THE ENDOCRINE SIGNIFICANCE OF HYPOPHYSEAL TUMORS IN MAN*

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Hypophyseal tumors of two common types have been accepted in man: "acidophil adenomas" which are associated with somatic overgrowth and manifestations of endocrine hyperactivity, and "chromophobe adenomas" which, although without endocrine function themselves, may lead to "hypopituitarism," allegedly through compression atrophy of other portions of the hypophysis.[1] However, patients are encountered occasionally who cannot be fitted readily into these categories.

Twenty-seven patients with hypophyseal disease were studied in order to determine, first, to what extent cytologic examination of the hypophysis justifies the clinical distinction between "acidophil" and "chromophobe" tumors, and, second, to review the anamnestic and anatomical data with respect to other endocrine organs.

MATERIAL AND METHODS

Pathologic material available at the Massachusetts General and Beth Israel Hospitals, Boston, Massachusetts, comprised 8 patients with somatic overgrowth (one man and 6 women with acromegaly as well as a non-acromegalic woman 185 cm. tall) and 19 with large "chromophobe adenomas" (12 men and 7 women). Pertinent clinical and anatomical data are summarized in Tables I and II.

Sections of hypophysis were stained with hematoxylin and eosin, modified Mallory's aniline blue, and the periodic acid-Schiff technique with orange G counterstain. Cells were classified according to cytoplasmic granulation and nuclear characteristics by the method previously described.[2] Typical cells may be characterized as follows:

Basophils. Granules numerous and intensely Schiff positive(Fig. 1).

Acidophils. Granules numerous and Schiff negative but staining with fuchsin or orange G (Fig. 2).

* Supported by a research grant (C-1451 C3) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

Presented, in part, at the Fifty-second Annual Meeting of the American Association of Pathologists and Bacteriologists, Houston, Texas, April 7, 1955.

Received for publication, December 12, 1955.

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TABLE I

Clinical and Anatomical Findings in Patients with Somatic Overgrowth

No.	Age	Sex	Duration	Onset	Therapy	Hypophysis	Adrenal glands	Gonads	Thyroid gland	Pancreas	Parathyroid glands	Uterus	Breast	Associated conditions	Cause of death
			yrs.												
1 MGH 12,704	50	M	23	Decreased libido	X-ray, 12 and 5 yrs.; estrogens, 4 yrs.; testosterone, 3 yrs.; none, 11 mos.	1.5 gm.; adenoma of multinucleate HA; Amp, few Ac	24 gm.; nodular hyperplasia; 17-ks, 5.3 to 12.3 mg.	Total atrophy; FSH, +7 m.u., negative after estrogen	41 gm.; fetal adenomas, colloid goiter	150 gm.; abundant large islands; FBS, normal; GTT, equivocal	10 x 5 mm.; abundant chief cells, clumps of oxyphils			Bleeding duodenal ulcer, hypertension	Cerebrovascular accident
2 MGH 13,468	25	F	8	Amenorrhea, hot flashes	Insulin, 6 yrs.; transsphenoidal resection, 3 yrs.; estrogens, 6 yrs. to death	2 x 1.5 x 1.8 cm.; adenoma; small Ac, rare B, pyknotic nuclei	18 gm.; moderate hyperplasia; 17-ks, 7.7 to 21.3 mg.	Active stroma, follicle cysts, no corpora lutea; FSH, +7 m.u., negative after estrogen	19 gm.; focal activity; BMR, −8 and +15	80 gm.; abundant islands; FBS, normal; GTT, diabetic	Acinar hyperplasia of chief cells	No data	Active lactation	Acne, pigmented spots on skin, hirsutism	Meningitis
3 BIH S49-922	32	F	7	Irregular menses	Stilbestrol, none for 1 yr.; transsphenoidal resection	Large tumor invading sphenoid; HA, Amp	No data	Scanty menses for 7 yrs., improved by stilbestrol	No data	No data	No data	No data	No data	Central obesity	Patient living
4 BIH A47-70	47	F	1	Amenorrhea	Insulin	Large tumor destroying sella and compressing brain; Amp, rare HA	"Normal size"; nodular hyperplasia	Inactive stroma, corpora albicantia	"Normal size"; cuboidal epith., fetal adenomas, exophthalmos	140 gm.; many large islands, minimal fibrosis	4 x 1 x 2 mm.; normal histology	Fibroids	Epithelial proliferation, microscopic secretion	Diabetes, obesity, hirsutism, cutaneous fibromas	Diabetic coma

5 MGH 10,473	58	F	25	Irregular menses	Craniotomy, 25 yrs.; x-ray, 9, 4, and 3 yrs.; radium, 1 yr.; thyroid, 3 yrs. to death	3 cm. diameter; adenoma invading brain; Chr, few Amp, HA, Ac	Nodular hyperplasia	Atrophic ovaries, corpora albicantia, FSH, negative	28 gm.; diffuse fibrosis, low epithelium	50 gm.; islands normal; FBS, normal; GTT, diabetic	Chief cell hyperplasia, many oxyphils	Cystic hyperplasia of endometrium, polyps	Dilated ducts, lobular hyperplasia	Hemangioma, cholangioma, myxedema	Tracheobronchitis
6 MGH 16,731	67	F	c.20	Menopause, hot flashes	Insulin, 11 yrs.; KI, 7 yrs.; I-131, 7 yrs.; x-ray, 6 yrs.; no therapy, 6 yrs.	0.60 gm.; no tumor, 5368 cells counted: Amp, 13.4%; HA, 2.8%; B, 18.3%; Ac, 16.8%; Chr, 48.4%; HyB, 0.3%	16 gm.; nodular hyperplasia, anisonucleosis	Moderate stromal hyperplasia	"Large" nodular goiter, fibrosis and calcification; exophthalmos; BMR, +72 and +94	75 gm.; islands normal	Acinar hyperplasia of chief cells, many oxyphils	Atrophic endometrium	No data	Diabetes, hirsutism, thyrotoxicosis, hypertension, arthritis, lipoma, osteoma	Cerebrovascular accident
7 MGH 10,057	74	F	c.30	Oophorectomy	None	2.25 gm.; 8 mm. adenoma; Amp, HA, few Ac	Nodular hyperplasia	Surgically absent, 30 yrs.	Not examined	100 gm.; islands normal	Not examined	Active glands in cervical stump	No data	Ca. of colon, meningioma, neuroma, lipoma	Cerebrovascular accident
8 MGH 13,929	40	F	?	Postmortem diagnosis	900 mg. testosterone 3 wks. before death	1.3 x 0.6 cm.; 0.6 x 0.4 cm. adenoma of Amp, HA, Ac, Chr	27 gm.; moderate nodular hyperplasia	Lt., simple cysts; Rt., normal stroma and degenerating corpus luteum	16 gm.; focal involution	60 gm.; adenomatous hyperplasia of islands	Not examined	Normal proliferative endometrium	Sclerosing adenosis	185 cm. tall, hirsutism, renal calculi, mucous colitis, ileal polyp, acute myelogenous leukemia	Acute myelogenous leukemia

Amp = Sparsely granulated amphophil
HA = Hypertrophic amphophil
Ac = Acidophil
B = Basophil
Chr = Chromophobe
HyB = Crooke's hyaline basophil
FBS = Fasting blood sugar
GTT = Glucose tolerance test
BMR = Basal metabolic rate

FSH = Follicle stimulating hormone in mouse units (m.u.); normally 6-12 m.u. for adults of reproductive age and 50 m.u. or more for post-menopausal women
17-ks = 17-Ketosteroids in mg. per 24 hours; normally 4-8 mg. for adult women and 12-20 mg. for adult men
PBI = Protein-bound iodine

Amphophils. Granules sparse, weakly Schiff positive, and staining variably with Mallory's technique (Fig. 1).

Hypertrophic Amphophils. Agranular cells with giant nuclei (Fig. 1).

Chromophobes. Agranular cells with small nuclei (Figs. 1 and 2).

The material was not suitable for the determination of cellular composition of the hypophyses outside of the tumors. Sections of the endocrine glands other than the hypophysis were stained with hematoxylin and eosin.

Hypophysis

Somatic Overgrowth (Patients 1 to 8, Table I). Seven patients with somatic overgrowth had tumors of the hypophysis. Four tumors were discrete and intrasellar; three were extrasellar, either compressing or frankly invading surrounding structures. In five of these seven tumors (cases 1, 3, 4, 7, 8), the sparsely granulated and hypertrophic amphophils rather than the acidophils constituted the dominant cell type (Figs. 3 to 6). It is suggested, therefore, that the amphophils rather than the acidophils are the source of growth hormone.

In two tumors there was a different picture in that only a few amphophils were present. Patient 5, having received thyroid medication for 3 years until death, had an extrasellar invasive tumor composed predominantly of agranular chromophobes with small nuclei. Patient 2 had a discrete intrasellar adenoma composed largely of tiny, well granulated acidophils with pyknotic nuclei (Figs. 7 and 8). In fact, this last patient was the only one of the series showing the traditional acidophilic adenoma of somatic overgrowth. However, the patient had been on stilbestrol prior to death, a medication which resulted in a distinct suppression of growth hormone (reduction in blood phosphorus, in growth of axillary hair, and in volume of hands and feet). We consider it possible that the cellular composition of these two hypophyseal tumors resulted from the hormonal medication; this is in keeping with previous observations indicating a suppressive effect of thyroid[3] and stilbestrol[4,5] upon the amphophils in non-tumorous hypophyses.

The hypophyseal tumors which had been irradiated showed cellular atypicality and nuclear pleomorphism, but the cell types remained identifiable and were similar to those seen in the non-irradiated tumors (Fig. 6).

The eighth patient (case 6), a classical acromegalic, showed neither tumor nor enlargement of the hypophysis. There was, however, a threefold increase of the amphophils, a two-fold increase of the basophils, and a reduction of the acidophils to half the expected value (Figs. 1, 2, and 9). In a case of Klinefelter's syndrome that we have previously

reported,[6] diffuse hyperplasia of the amphophils was observed in association with mild acromegaly, but the proportion of acidophils was within normal limits. Acromegaly in patients with non-tumorous hypophyses of normal size has been reported also by others.[7] All these observations indicate that non-tumorous hyperplasia of amphophils may be as productive of excessive growth hormone as hypophyseal tumors.

"Chromophobe Adenomas" (Patients 9 to 27, Table II). The dominant cell type in most of the 19 "chromophobe adenomas" was again the sparsely granulated amphophil (Figs. 10 and 11). In some, but by no means all, of these patients the tumor cells were smaller and the nuclei more uniform than those characteristically seen in acromegaly (cf. Figs. 3, 5, and 10). Following administration of testosterone, thyroid, ACTH, cortisone, or crude adrenal extract, the proportion of agranular chromophobes with small pyknotic nuclei was increased (Fig. 12).

Four of the 12 men with the clinical diagnosis of "chromophobe adenoma" had physical or radiologic evidence of mild somatic overgrowth (cases 9, 10, 15, and 16).

Adrenal Glands

Somatic Overgrowth. The adrenal glands were large, with a combined weight of from 16 to 27 gm., and all showed nodular cortical hyperplasia.[8]

In one woman the 17-ketosteroid excretion was elevated and became reduced following the administration of estrogen (case 2). The excretion was low in the patient who had received prolonged thyroid medication (case 5). It was within normal limits for the single male of this series (case 1).

Hirsutism was recorded for 4 women.

"Chromophobe Adenomas." Although patients with "chromophobe adenomas" frequently are considered to have "panhypopituitarism," the adrenal glands, like the hypophyses, resembled the glands of the acromegalic patients. Adrenal weight was increased in the majority, ranging from 13.5 to 30 gm. Nodular cortical hyperplasia was present in 11 patients. One woman (case 24) had a well defined cortical adenoma, 1 cm. in diameter. There were only 3 cases in which adrenal weight was below normal (cases 10, 12, and 27).

Three patients (cases 21, 22, and 25) had, variously, central obesity, hypertension, diabetes mellitus, and hirsutism, i.e., elements of Cushing's syndrome. In one patient (case 21) the 17-ketosteroid excretion

TABLE II

Clinical and Anatomical Findings in Patients with "Chromophobe Adenomas"

No.	Age	Sex	Duration	Onset	Therapy	Hypophysis	Adrenal glands	Gonads	Thyroid gland	Pancreas	Parathyroid glands	Prostate or Uterus	Breast	Associated conditions	Cause of death
9 BIH A41-37	41	M	*yrs.* 3	Impaired vision	Craniotomy, 3 days	4.5 x 4.5 cm.; tumor eroding sphenoid and extending to base of brain; Amp, HA	"Normal size"; nodular hyperplasia	Hypospermatogenesis, tubular sclerosis, abundant Leydig cells	"Large"; focal involution and hyperplasia	"Normal size"; abundant islands, some very large	No data	High columnar epithelium with papillary infolding		Fibromas of skin; polyposis of colon; large bones; large hands and feet; jaw normal	Craniotomy
10 MGH 15,148	48	M	13	Decreased libido, hot flashes	X-ray, 11 yrs. and terminally; thyroid and testosterone, 11 yrs.; ACTH, cortisone, testosterone, terminally	17 gm.; huge, hemorrhagic Amp tumor with pyknotic nuclei	8.7 gm.; cortex normal; 17-ks, 0.8 mg. terminally	21 gm.; severe hypospermatogenesis; no Leydig cells; FSH, negative terminally	14.5 gm.; low epithelium, pyknotic nuclei; BMR, −20 and −33	100 gm.; abundant, large islands; FBS, normal	Normal	Chronic prostatitis, low pyknotic epithelium		Myotonia atrophica; osteoma of skull; large hands and feet; spacing of teeth; decreased body hair	Spontaneous hemorrhage into hypophysis
11 MGH 15,473	51	M	9	Headaches	Craniotomy, terminally; 125 mg. cortisone, terminally	Large tumor of Amp, HA, with few Ac peripherally	14 gm.; slight nodular hyperplasia	Rt., 14 gm.: total atrophy (mumps orchitis); Lt., 35 gm.: active spermatogenesis and Leydig cells; FSH, 13 m.u.	20 gm.; high epithelium, mild fibrosis, lymphocytic infiltration; BMR, +3 and +8	110 gm.; abundant islands, some large; FBS, normal	Dense chief cells, little fat	High columnar epithelium, papillary infolding	Gynecomastia with microscopic secretion	Rheumatoid arthritis	Craniotomy
12 MGH 12,893	52	M	3	Myxedema	Craniotomy, 3 days; lipoadrenal extract, ACTH, DOCA, 3 days	5 x 4 x 3.5 cm.; Amp with small, pyknotic nuclei; necrotic areas	9 gm.; thin cortex; 17-ks, 2.0 mg.	Few mature sperm and Leydig cells, some tubular fibrosis; FSH, +13 m.u.	9 gm.; diffuse fibrosis, lymphocytes, cuboidal to high epithelium; BMR, −29; PBI, 2.6 gamma %	75 gm.; normal islands; FBS, normal; GTT, flat	Normal	Benign prostatic hypertrophy		Decreased body hair	Craniotomy

13 BIII S51-2406	53	M	12	Impaired vision	Cranio-otomies, 12 yrs., 5 yrs.; trans-sphenoidal resection, present admission	2 x 1 x 0.6 cm. tumor removed; Amp with small nuclei	No data	No data	No data	No data	No data	No data			Patient living
14 MGH 12,781	54	M	9	Impaired vision	X-ray, 5 yrs.; cranio-otomy, terminally	Large tumor, Amp, Chr, rare HA	24 gm.; nodular hyper-plasia	Mature sperm, Leydig cells, some tubular thicken-ing	"Normal size"; active acini	120 gm.; many large islands	No data	Acute prostatitis		Diabetes	Craniotomy
15 BIII S46-959 S51-3285	55	M	15	Headache	X-ray, 5 yrs.; trans-sphenoidal resection, 5 yrs. and present admission	Large tumor eroding sella; Amp, rare HA	17-ks, 7 mg. on 1st adm.; 2.2 mg. on 2nd adm.	Decreased libido	BMR, +9	GTT, normal	No data	No data		Obesity; osteo-porosis; large hands and jaw; decreased body hair; fibroma, skin	Patient living
16 MGH 9,238	55	M	10	Decreased libido	Cranio-otomies, 7 yrs. and termin-ally; x-ray, 1 mo.; adrenal extract, thyroid, pituitrin, antuitrin S, terminally	3.5 x 2.5 cm.; Amp Chr tumor with rare Ac; mitotic figures	15 gm.; recent hemor-rhagic infarction	Atrophy, fibrosis	9 gm.; severe fibrosis, focal lym-phocytes, cuboidal epith-elium; BMR, −26	Normal islands; FBS, 180 mg. %; GTT, equivocal	Large but with much fat	Normal size; inactive epith-elium		Skeletal x-rays suggest acro-megaly; decreased body hair; diabetes	Craniotomy
17 BIII S49-3039	60	M	1	Impaired vision	Trans-sphenoidal resection	Sella, 2.3 cm.; tumor invading sphenoid; Amp with small, uniform nuclei	Eosinophil count, 312; 206 after epi-nephrine	Decreased libido	BMR, −38 and −34	No data	No data	No data		Kyphosis and scoliosis; obesity; decreased body hair	Patient living

TABLE II (continued)

No.	Age	Sex	Duration	Onset	Therapy	Hypophysis	Adrenal glands	Gonads	Thyroid gland	Pancreas	Parathyroid glands	Prostate or Uterus	Breast	Associated conditions	Cause of death
			yrs.												
18 MGH 15,117	62	M	?	Post-mortem diagnosis	Insulin, 10 yrs.	1.5 x 2.0 cm. tumor eroding posterior clinoids; Amp, few Ac	20 gm.; nodular hyperplasia	Hypospermatogenesis, focal tubular atrophy, abundant Leydig cells	37 gm.; active epithelium, fetal adenomas, lymphocytic infiltration	130 gm.; normal islands	No data	Grossly normal		Diabetes; ca. and polyposis of colon; papillomas of skin; rheumatoid arthritis	Ca. of colon
19 MGH 9,945	72	M	40	Mumps orchitis	Testosterone, 2½ mos.	3 x 2.5 x 2 cm.; 1.5 cm. Amp adenoma with pyknotic nuclei, few HA	Narrow cortex; 17-ks, 1.2 mg.	Total atrophy, no Leydig or Sertoli cells; FSH, negative	10 gm.; fibrosis, low epithelium; BMR, −8 and −15	Grossly normal; FBS, 92 mg. %	No data	No data		Decreased body hair	Coronary thrombosis
20 MGH 15,990	77	M	?	Post-mortem diagnosis	None	2 gm.; Amp with rare Ac, HA	15 gm.; moderate nodular hyperplasia, focal anisonucleosis	Hypospermatogenesis, tubular thickening, few Leydig cells	24.5 gm.; hyperinvolution	150 gm.; large islands suggest adenomatous hyperplasia	"Large"; small papillary adenoma, large clumps of oxyphils	Grossly normal		Duodenal ulcer	Ruptured abdominal aneurysm
21 MGH 12,661	36	F	10	Menstrual irregularities	Craniotomy, terminally	1.5 x 1 x 1 cm. adenoma; HA, Amp, Chr	"Normal size"; severe nodular hyperplasia, anisonucleosis	"Small"; active stroma, thecomatosis; corpora albicantia, no ova or follicles	Not examined	140 gm.; islands normal; FBS, normal	No data	Tuberculous salpingitis	Simple mastectomy; mastopathia cystica, 10 yrs.	"Cushing's syndrome"; central obesity; hirsutism; hypertension	Craniotomy
22 MGH 11,535	41	F	12	Amenorrhea	Insulin, 4 yrs.; craniotomy, terminally	Amp adenoma	30 gm.; moderate nodular hyperplasia; 17-ks, 6.7 mg.	Active stroma, rare ova; corpora albicantia; FSH, >13 m.u., <48 m.u.	Focal involution, moderate fibrosis; BMR, −12 and −13	Normal	No data	Grossly normal	Persistent lactation, 10 yrs.	Central obesity; diabetes	Craniotomy
23 BIH S52-1045	48	F	1	Amenorrhea	X-ray and cortisone, 3 wks., followed by transsphenoidal resection	2 gm. tumor; pyknotic chromophobes	No data	No data	No data	No data	No data	No data	Milky discharge bilaterally	Hodgkin's (?) disease, "cured" by spray radiation, 20 yrs.	Patient living

24 MGH 14,075	69	F	?	Post-mortem diagnosis	None	3 x 2 cm.; Amp, HA, Chr with peripheral rim of small Ac	16 gm.; 1 cm. adenoma, nodular hyperplasia	Severe stromal hyperplasia, thecomatosis	17 gm.; active epithelium	43 gm.; numerous large islands	Numerous small clusters of oxyphils	Cystic hyperplasia, endometrium; cervical and endometrial polyps	Carcinoma; mastopathia cystica	Hypertension; ca. of breast; polyposis and leiomyoma of stomach	Arteriosclerotic heart disease; pulmonary emboli
25 BIH A53-145	77	F	?	Post-mortem diagnosis; oophorectomy, 35 yrs.	None	"Unusually large"; small tumor of relatively well granulated Amp	17.5 gm.; thick cortex, slight nodular hyperplasia	Surgically absent, 35 yrs.	21 gm.; involutional nodule	70 gm.; very large, abundant islands; acute pancreatitis	2 cm. chief cell adenoma, huge clumps of oxyphils; Ca, 11.3 mg. %; P, 2.9 mg. %	Surgically absent, 35 yrs.	Abundant lobules; secretion and intraductal hyperplasia	Central obesity; hypertension; decreased body hair; arthritis; cataracts; renal calculi	Pyelonephritis; uremia
26 MGH 15,702	80	F	?	Post-mortem diagnosis; total ovarian atrophy	None	2.3 gm.; tumor of Amp mixed with Chr, rare Ac, B	13.5 gm.; nodular hyperplasia, focal anisonucleosis	Totally atrophic, not found grossly	12 gm.; cuboidal high epithelium	60 gm.; abundant, large islands	No data	Hyperplastic endometrium; mitotic figures	Rt., carcinoma; Lt., intraductal hyperplasia, secretion	Hypertension; cataracts; duodenal ulcer; bronchial asthma; osteoarthritis; rheumatic heart disease; ca. of breast and bladder	Coronary thrombosis
27 BIH A53-139	87	F	?	Post-mortem diagnosis; amenorrhea for 53 yrs.	None	"Large"; 7mm. Amp adenoma; Amp hyperplasia in rest of gland	9 gm.; peripheral nodules, nodular hyperplasia, anisonucleosis	Severe atrophy	25 gm.; normal	7 cm. duct cell cystadenoma; abundant, very large islands suggest hyperplasia	Large oxyphil adenoma	"Infantile"	No data	Bladder calculi; arthritis; cystadenoma of pancreas	Arteriosclerotic heart disease; congestive failure

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17-ks = 17-Ketosteroids in mg. per 24 hours; normally 4-8 mg. for adult women and 12-20 mg. for adult men
PBI = Protein bound iodine

was elevated. It was normal in one (case 22) and depressed in 4 (cases 10, 12, 15, and 19).

There was decreased body hair in 6 males and one female.

Gonads

Somatic Overgrowth. The histologic features of the ovaries, known in 5 patients, were those of stromal hyperplasia twice and atrophy twice. The unduly tall non-acromegalic woman (case 8) had one ovary which was multicystic. The other ovary was seemingly functional in that it contained a degenerating corpus luteum. Menstrual irregularities were followed by amenorrhea in 3 of the 4 women who were less than 35 years of age at the onset of their disease. The fourth, the woman 185 cm. tall, had regular menses until the time of her death at the age of 40. In the remaining 3 women of the series, the disease became manifest subsequent to either a surgical or spontaneous menopause.

The male acromegalic patient (case 1) complained of decreased libido throughout his illness. At necropsy the testicular tubules were fibrosed, containing rare pyknotic Sertoli cells and no germinal epithelium. Leydig cells were absent.

Hot flashes were noted early in 2 patients (cases 2 and 6). Gonadotropin excretion was low in 2 patients when determined late in the course of the disease and disappeared entirely following estrogen therapy (cases 1 and 2).

"Chromophobe Adenomas." The ovaries were studied in 5 women with "chromophobe adenomas." There was hyperplasia of the stroma in 3 (cases 21, 22, and 24) and severe atrophy in 2 (cases 26 and 27).

Gonadal dysfunction often preceded the local manifestations of hypophyseal enlargement. In 3 of the 7 women of this group the menses ceased prematurely at ages 26 to 34 (cases 21, 22, and 27). It seems unlikely that amenorrhea was due to primary hypophyseal failure, because one of these patients (case 22) excreted normal amounts of gonadotropin after her illness had become well established. As in the somatic overgrowth group, symptoms of hypophyseal tumor appeared shortly after a spontaneous menopause in one patient (case 23) and after surgical castration in another (case 25).

Six of 9 patients in whom the testes could be studied showed bilateral hypospermatogenesis or aspermatogenesis (cases 9, 10, 16, 18, 19, and 20). In another man aspermatogenesis was confined to one testis and probably was related to previous mumps orchitis (case 11). In 2 patients mature spermatozoa were found in both testes (cases 12 and

14); Leydig cells were present in 6 men (cases 9, 11, 12, 14, 18, and 20).

Among the 12 male patients, gonadal deficiency clearly preceded symptoms of hypophyseal neoplasia in 3 (cases 10, 16, and 19). In one of these (case 19) bilateral testicular atrophy was caused by mumps orchitis; in the other 2 the etiologic factors were unknown. In 5 patients (cases 9, 10, 16, 18, and 20) functional or anatomical evidence of gonadal deficiency developed during the course of the illness but exact time relationships could not be determined. In 3 patients (cases 11, 12, and 14) normal libido was present until death. No data were available on the testicular function of patient 13. In one patient (case 10) hot flashes were an early symptom. Gonadotropin was absent in the urine of 2 patients, but determinations were done late in the course of the disease (cases 10 and 19). Gonadotropin excretion was normal in 2 men (cases 11 and 12).

Thyroid Gland

Somatic Overgrowth. At necropsy, the thyroid glands were nodular in 3 patients (cases 1, 4, and 6), fibrosed in one (case 5), and normal in 2 (cases 2 and 8).

Thyroid function varied widely; one patient (case 5) developed myxedema after acromegaly had become established, and another (case 6) developed fulminating thyrotoxicosis. Six patients appeared to be euthyroid.

"Chromophobe Adenomas." The thyroid glands were small or fibrosed in 5 patients (cases 10, 12, 16, 19, and 22). In 3 they were nodular or unusually large (cases 9, 18, and 25). In the remainder they were within normal anatomical limits.

One patient had clinical myxedema which, it is of note, preceded the manifestations of hypophyseal neoplasia (case 12). The basal metabolic rate was abnormally low in 3 other patients (cases 10, 16, and 17), but was not obtained until after sellar symptoms were manifest.

Pancreas

Somatic Overgrowth. The islands of Langerhans appeared histologically normal in all but one patient (case 8), in whom they were hyperplastic. Four of the 6 acromegalic patients whose island function was investigated had either manifest or occult diabetes (cases 2, 4, 5, and 6).

"Chromophobe Adenomas." Sections of pancreas were available from 15 patients with "chromophobe adenomas." Islands were un-

usually large or abundant in 9 (cases 9, 10, 11, 14, 20, 24, 25, 26, and 27). Four of 9 patients investigated clinically had manifest diabetes mellitus (cases 14, 16, 18, and 22). Blood sugar was normal in 5 patients (cases 10, 11, 12, 15, and 19).

Parathyroid Glands

Somatic Overgrowth. There was hyperplasia of the parathyroid glands by the anatomical criteria of Castleman and Mallory[9] in 4 of 5 patients from whom they were available, although none had clinical signs of hyperparathyroidism.

"Chromophobe Adenomas." Parathyroid glands of 8 of 19 patients with "chromophobe adenomas" were examined. Three cases showed adenoma, hyperplasia, or both (cases 20, 25, and 27). One of the 3 (case 25) had clinical hyperparathyroidism of 30 years' duration.

Endometrium

Somatic Overgrowth. The endometrium of 3 women was examined. One had a large endometrial polyp with atrophic ovaries (case 5), another had atrophic endometrium with hyperplastic ovaries (case 6), and a third had normal proliferative endometrium with one normal ovary (case 8).

"Chromophobe Adenomas." The endometrium was studied in 2 patients with "chromophobe adenomas." One (case 24) had endometrial and cervical polyps with marked stromal hyperplasia of the ovaries; the other (case 26), an 80-year-old woman, had marked glandular hyperplasia in the presence of totally atrophic ovaries.

Breast

Somatic Overgrowth. There was mammary stimulation in all of the 4 women from whom breast tissue was submitted for examination. In patient 2, a 25-year-old nulligravida, this had progressed to active lactation.

"Chromophobe Adenomas." The breasts of 6 of the 7 women with "chromophobe adenomas" showed anatomical or functional abnormalities. There was secretory activity in 3 patients past 40 years (cases 22, 23, and 25). Patient 21 was operated upon for mastopathia cystica, while patients 24 and 26 had carcinomas of the breast. The breasts of the seventh woman were not examined. Secretory activity and intraductal hyperplasia characterized the single male breast studied (case 11).

Associated Extra-Endocrine Tumors

Somatic Overgrowth. Five individuals of this series had a total of eleven extra-endocrine tumors as follows: carcinoma of the colon, acute myelogenous leukemia, polyp of the ileum, meningioma, neuroma, lipomas (2 patients), multiple skin fibromas, osteoma, hemangioma, and cholangioma.

"Chromophobe Adenomas." There were thirteen extra-endocrine tumors in seven individuals with "chromophobe adenomas," as follows: carcinoma of the colon, carcinoma of the breast (2 patients), carcinoma of the bladder, polyposis of the colon (2 patients), polyposis of the stomach, fibromas of the skin (2 patients), multiple skin papillomas, leiomyoma of the stomach, osteoma, and cystadenoma of the pancreas.

Discussion

For many years, the origin of most, if not all, of the tropic hormones has been ascribed to the "acidophils."[10,11] This hypothesis was based on the histologic appearance of the hypophysis stained with trichrome techniques. Ever since the introduction of the PAS technique, however, emphasis has shifted to the mucoprotein-containing "basophils" because of the increase of Schiff-positive elements in the hypophysis associated with increased activity.[12,13] It seems possible that both schools actually described the same cell, which is here referred to as an "amphophil" and which, as noted previously,[6] can be stained either red or blue by trichrome methods.

The hypophyseal adenomas of both the "acidophil" and "chomophobe" varieties, as here reported, are composed predominantly of amphophils. These cells have been implicated in the production of tropic hormones acting upon various target organs.[2,3,5,14] Animal experiments, as well as clinical observations in man, suggest that deficiency in an endocrine target organ may cause hypophyseal hyperplasia or neoplasia together with increased hypophyseal secretion stimulating in turn the deficient target gland or, occasionally, other endocrine organs.

Gonadal Deficiency. In some strains of mice, early gonadectomy is followed commonly by hypophyseal hyperplasia of "basophil cells resembling hypertrophic amphophils."[15] In addition, the adrenal glands and the breasts react with hyperplasia or even carcinoma. These experimental observations may parallel those of the patients of this report whose hypophyseal tumors were associated with early gonadal failure, adrenal hyperplasia, and mammary hyperplasia or carcinoma.

The increased height and acromegalic features of eunuchs are old folk observations. The concurrence of hypophyseal tumors and castrate acromegaly has been documented in the Skopecs of eastern Europe, a religious sect practicing ritual castration.[16] In canine[17] and in human[18] surgical castrates, hyperplasia of "large chromophobes" or "unripe acidophils" has been reported. Judging by the illustrations, these designations refer to cells here called "amphophils."

Thyroid Deficiency. The association of thyroid deficiency with hypophyseal enlargement in man[19] and animals[17] has been known for a long time. By destroying thyroid glands with I^{131}, hypophyseal tumors which secrete thyrotropin and, possibly, small amounts of gonadotropin have been produced in mice.[20] By the same sequence, thyroid failure may have initiated hypophyseal neoplasia in case 12 of this report.

Adrenal Deficiency. In animals, "chromophobe" hyperplasia can be induced by the agency of relative adrenal insufficiency incident to prolonged stress.[21] Enlargement of the hypophysis in association with hyperplasia and mitotic activity of amphophils has been reported in patients with Addison's disease.[2] "Chromophobe adenomas" of microscopic dimensions are exceedingly common in the hypophyses of patients dying after long illnesses,[22] presumably the result of a stressing mechanism. Although overt adrenal insufficiency was not demonstrated in any of our patients, relative hypocorticism might have operated in the pathogenesis of some hypophyseal tumors, particularly in those patients in whom no other target organ deficiency was found.

Irradiation. Hypophyseal tumors stimulating the gonads, adrenal and thyroid glands, breasts, and somatic growth have been observed following whole body irradiation in various strains of mice.[23] It is not known whether irradiation produces this effect through non-specific stress or through gonadal damage. Patient 23 of this report had received a course of spray radiation for presumed Hodgkin's disease 20 years before the onset of her hypophyseal tumor. Secretion could be expressed from her breasts. No data are available on other target organs.

Estrogens. The development of hypophyseal hyperplasia and tumors by means of estrogenic stimulation constitutes a mechanism which is not only different from the pathogenic sequence just outlined but also one which seemingly is operative only in animals. Thus in rats[24] and mice[25] prolonged estrogen treatment will result in the formation of "chromophobe adenomas." In striking contrast, the hypophyses of women given estrogens for long periods tend to be smaller than nor-

mal and the amphophil series of cells is diminished.[4] It is possible that in animals, some phenomena commonly attributed to estrogen treatment per se, such as adrenal hyperplasia,[26] Leydig cell hyperplasia and tumors,[27] and mammary carcinomas,[25,27] are in fact mediated through the amphophils.

There was predominance of amphophils both in the patients of our series with somatic overgrowth and in the patients with "chromophobe adenomas." This, together with the associated anatomical and clinical observations, suggests that the amphophils are capable of producing growth hormone, ACTH, gonadotropin, thyrotropin, and mammotropin. However, it is not implied that these hormones are all produced either simultaneously or by all tumors. The amphophils, it appears, have some direct or indirect relation to diabetes, to hyperplasia of the islands of Langerhans, and to hyperplasia of the parathyroid glands. The difference between the hypophyseal tumors of acromegalic and non-acromegalic patients seems to be quantitative rather than qualitative. It also appears that some of the symptoms of patients with "chromophobe adenomas" are due to hypophyseal hyperfunction rather than to hypophyseal hypofunction or "panhypopituitarism" as usually stated.

Summary

The hypophyses of 7 acromegalic patients, one non-acromegalic woman 185 cm. tall, and 19 patients with so-called chromophobe adenomas were studied histologically. Regardless of the presence or absence of acromegaly, the patients who had not received previous endocrine medication had hypophyseal tumors which were composed of weakly Schiff-positive amphophils rather than Schiff-negative acidophils or chromophobes. Administration of thyroid extract, sex hormones, or adrenal steroids tended to reduce cell size, to produce nuclear pyknosis, and to increase the proportion of acidophils and chromophobes. One patient with classic acromegaly had a nontumorous hypophysis of normal size in which the proportion of amphophils was increased.

Review of clinical and anatomical data with respect to other endocrine glands suggested that gonadal or thyroid failure may have preceded the appearance of the hypophyseal tumor in some patients. Adrenal hyperplasia often was found both with acromegaly and with "chromophobe adenomas." Parathyroid hyperplasia, hyperplasia of the islands of Langerhans, evidence of mammary and endometrial stimulation, and multiple extra-endocrine tumors frequently were

present in both groups of patients. Many patients in both groups had diabetes mellitus.

The hypotheses are advanced, first, that the amphophil cells may secrete growth hormone, ACTH, thyrotropin, gonadotropin, and mammotropin, although not necessarily simultaneously, and, second, that target organ deficiency may be involved in the pathogenesis of some hypophyseal tumors in man.

We are grateful to Drs. Samuel L. Gargill and Oscar Hirsch for their permission to use the clinical data of several of the cases here reported, and to Miss Theresa J. Heneghan for technical assistance.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

All illustrations except Figure 8 were made from sections stained by the periodic acid-Schiff method (PAS) and counterstained with orange G.

FIG. 1. Cell types in the hypophysis of patient 6, acromegaly with no hypophyseal tumor. Amp=sparsely granulated amphophil, HA=hypertrophic amphophil, B=basophil, Chr=chromophobe. × 900.

FIG. 2. Cell types in the hypophysis of patient 6. HyB=basophil showing Crooke's hyaline change, Ac=acidophil, Chr=chromophobe. × 900.

FIG. 3. Invasive amphophil tumor in the hypophysis of patient 3, acromegaly with no recent hormone therapy, no irradiation. There are large, pleomorphic nuclei and prominent nucleoli. × 450.

FIG. 4. High-power view of amphophil tumor, patient 3, to show fine cytoplasmic granulation, nuclear detail, and large vesicular nucleolus. × 972.

FIG. 5. Extrasellar amphophil tumor in the hypophysis of patient 4, acromegaly with no hormone therapy or irradiation. Nuclei are smaller and more uniform than in the tumor illustrated in Figure 3. × 450.

FIG. 6. Intrasellar amphophil adenoma in the hypophysis of patient 1, acromegaly with two courses of irradiation, no recent hormone therapy. Of note are nuclear pleomorphism and similarity to Figure 4 in spite of x-ray therapy. × 972.

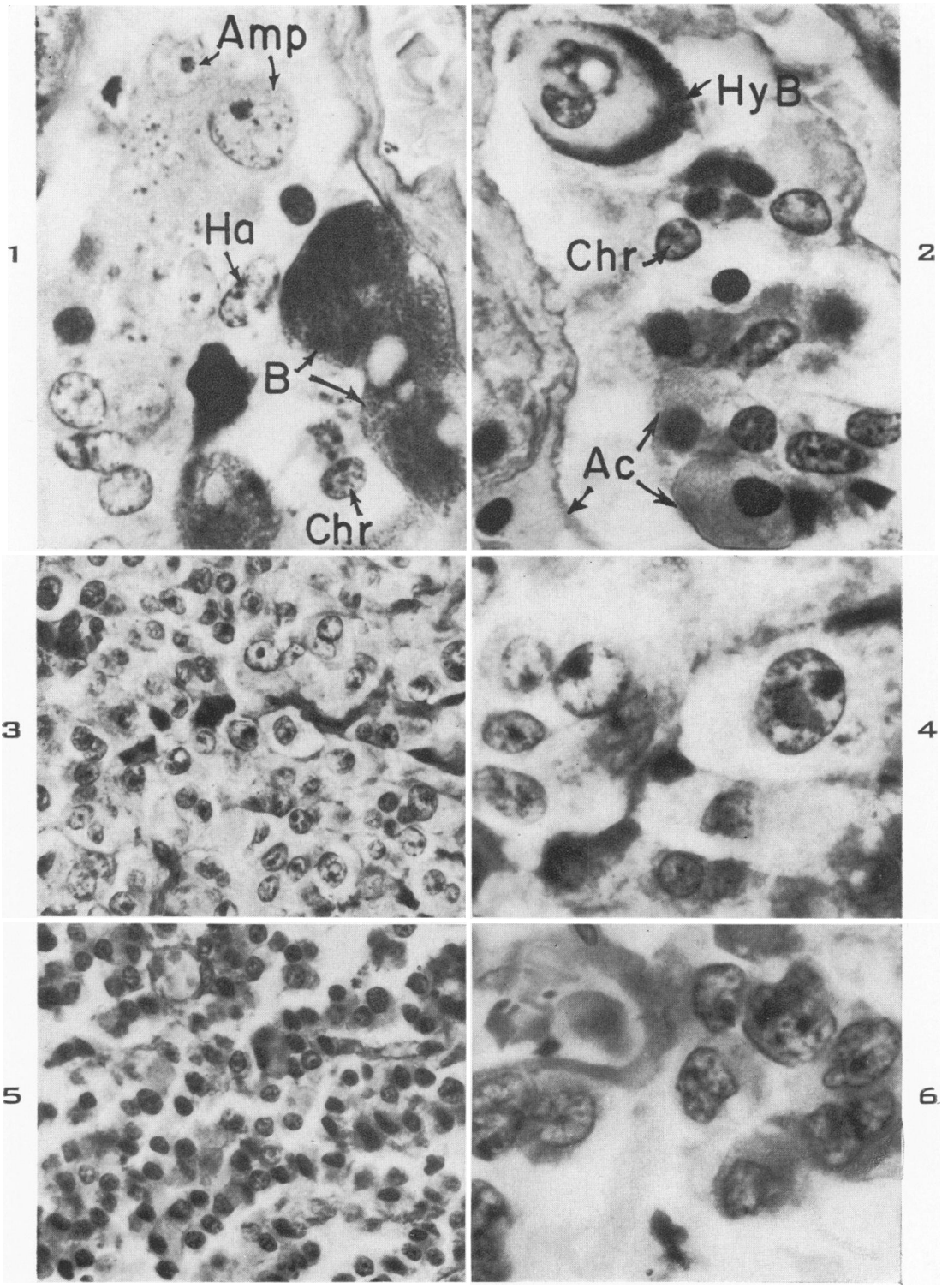

1
Amp
Ha
B
Chr
2
HyB
Chr
Ac
3
4
5
6

FIG. 7. Intrasellar acidophil adenoma in the hypophysis of patient 2, acromegaly treated with estrogens for 6 years, no irradiation. Pyknotic nuclei are small as compared with the tumors shown in Figures 3 and 5. × 450.

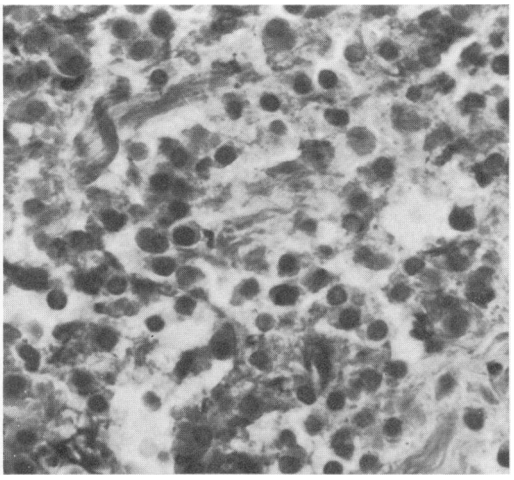
FIG. 8. High-power view of acidophil adenoma, patient 2, showing distinct cell boundaries, uniform nuclei, and over-all resemblance to mature acidophils in Figure 2. Hematoxylin and eosin stain. × 972.

FIG. 9. Hypophysis of patient 6, acromegaly without hypophyseal tumor. One course of irradiation; no therapy for 6 years. Without a differential count, this gland could be confused with a normal hypophysis. × 450.

FIG. 10. Intrasellar amphophil adenoma in the hypophysis of patient 24, with a clinical diagnosis of "chromophobe adenoma." No irradiation or hormone therapy. Cells are smaller and more uniform than those of the acromegalic patient shown in Figure 3, but larger and more variable than those of the acromegalic patient shown in Figure 5. × 450.

FIG. 11. High-power view of intrasellar amphophil adenoma of patient 11, with a clinical diagnosis of "chromophobe adenoma." No irradiation. Surgical specimen obtained before terminal hormone therapy. There is a large vesicular nucleolus similar to that found in acromegalic patient 3, Figure 4. × 972.

FIG. 12. Intrasellar chromophobe adenoma in the hypophysis of patient 23. Irradiation and cortisone therapy 3 weeks before surgical removal. Extensive nuclear pyknosis and hydropic cytoplasm may be noted. × 450.



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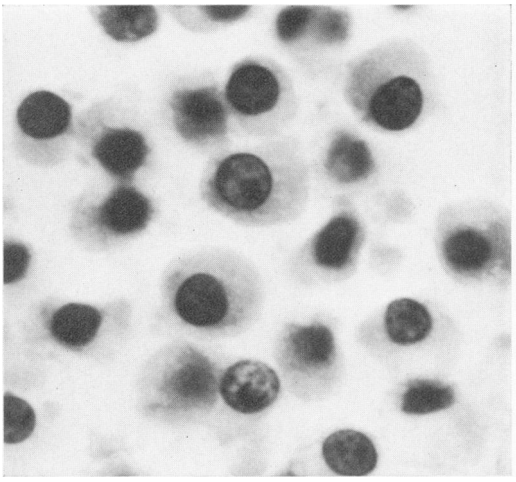

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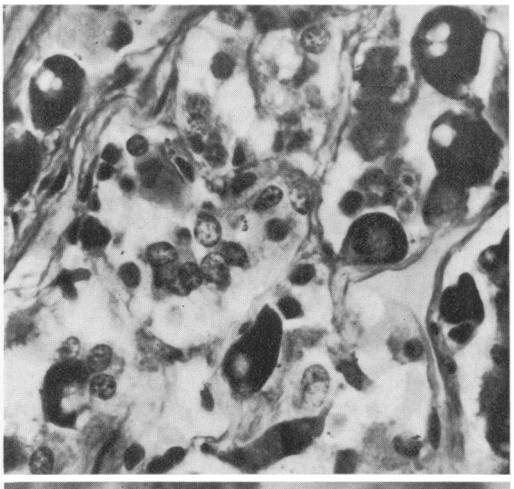

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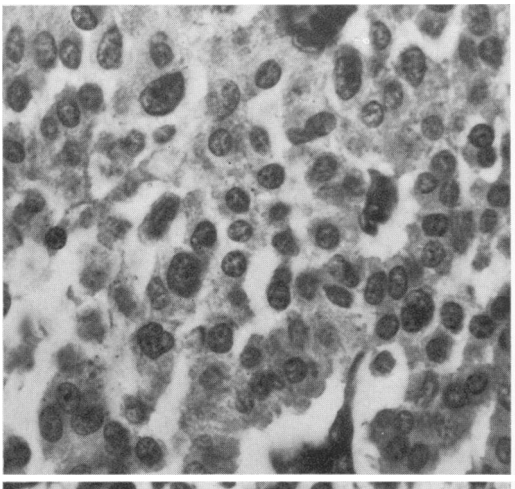

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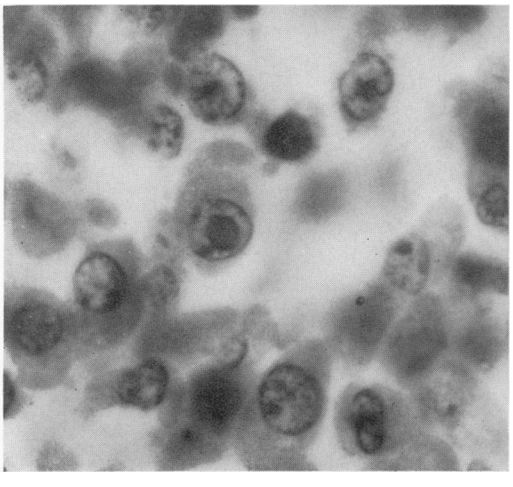

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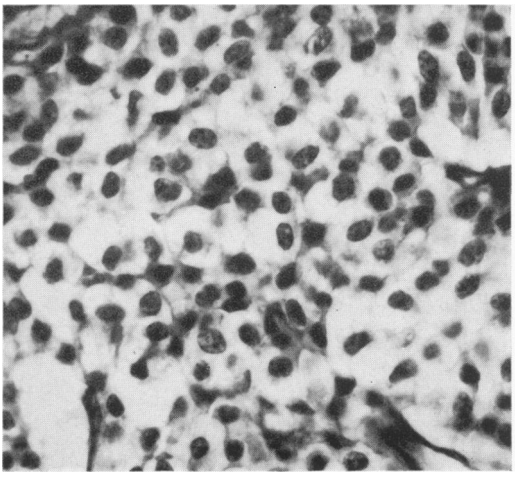

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