Adrenal Medullary Hyperplasia

A Morphometric Analysis in Patients With Familial Medullary Thyroid Carcinoma

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The syndrome of familial medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia is inherited as an autosomal dominant trait, and is characterized by development of bilateral and multicentric thyroidal and adrenal medullary tumors. One of the earliest manifestations of adrenal medullary hyperfunction in patients with this syndrome is an increased ratio of epinephrine to norepinephrine in urine. In order to define the morphologic correlates of these early catecholamine abnormalities in a large kindred with familial MTC, a morphometric analysis based on a point-counting system to assess adrenal medullary volume was undertaken. These studies clearly revealed adrenal medullary hyperplasia as reflected by a two- to three-fold increase in medullary volume and weight as compared to age- and sex-matched controls. The increase in total medullary mass resulted from diffuse and multifocal nodular proliferations of adrenal medullary cells primarily within the head and body regions of the glands. These results support the hypothesis that the pheochromocytomas in patients with familial MTC may, in fact, represent extreme degrees of nodular hyperplasia of the medulla. (Am J Pathol 83:177–196, 1976)

THE SYNDROME OF MEDULLARY THYROID CARCINOMA (MTC), pheochromocytoma, and parathyroid hyperplasia (Sipple's syndrome, Type II multiple endocrine adenomatosis) is inherited as an autosomal dominant trait.[1,2] Based on a highly sensitive radioimmunoassay for calcitonin, it has been shown that the thyroid tumors, which are frequently bilateral and multicentric, are preceeded by a clinically and pathologically evident phase of calcitonin hypersecretion and bilateral C-cell hyperplasia.[3] Interestingly, the pheochromocytomas in this syndrome are also commonly bilateral and multicentric. In a review of 59 previously reported cases of pheochromocytoma associated with MTC, bilateral tumors were found in 66% of cases, while multicentric pheochromocytomas were present in 30% of patients with unilateral adrenal medullary abnormalities.[2,4-22]

Identification of the earliest stages of adrenal medullary hyperfunction has been hampered by the absence of a screening test which is as sensitive and as reliable as the calcitonin assay for early C-cell abnormalities. The use of urinary vanillyl mandelic acid (VMA) excretion studies as the sole index of hyperfunction is unreliable, especially in patients with early disease. It has been shown, for example, that there is a faster turnover rate of catecholamines in patients with small pheochromocytomas as compared to those with larger tumors.[23,24] Consequently, patients with small tumors may have increased amounts of urinary free catecholamines with a normal or only slightly elevated VMA. Moreover, while total urinary free catecholamines may be normal in some patients with pheochromocytomas, fractionation studies may reveal abnormalities in the ratio of epinephrine (E) to norepinephrine (N). In a large kindred with familial MTC, the E:N ratio in 24-hour urine specimens has proven to be of great value in screening family members for early adrenal medullary disease, and epinephrine has been found to be the major catechol secretory product in these patients.[22]

The close surveillance of those kindred members at high risk for the development of pheochromocytomas by the use of fractionated urinary catecholamine analysis has offered a unique opportunity to characterize a spectrum of early morphologic abnormalities within the medulla. Accordingly, we reviewed in detail the pathologic findings in the adrenal glands of 10 patients from a large kindred with familial MTC. The results of morphometric analyses to estimate relative medullary volumes and weights support the hypothesis that the pheochromocytomas in this syndrome may represent extreme degrees of nodular hyperplasia of the adrenal medulla.

Materials and Methods

Estimates of relative adrenal cortical and medullary volumes were derived by standard light microscopic morphometric techniques.[25] After dissection of periadrenal adipose tissue, the adrenal glands were weighed and were fixed in 10% neutral formalin for 24 to 48 hours. Each adrenal was then serially blocked at 3-mm intervals and was embedded in paraffin in its entirety. Three representative hematoxylin and eosin–stained sections from each of 14 to 16 blocks per gland were subjected to analysis by a point counting method.[25] Selected slides were stained with the periodic acid–Schiff technique (PAS) with and without prior diastase digestion.[26] The slides were examined at a final magnification of 80 × utilizing a 144-point simple square lattice test system on the screen of a Zeiss automatic sampling stage microscope. The volume of the medulla was derived as a function of the areal density of the medulla divided by the areal density of the gland. Medullary weight was estimated from the percent medullary volume multiplied by the weight of the gland. Planar areas were derived in square millimeters by equilibrating the distance between points on the test lattice with a stage micrometer and by counting those squares whose upper left hand corners were in the profile.

Corticomedullary (C : M) ratios were obtained separately for each block of the gland. and average C : M ratios were obtained for the head and body regions.

Four glands from 3 patients in this series (Table 1. Cases 1. 2. and 3). both adrenals from a 70-year-old woman with nonfamilial MTC. and 10 adrenals obtained at surgery or autopsy from 6 sex- and age-matched control patients were subjected to morphometric analysis. The gross surgical descriptions and an average of three microscopic slides per gland were available for review in the remaining patients of the J-kindred (Table 1. Cases 4–10). Urinary VMA and catecholamine studies in these patients are also summarized in Table 1.

Results

Control Adrenals

The control adrenals in this series had a mean weight of 6.03 ± 1.26 g. with a range of 3.8 to 7.2 g. The distribution of medullary tissue is presented diagramatically in Figure 1. The abscissa in this histogram represents the section number from the head or most medial aspect of the gland (section number 1) to the tail region (section number 16). The ordinate represents sectional area in square millimeters. The black areas represent medulla while the white areas represent cortex. C : M ratios are expressed at the tops of the bars for the head. body. and tail regions.

Based on this graphic representation. it is readily apparent that all of the medullary tissue is concentrated in the head and body regions of the gland. as has been reported by Dobbie and Symington.[27] The average C : M ratios from the 10 control adrenals in the head and body were 5 and 14.7. respectively. with a combined average C : M ratio of approximately 10 : 1. The medullary regions of these control glands represented 8.1 ±2.4% of the total gland volumes. and the estimated mean control medullary weight was 0.47 ± 0.15 g gland. There were no significant

Table 1—Urinary Catecholamines and Adrenal Medullary Abnormalities in the J-Kindred

Case No.	Age	Sex	VMA*	E*	N*	E : N*	Right adrenal	Left adrenal
1 (TJ)	68	M	5.3–8.2	—	—	—	DNH	DH
2 (HJ)	65	M	8.4	60	154	0.39	S	DNH
3 (JT)	19	F	7.1	18	50	0.36	—	DNH
4 (CG)	11	F	25.4	252	486	0.52	—	S
5 (PJ)	34	M	8.4	60	111	0.53	—	M
6 (JP)	38	F	31	—	—	—	S	—
7 (WT)	27	M	11	—	—	—	—	M
8 (BD)	39	F	—	—	—	—	M	M
9 (JS)	27	F	12.8	—	—	—	S	M
10 (LG)	30	F	25	—	—	—	S	—

S = single nodule, M = multiple nodules, DNH = diffuse and nodular hyperplasia. DH = diffuse hyperplasia. VMA = vanillyl mandelic acid, E = epinephrine. N = norepinephrine.
* Normal values: in unaffected kindred members, epinephrine is less than 6 μg/24 hours. norepinephrine is less than 42 μg/24 hours. and E:N is 0.15; VMA, less than 8 mg/24 hours.

differences in the distribution or quantity of medullary tissue between males and females. The medullary cells measured 10 to 12 μ in diameter, while nuclei measured 6 to 8 μ. Occasional cellular and nuclear gigantism were observed, especially in juxtacortical areas, but mitotic figures were not observed. Very few cells contained PAS-positive, diastase-resistant cytoplasmic droplets.

Nonfamilial Medullary Thyroid Carcinoma

In 1 patient with metastatic nonfamilial MTC, medullary regions occupied 5.7 and 6% of the right and left adrenal volumes with calculated weights of 0.39 and 0.43 g, respectively. These values did not differ significantly from those obtained in the control group. Corticomedullary ratios of the gland were within normal limits. Histologic examination revealed no differences from control adrenals.

Quantitative Studies of Adrenals in the J-Kindred

Results of morphometric analysis of four adrenal glands from 3 patients in this series (Cases 1, 2, and 3) are presented in Figures 2 to 5. Corticomedullary ratios, relative medullary volumes, and estimated medullary weights are summarized in Table 2.

TJ (Case 1), a 68-year-old man with a long history of coronary heart disease, underwent total thyroidectomy for bilateral MTC in 1970. Urinary VMA concentrations between 1970 and 1974 ranged between 5.3 and 8.2 mg/24 hours. In 1974, the patient died from an acute myocardial infarct. Autopsy revealed no evidence of recurrent or metastatic MTC. The right and left adrenals weighted 4.5 and 4.3 g, respectively, and both medullary regions appeared diffusely expanded in the head and body regions. The left adrenal medulla (Figure 2A and 2B) had a relative volume of 25%, with a calculated weight of 1.07 g. The C:M ratios in the head and body were 1.7 and 5.1, respectively, with a combined ratio of 3.4. In the head of the right gland, a single ill-defined

Table 2—Quantitative Studies of the Adrenal in the J-Kindred and in Control Populations

	C:M			Relative medullary volume (percent total)	Estimated medullary weight (g)
	Head	Body	Combined		
Controls	5.2	14.7	9.9	8.1 ± 2.4	0.47 ± 0.15
Case 1 (Right)	1.8	5.7	3.7	25	1.12
Case 1 (Left)	1.7	5.1	3.4	25	1.07
Case 2	3.7	2.6	3.1	20	0.88
Case 3	1.5	7.2	4.3	31	1.6

nodule measuring approximately 3 mm in diameter was noted. The medulla represented 25% of the volume of the entire gland and had a calculated weight of 1.12 g. The C:M ratios of the head and body were 1.8 and 5.7, respectively, with a combined average ratio of 3.7 (Figure 3A and 3B).

Microscopically, diffuse expansion of both medullary regions was apparent. Individual cells exhibited a wide variation in nuclear size and shape. Nuclei measured up to 50 μ in diameter with frequent irregular hyperchromatic forms. In many areas, the cytoplasm appeared highly vacuolated (Figure 3C), while other areas were composed of cells with finely granular basophilic cytoplasm. The cells, generally polyhedral in shape, measured up to 80 μ in diameter (Figure 3D) and contained numerous round PAS-positive, diastase-resistant cytoplasmic hyaline droplets (Figure 4D). There was no compression of the medullary tissue surrounding the nodule in the right gland. Cytologic features, including giant nuclei, cytoplasmic hyaline droplets, and cytoplasmic vacuoles, were identical both within the nodule and in surrounding medullary tissue. Occasional mitoses were observed within both glands.

HJ (Case 2), a 65-year-old man, underwent total thyroidectomy for bilateral MTC in 1970. Adrenal arteriographic study in 1974 was interpreted as showing a right-sided pheochromocytoma and a suspiciously enlarged left adrenal gland. On admission to the hospital in 1974, the blood pressure was 160/100 mm Hg. During calcium infusion studies, the blood pressure rose to 240/130 mm Hg. Preoperative studies for urinary catecholamines and their metabolites were as follows: VMA, 8.4 mg/24 hours; epinephrine, 60 μg/24 hours; and norepinephrine, 154 μg/24 hours. Bilateral adrenalectomy was performed. The right gland weighed 30 g and contained a single, 3.5 cm in diameter, mass in the head of the gland. The medulla in the adjacent body appeared diffusely thickened without evidence of nodule formation. The left gland weighed 4.4 g and had a normal external configuration. On sectioning, the medulla appeared diffusely expanded and contained at least five poorly defined nodules measuring 2 to 6 mm in diameter. The medulla represented 20% of the gland volume and had a calculated weight of 0.88 g (Figure 4A and 4B). The C:M ratios in the head and body were 3.7 and 2.6, respectively, with a combined C:M ratio of 2.9.

The nodules exhibited a wide range of cytologic characteristics. In some, the predominant cells resembled neuroblasts or pheochromocytoblasts (Figure 4C) and measured 5 to 6 μ in diameter with small centrally placed hyperchromatic nuclei, scanty cytoplasm, and ill-defined cell borders. Other nodules were composed of large polyhedral cells similar to

those seen in the first case and contained PAS-positive hyaline droplets (Figure 4D). Medullary regions between zones of nodule formation appeared diffusely expanded and showed rare mitotic figures.

JT (Case 3), a 19-year-old woman, underwent total thyroidectomy in 1972 for C-cell hyperplasia. Adrenal arteriography during that year revealed questionable enlargement of both adrenal medullary regions. Urinary VMA levels were within normal limits except for one value of 11.5 mg/24 hours. In 1974 she experienced attacks of nervousness and palpitations. Repeat adrenal arteriography revealed enlargement of the left adrenal medulla. Preoperative studies for urinary catecholamines and their metabolites revealed the following data: VMA, 7.1 mg; epinephrine, 18 μg/24 hours; and norephinephrine, 50 μg/24 hours. A left-sided adrenalectomy was performed.

The left adrenal weighed 5.3 g and had a normal external configuration. The medullary regions in the head and body of the gland appeared diffusely thickened. At the junction of the head and body of the gland, a soft gray-tan nodule 1 cm in diameter was noted. A nodule 4 mm in diameter of similar consistency was present in the head. The medulla—which represented 31% of the volume of the gland, with an estimated weight of 1.6 g—extended into the tail region. The C:M ratios in the head and body were 1.5 and 7.0, respectively, with a combined C:M ratio of 4.3 (Figure 5). The larger nodule was composed of spindle-shaped cells while the smaller nodule and remaining medullary tissue were composed of polyhedral type cells (Figure 5B and 5C).

Retrospective Studies

Gross descriptions and representative microscopic sections of adrenals were available for review in the remaining patients of this series (Table 1, Cases 4–10). Five of the glands which contained multiple medullary nodules ranged in weight from 9.5 to 25 g. Individual nodules measured 0.2 to 3.5 cm in diameter and exhibited a wide range of cytologic appearances. While most of the nodules were composed of medium to large sized polyhedral cells, other nodules were composed of spindle-shaped or small neuroblast like cells similar to those noted in Case 2. Intervening medullary areas often appeared diffusely expanded and frequently exhibited giant nuclei, numerous cytoplasmic hyaline droplets, and abundant cytoplasmic vacuoles. In addition, both alae in the body of the glands frequently contained medullary tissue (Figure 6). In most cases, the nodules blended imperceptibly into the adjacent adrenal medulla without evidence of compression of the latter structure (Figure 6). Capsule formation was not observed in any case.

Five of the glands, including the right adrenal from Case 2, contained apparently single tumor nodules which measured 3.5 to 8 cm in diameter and weighed 30 to 135 g. These nodules often contained a mixture of histologic patterns similar to those seen in glands with multiple nodules. One of these apparently single tumors appeared to be formed by a coalescence of multiple smaller nodules (Figure 7). Medullary tissue adjacent to nodules appeared diffusely expanded. One of the tumors in this series contained a focus of metastatic medullary thyroid carcinoma.

Postoperative catecholamine levels both in those patients with bilateral and with unilateral adrenal medullary abnormalities in this series were within normal ranges.[22] Follow-up studies, however, will be required to determine if those patients subjected to unilateral adrenalectomy will develop contralateral adrenal medullary abnormalities.

Discussion

While the pathology of pheochromocytomas has been well described in the literature, there have been few well-documented reports of adrenal medullary hyperplasia (AMH). In man, at least part of the difficulty in identifying AMH is due to the fact that the medulla is not homogenously distributed throughout the gland and is extremely difficult to accurately dissect from the overlying cortical tissue. Virtually all of the medullary tissue in man resides in the head (medial) and body regions of the gland, while the tail (lateral) is composed exclusively of cortical tissue.[27] Random sectioning techniques, therefore, cannot be used to assess adrenal medullary pathology or to quantitate medullary volume in normal or disease states.

Review of Literature

Most of the previously reported studies of AMH in man have not employed quantitative techniques and have been based on the examination of random sections which have shown hypercellularity, nuclear and cytoplasmic pleomorphism, or increased mitotic activity (Table 3).[28-31,34,37] From a clinical standpoint, the case reported by Montalbano was most convincing since hypertension disappeared after resection of a diffusely enlarged right adrenal and biopsy of an apparently normal left gland.[30]

The presence of numerous intracytoplasmic PAS-positive hyaline droplets, together with large numbers of extensively vacuolated or granular cells, has been suggested as possible criteria for the diagnosis of AMH.[29-31] These changes are thought to reflect enhanced secretory activity. Similar findings have been noted frequently in pheochromocytomas and less

commonly in normal adrenals. Hyaline droplets, for example, may be found in almost 80% of adrenal glands obtained at autopsy but are numerous in only 3% of cases.[32]

In 1969, Neville proposed that a diagnosis of AMH should be made only when there was a significant decrease in the C:M ratio in the head and body of the gland with or without extension of the medulla into the tail.[33] These criteria were met in the case reported by Carney, but estimates of total adrenal medullary volume or weight were not available.[34]

Normal Adrenal Medulla

There are relatively few quantitative data available in the literature on the normal human adrenal medulla. In an autopsy study of 50 pairs of glands from patients who died suddenly, Quinan and Berger, after careful dissection of cortical tissue, found mean medullary weights of 0.43 and 0.44 g for the left and right adrenals, respectively.[35] The medulla in these patients accounted for approximately 10% of the total adrenal weight. These figures are in excellent agreement with our data as determined by a point-counting system. In our series, the medulla accounted for 8.1 ± 2.4% of the total adrenal volume with an average estimated weight of 0.47 ± 0.15 g. Average C:M ratios from the control adrenals in our series were 5:1 and 14.7:1 in the head and body regions, respectively, with an average C:M ratio of approximately 10:1. These data are in agreement with those obtained by Dobbie and Symington.[27,33]

Current Case Material

In contrast, relative medullary volumes of four glands subjected to morphometric analysis ranged from 20 to 31% with calculated weights ranging from 0.88 to 1.6 g, figures which dramatically exceed our and other previously reported ranges of normalcy (Table 2). Microscopically, the medullary cells exhibited a wide variation in nuclear size and shape. Both within the nodules and in adjacent medullary tissues, nuclei measured up to 50 μ in maximum dimensions with frequent irregular hyperchromatic forms. These giant nuclei were frequently, but not exclusively, located in a juxtacortical position. Similar giant nuclear forms, found commonly in pheochromocytomas and occasionally in normal medullary tissue, have been shown to have greater than 20 times the DNA content than diploid nuclei by quantitative Feulgen analysis.[36] Their presence is thought to reflect increased secretory activity rather than neoplastic transformation. The presence of occasional mitotic figures both within and adjacent to the medullary nodules of the adrenals is also

consistent with a diffuse proliferative process. In our control series of adrenals, mitotic figures were not observed in any of the cases.

The findings reported in this analysis demonstrate the importance of subjecting the adrenal medulla to thorough morphologic and morphometric analysis if early changes are to be detected and characterized. Employing a morphometric technique similar to that used in our study, Visser and Axt have convincingly demonstrated AMH in a patient with hypertension and increased urinary VMA (Table 3).[37] Future studies using similar techniques may identify other new clinicopathologic correlates and lead to a better understanding of an important, yet poorly understood, organ system—the human adrenal medulla.

Experimental Animal Models

Pheochromocytomas are common spontaneous tumors of old rats and are frequently associated with medullary thyroid carcinomas, pancreatic islet cell neoplasms, and interstitial cell tumors of the testis. Gillman *et al.* have reported that the medullary nodules in these animals were frequently multicentric and that larger tumors were formed by coalescence of smaller nodules.[38] Adrenal medullary hyperplasia has been produced experimentally in rats by the administration of a variety of agents including thiouracil, growth hormone, nicotine and estrogens.[39-41] Following the administration of nicotine in one study, adrenal medullary volume doubled, due to the appearance of multiple small nodules at the periphery of the medulla. Nicotine-treated animals revealed a marked increase in medullary noradrenaline content represented as percent of dry weight and as percent of total catecholamines. Noradrenaline content increased from 2.6 μg/gland in the controls to 12.0 μg/gland in the nicotine-treated group.[41]

Detailed cytologic studies have been performed on the adrenal medullary regions of growth hormone–treated rats.[40] In these animals, medullary cells were generally polyhedral in shape, with pale cytoplasm, and had large vesicular nuclei with prominent nucleoli. Hyperplastic nodules revealed a wide spectrum of histologic patterns and were composed of small cells with hyperchromatic nuclei, large cells with vesicular nuclei, or spindle-shaped cells. Occasional nodules displaced and focally invaded the adrenal cortex. These histologic features are remarkably similar to those noted in patients with familial MTC in our series.

Adrenal Medullary Hyperplasia and Pheochromocytoma

The stimulus for proliferation of adrenal medullary cells in patients with familial MTC remains unknown. Results of recent studies have

Table 3—Adrenal Medullary Hyperplasia: Summary of Reported Cases

Author	Age	Sex	Clinical history	Elevated urinary catechols	Description of pathologic findings
Drukker et al.[28] (1957)	57	F	Episodic hypertension	—	Marked local hypertrophy of left and right medullary regions
Bialestock[29] (1961)	5	M	Renal disease, hypertension	NS	Hypercellular medullary regions with nuclear and cytoplasmic hypertrophy and mitoses
	11	M	Renal disease, hypertension	NS	Combined adrenal weight, 8 g; hypercellular medullary regions with nuclear and cytoplasmic hypertrophy
Montalbano et al.[30] (1962)	23	F	Hypertension	+	Right adrenal weighed 8 g and had 2 to 50 times more medullary tissue than seen in a biopsy of the left gland; normotensive following surgery
Sherwin[31] (1964)	NS	NS	Three patients with hypertension	NS	Medullary expansion adjacent to pheochromocytomas; cellular and nuclear pleomorphism
Carney et al.[34] (1975)	11	F	Familial MTC	+	Combined adrenal weight 7.6 g: Combined corticomedullary ratios of left and right glands were 2.5 and 5.6, respectively; mitoses in medulla
Visser and Axt[37] (1975)	36	M	Hypertension	+	Adrenal medullary weight determined morphometrically was 2 times greater than normal; pleomorphism of medullary cells with cytoplasmic vacuoles; medulla extended into both alae

NS = not stated.

shown that both C cells and adrenal medullary cells share a common embryologic origin from the neural crest.[42] The frequent association of thyroid and adrenal medullary neoplasms in these patients, as well as their occasional association with mucosal neuromas, suggests a basic defect in the development or regulation of these neuroectodermal derivatives. In those patients with nonfamilial MTC, pheochromocytomas occur much less commonly than in those patients with familial disease.[20] It is of considerable interest, therefore, that in the 1 patient in this series with nonfamilial MTC, adrenal medullary weights were entirely within normal limits.

The results of the present study clearly demonstrate, moreover, that early biochemical abnormalities of catecholamine secretion, particularly increased epinephrine : norepinephrine ratios, are accompanied by widespread structural abnormalities of the adrenal medulla. In this regard, diffuse medullary hyperplasia may represent the earliest morphologic correlate of catecholamine hypersecretion, followed by the development of multiple medullary hyperplastic nodules (Text-figure 1). In a review of adrenal pathology associated with hypertension, Sherwin noted that continuity of tumor nodules with the adjacent medulla supported the hypothesis that pheochromocytomas represent exaggerated forms of hyperplasia,

TEXT-FIGURE 1—Histogenesis of adrenal medullary abnormalities associated with familial medullary thyroid
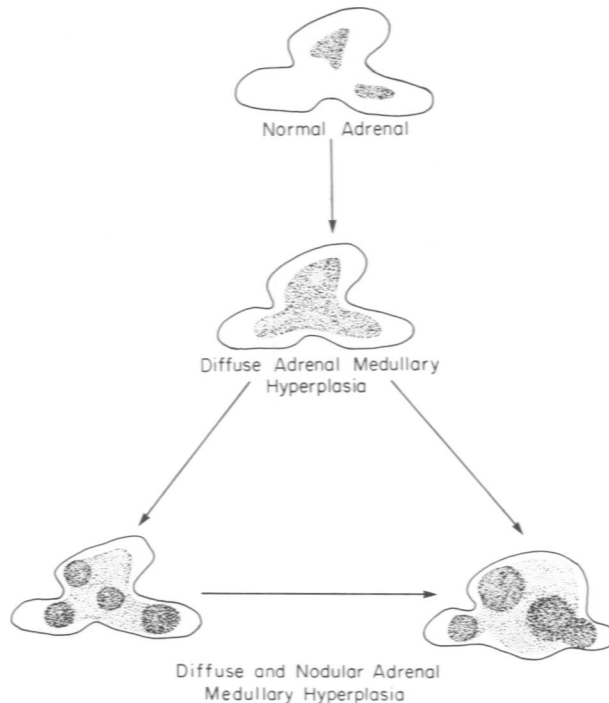
as had been originally suggested by Propst.[29] The morphometric data presented in the current report fully establishes the concept of AMH as a distinctive clinicopathologic entity. These studies further support the concept that the bilateral and multicentric pheochromocytomas in familial MTC may, in fact, represent extreme degrees of nodular hyperplasia of the adrenal medulla.

References

1. Sipple JH: The association of pheochromocytoma with carcinoma of the thyroid gland. Am J Med 31:163–166, 1961
2. Steiner AL, Goodman AD, Powers SR: Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: Multiple endocrine neoplasia, Type 2. Medicine 47:371–409, 1968
3. Wolfe HJ, Melvin KEW, Cervi-Skinner SJ, Al Saadi AA, Juliar JF, Jackson CE, Tashjian AH: C-cell hyperplasia preceding medullary thyroid carcinoma. N Engl J Med 289:437–441, 1973
4. Cushman P Jr: Familial endocrine tumors: Report of two unrelated kindred affected with pheochromocytomas, one also with multiple thyroid carcinomas. Am J Med 32:352–360, 1962
5. Finegold MJ, Haddad JR: Multiple endocrine tumors: Report of an unusual triad in a family. Arch Pathol 76:449–455, 1963
6. Manning PC, Molnar GD, Black BM, Priestly JT, Woolner LB: Pheochromocytoma, hyperparathyroidism, and thyroid carcinoma occurring coincidentally: Report of a case. N Engl J Med 268:68–72, 1963
7. Nourok DS: Familial pheochromocytoma and thyroid cancer. Ann Intern Med 60:1028–1040, 1964
8. Williams ED: A review of 17 cases of carcinoma of the thyroid and pheochromocytoma. J Clin Pathol 18:288–292, 1965
9. Sapira JD, Altman M, Vandyk K, Shapiro AP: Bilateral adrenal pheochromocytoma and medullary thyroid carcinoma. N Engl J Med 273:140–143, 1965
10. Williams ED, Pollock DJ: Multiple mucosal neuromata with endocrine tumours: A syndrome allied to von Recklinghausen's disease. J Pathol Bacteriol 91:71–80, 1966
11. Schimke RN, Hartmann WH, Prout TE, Rimoin DL: Syndrome of bilateral pheochromocytoma, medullary thyroid carcinoma, and multiple neuromas: A possible regulatory defect in the differentiation of chromaffin tissue. N Engl J Med 279:1–7, 1968
12. Gorlin RJ, Sedano HO, Vickers RA, Cervenka J: Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid: A syndrome. Cancer 22:293–299, 1968
13. Sarosi G, Doe RP: Familial occurrence of parathyroid adenomas, pheochromocytoma, and medullary carcinoma of the thyroid with amyloid stroma (Sipple's syndrome) Ann Intern Med 68:1305–1309, 1968
14. Huang S, McLeish WA: Pheochromocytoma and medullary carcinoma of thyroid. Cancer 21:302–311, 1968
15. Palovan E, Scanu A, Straus FH, Pickleman JR, Palovan D: Familial pheochromocytoma, medullary thyroid carcinoma, and parathyroid adenomas. JAMA 214:1443–1447, 1970
16. Bartlett RC, Myall RWT, Bean LR, Mandelstam P: A neuropolyendocrine syndrome: Mucosal neuromas, pheochromocytomas, and medullary thyroid carcinoma. Oral Surg 31:206–220, 1971

17. Melvin KEW, Miller HH, Tashjian AH Jr: Early diagnosis of medullary carcinoma of the thyroid gland by means of a calcitonin assay. N Engl J Med 285:1115–1120, 1971

18. Catalona WJ, Engelman K, Ketcham AS, Hammond WG: Familial medullary thyroid carcinoma, pheochromocytoma and parathyroid adenoma (Sipple's syndrome): Study of a kindred. Cancer 28:1245–1254, 1971

19. Ljungberg O: On medullary carcinoma of the thyroid. Acta Pathol Microbiol Scand [A] Suppl 231:1–57, 1972

20. Hill CS, Ibanez ML, Samaan NA, Ahearn MJ, Clark RL: Medullary (solid) carcinoma of the thyroid gland: An analysis of the M.D. Anderson Hospital experience with patients with the tumor, its special features, and its histogenesis. Medicine 52:141–171, 1973

21. Keiser HR, Beaven MA, Doppman J, Wells S Jr, Buja LM: Sipple's syndrome: medullary thyroid carcinoma, pheochromocytoma, and parathyroid disease: Studies in a large family. Ann Intern Med 78:561–579, 1973

22. Gagel RF, Melvin KEW, Tashjian AH, Miller HH, Feldman ZT, Wolfe HJ, DeLellis RA, Cervi-Skinner S, Reichlin S: Natural history of the familial medullary thyroid carcinoma—pheochromocytoma syndrome and the identification of preneoplastic stages by screening studies: A five year report. Assoc Am Phys (In press)

23. Crout JR, Sjoerdsma A: Turnover and metabolism of catecholamines in patients with pheochromocytoma. J Clin Invest 43:94–102, 1964

24. Cervi-Skinner SJ, Castleman B: Case records of the Massachusetts General Hospital (Case 35–1973). N Engl J Med 289:472–479, 1973

25. Weible ER: Stereological techniques for electron microscopy. Principles and Techniques of Electron Microscopy, Biological Applications, Vol. 3. Edited by MA Hayat. New York, Van Nostrand-Rheinhold, 1973, pp 239–296

26. Bowling MC: Histopathology Laboratory Procedures of the Pathologic Anatomy Branch of the National Cancer Institute. Washington, DC, US Government Printing Office, 1967

27. Dobbie JW, Symington T: The human adrenal gland with special reference to the vasculature. J Endocrinol 34:479–489, 1966

28. Drukker W, Formijne P, vd Schoot JB: Hyperplasia of the adrenal medulla. Br Med J 1:186–189, 1957

29. Bialestock D: Hyperplasia of the adrenal medulla in hypertension of children. Arch Dis Childh 36:465–473, 1961

30. Montalbano FP, Baronofsky ID, Ball H: Hyperplasia of the adrenal medulla: A clinical entity. JAMA 182:264–267, 1962

31. Sherwin RP: Present status of the pathology of the adrenal gland in hypertension. Am J Surg 107:136–143, 1964

32. Dekker A, Oehrle JS: Hyaline globules of the adrenal medulla of man: A product of lipid peroxidation? Arch Pathol 91:353–364, 1971

33. Neville AM: The adrenal medulla. Functional Pathology of the Human Adrenal Gland. Edited by T Symington. Baltimore, Williams and Wilkins, 1969

34. Carney JA, Sizemore GW, Tyce GM: Bilateral adrenal medullary hyperplasia in multiple endocrine neoplasia, Type 2: The precursor of bilateral pheochromocytoma. Mayo Clin Proc 50:3–10, 1975

35. Quinan C, Berger AA: Observations on human adrenals with especial reference to the relative weight of the normal medulla. Ann Intern Med 6:1180–1192, 1933

36. Lewis PD: A cytopathologic study of benign and malignant pheochromocytomas. Virchows Arch Zellpathol 9:371–376, 1971

37. Visser JW, Axt R: Bilateral adrenal medullary hyperplasia: A clinicopathological entity. J Clin Pathol 28:298–304, 1975

38. Gillman J, Gilbert C, Spence I: Pheochromocytoma in the rat: Pathogenesis and

collateral reactions and its relation to comparable tumours in man. Cancer 6:494–511, 1953

39. Marine D, Baumann EJ: Hypertrophy of the adrenal medulla of white rats in chronic thiouracil poisoning. Am J Physiol 144:69–73, 1945

40. Moon HD, Simpson ME, Li CH, Evans HM: Neoplasms in rats treated with pituitary growth hormone. II. Adrenal Glands. Cancer Res 10:364–370, 1950

41. Eranko O: Nodular hyperplasia and increase of noradrenaline content in the adrenal medulla of nicotine-treated rats. Acta Pathol Microbiol Scand 36:210–218, 1955

42. Pearse AGE: The APUD cell concept and its implications in pathology. Pathol Annu 9:27–41, 1974
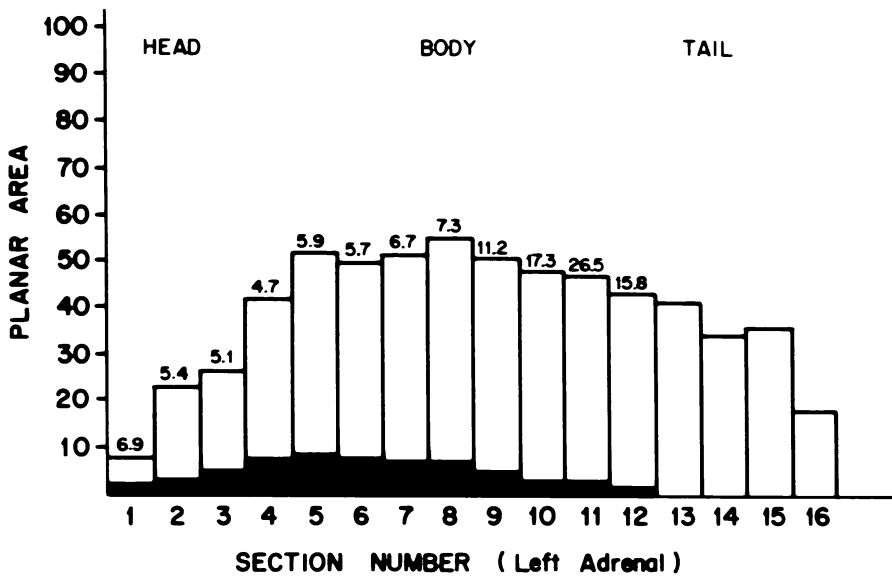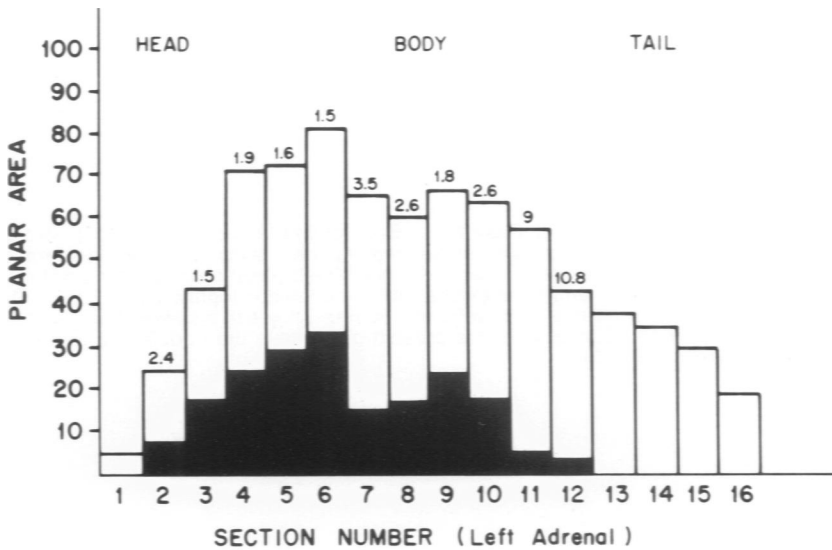
Figures 1-5—Histograms of adrenal cortical and medullary distribution in representative control adrenal and in Cases 1, 2, and 3. The x-axis represents section number from the head of the gland (*left*) to the tail region (*right*). The y-axis represents the planar area in square millimeters. (Medullary areas, *solid columns;* cortex, *open columns*). Corticomedullary ratios for each section are shown at the tops of the columns.   **Figure 1**—Histogram of control left adrenal.   **Figure 2A**—Histogram of left adrenal, Case 1.   **B**—Cross section of head of left adrenal, Case 1. There is diffuse expansion of the entire medullary region which is outlined by black dots. (× 4)

Figure 3A—Histogram of right adrenal, Case 1.   **B**—Cross section of head of right adrenal, Case 1. In addition to the diffuse expansion of the medulla, there is incipient nodule formation (*arrow*). (× 4.8)   **C**—Right adrenal, Case 1. Medullary cells in this field exhibit a mild degree of nuclear pleomorphism, and have extensively vacuolated cytoplasm. (× 250)   **D**—Right adrenal, Case 1. Two bizarre giant cells with marked nuclear pleomorphism and hyperchromasia are apparent. Similar cells are present both within the nodule and in the adjacent medullary tissue. (× 250)

HEAD   BODY   TAIL

A

SECTION NUMBER (Right Adrenal)

B

C

D
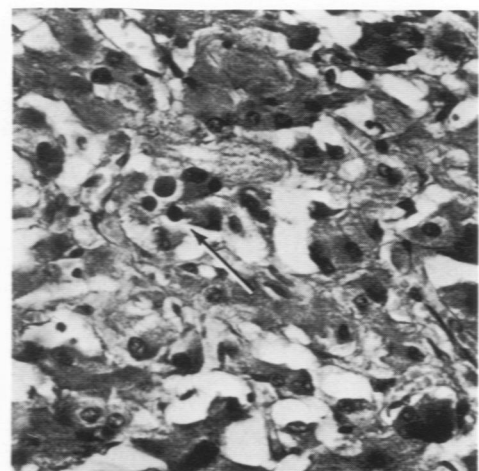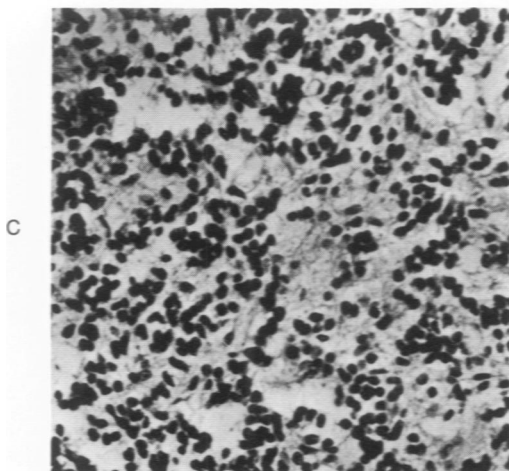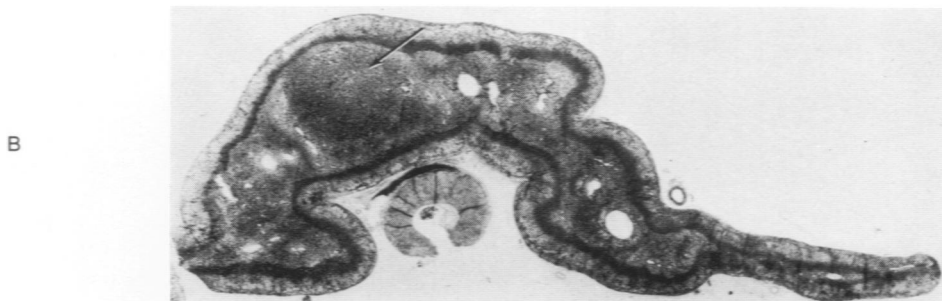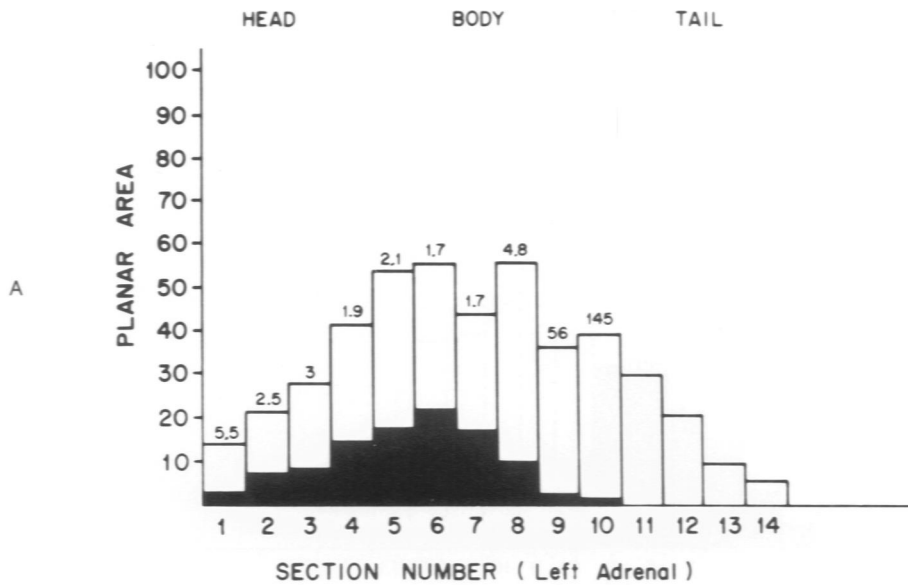
Figure 4A—Histogram of left adrenal, Case 2. **B**—Cross section of head of left adrenal, Case 2. One of the the nodules is evident in a diffusely expanded medulla. (× 4.5) **C**—Left adrenal, Case 2. The nodule in Figure 4B is composed of small pheochromocytoblast or neuroblast-like cells. (× 250) **D**—Left adrenal, Case 2. In this internodular area, medullary cells have a finely granular cytoplasm and occasional PAS-positive hyaline droplets (*arrow*). (× 250)
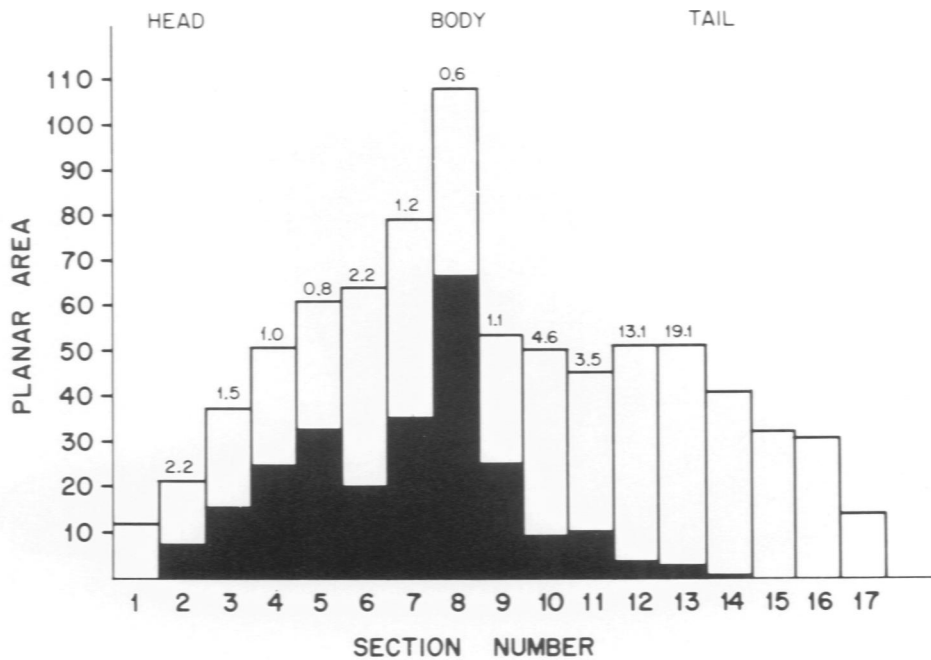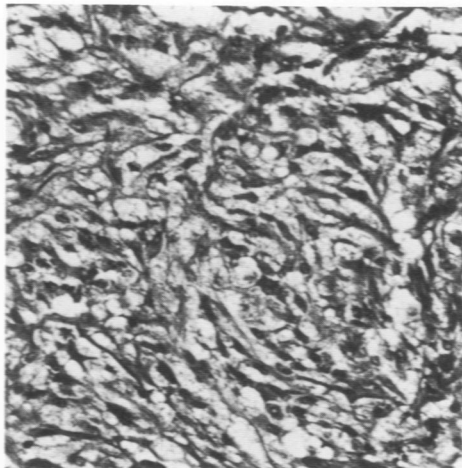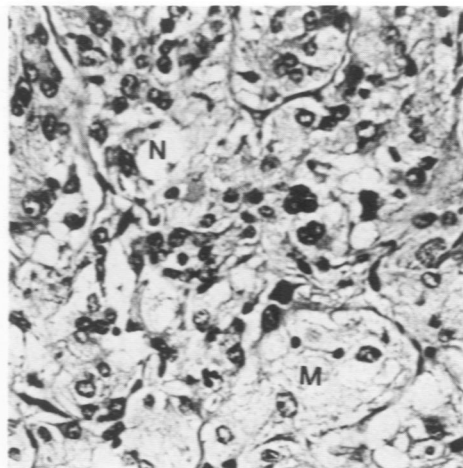
Figure 5A—Histogram of left adrenal, Case 3.   B—Left adrenal, Case 3. The larger nodule present at the junction of the head and body is composed of spindle-shaped cells. (× 250)   C—Left adrenal, Case 3. The smaller nodule (N) in the head of the gland is composed of small vacuolated medullary cells while the adjacent medulla (M) is composed of larger vacuolated cells. There is no evidence of encapsulation of the nodule or of compression of the medulla (× 250)
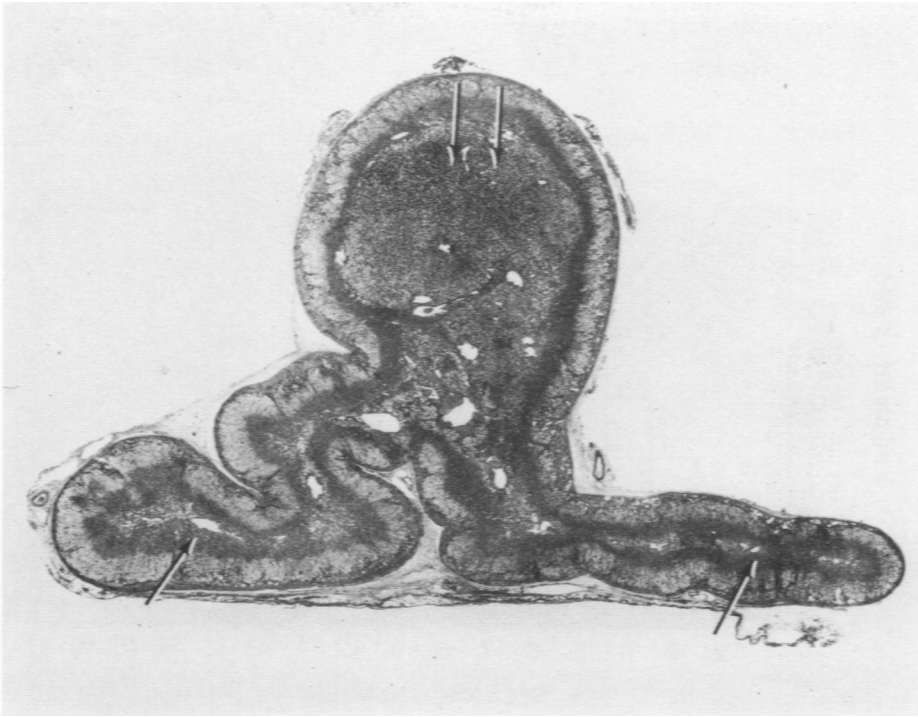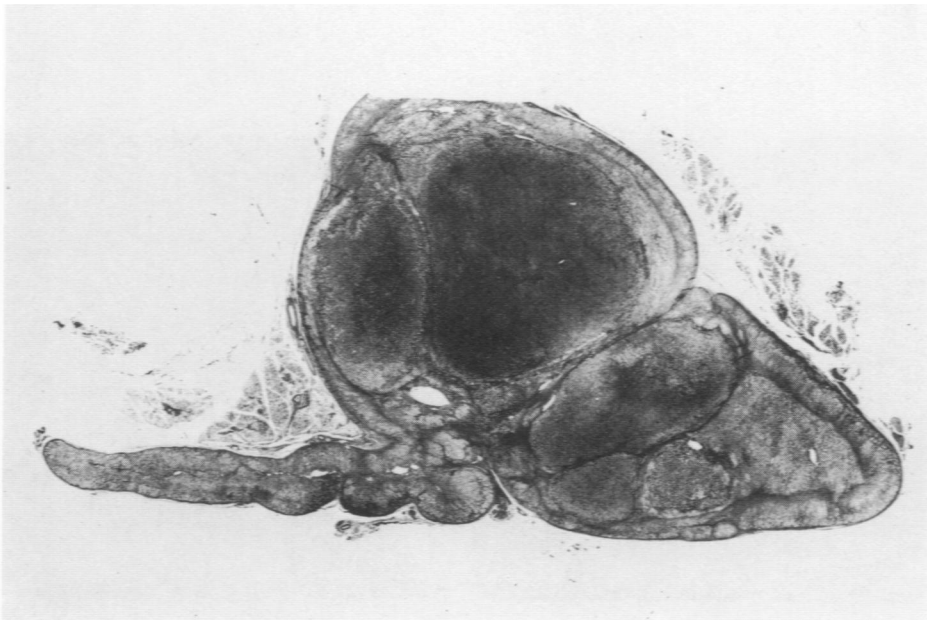
Figure 6—Left adrenal, Case 5. A nodule (*double arrows*) is present in the crest of the body of this gland. Medullary tissue extends into both alae (*single arrows*). (× 6)   Figure 7—Left adrenal, case 7. Multiple nodules are present in the crest and right alar region. A thin band of medulla is present in the left ala. (× 4.5)