension. From his studies and those of others he also suggested that the adrenal factor concerned with hypertension was glucocorticoid and not mineralocorticoid hormones.

Hypophysectomy has also been reported to prevent deoxycorticosterone (DC) hypertension,28-31 adrenal regeneration hypertension (by inhibiting cortical regeneration),32 and renal hypertension.33 Contrariwise, other reports indicate that DC hypertension can be induced34 and that renal hypertension persists35 following hypophysectomy.

It is conceivable that in hypophysectomized rats with P implants the markedly elevated circulating catecholamines are incapable of causing vasoconstriction and of inducing hypertension if adrenal and thyroid insufficiency exist. Glucocorticoids impede extraneuronal uptake (uptake 2) of catecholamines,36 inhibit catechol-O-methyl transferase,37, 38 and monoamine oxidase,39 and enhance vasoconstriction caused by catecholamines.40 Glucocorticoid deficiency may therefore increase catecholamine uptake and catabolism and thereby impair the ability of catecholamines to induce vasoconstriction.
Hypophysectomy causes severe atrophy of the zona fasiculata and reticularis but can cause hyperplasia of the glomerulosa. Following hypophysectomy, adrenal insufficiency of a hypertensive factor probably results from deficiency of hormones secreted by the fasiculata (glucocorticoids) rather than hormones secreted by the reticularis (androgens) or glomerulosa (mainly aldosterone and some DC). This contention is strengthened by the finding that aldosterone administration did not prevent the decline of BP or restore hypertension following adrenalectomy in renal or genetic hypertension. Furthermore, administration of cortisone but not DC to adrenalectomized animals caused hypertension. The fact that serum sodium and potassium values in our hypophysectomized rats were similar to those in controls also suggests that there was no pronounced deficiency of mineralocorticoids.

The high incidence and frequent bilaterality of P in NEDH rats suggest a genetic abnormality in its causation. Chronic administration of growth hormone (perhaps a form circulation when used 20 or more years ago) was reported to cause P. Certain other tumors, and pituitary cell changes in Long-Evans rats. However, Moon et al. found that prolonged administration of growth hormone to hypophysectomized rats (while producing growth) did not produce neoplasms.

The NEDH rat appeared to be an ideal model to test the hypothesis that growth hormone or other pituitary hormones may be implicated in the genesis of spontaneous P. The mechanism whereby hypophysectomy inhibits spontaneous tumors in NEDH rats is unknown. How alterations of growth, endocrine balance, and metabolism caused by hypophysectomy interfered with tumorogenesis remains to be determined. Hypophysectomized rats had a normal life span and appeared to be in good health except for the development of anemia in older rats. The incidence of pituitary tumors and P in 404 control NEDH rats was 3.7% and 59% respectively. Since the incidence of P in rats with pituitary tumors was 47% (no greater than the overall incidence of P), there seemed to be no correlation between the occurrence of these two tumors. However, studies on the functional activity of the pituitary and its possible relationship to the genesis of P in NEDH rats are needed.

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