PARAGANGLIOMAS

REVIEW OF SUBJECT AND REPORT OF FIVE ORIGINAL CASES *

OSBORNE A. BRINES, M.D., and ELMER R. JENNINGS, M.D.

(From the Department of Pathology, Wayne University, and Receiving Hospital, Detroit, Mich.)

Since Manasse [1] first described an undoubted case of paraganglioma of the suprarenal gland, many interesting facts have come to light regarding these rare tumors. Kohn [2] described the chromaffin system to which these tumors are related. Suzuki [3] first reported a case associated with neurofibromatosis. Labbé, Tinel, and Doumer [4] described the clinical syndrome of paroxysmal hypertension. However, most of the papers dealing with this subject have been isolated case reports with emphasis on some one phase or another. It is our primary purpose to review the literature of this subject, and on the basis of embryogenesis and histology of the paraganglion cells, to evaluate the previously reported cases and to add 5 cases not previously reported.

ORIGIN AND DISTRIBUTION OF PARAGANGLION CELLS

Hollingsworth [5] has recently reviewed the literature concerning the development of the sympathetic system. By a process of maturation and differentiation, ganglion cells of the sympathetic system, paraganglion cells, and the sheath cells (Schwann or neurilemma cells) are derived from the cells of the neural crest. The cells destined to become paraganglion cells migrate to the dorsal surface of the sympathetic ganglia to form small, rounded masses in depressions of these ganglia. Because of this close association, the term *paraganglion* has been applied. Similar masses occur in the sympathetic plexuses, the best known of which are the organs of Zuckerkandl which develop along the aorta near the root of the inferior mesenteric artery. Similar collections of these cells have been described in the liver, testes, kidneys, and heart. The paraganglion cells which form the suprarenal medulla are derived from the celiac plexus; in embryos of 7 weeks, masses of these cells grow into the cortical primordium (from mesoderm) and gain a central position.

Several other tissues have been included in the paraganglionic or chromaffin system, prominent among which are the carotid body, the argentaffin cells of the appendix and intestines, and the coccygeal body. The most dispute has concerned the carotid body. Kohn,[2] studying man and the pig, thought the carotid bodies belonged to the paraganglionic system. He stated that the cells of these tissues are chromaffin cells; that brown granules appear with the use of chromate solutions.

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It is true that the carotid body of pigs contains chromaffin cells, but other workers [6] do not agree that human carotid bodies have chromaffin cells. The carotid body arises from the mesenchyme of the wall of the third branchial cleft and is closely related to the development of a branch of the glossopharyngeal nerve; thus, its origin is different from that of the paraganglion cells. Smith [6] has shown that its connections with the cervical sympathetic nerves are made late in the development of the embryo. She stated that chromaffin cells are not constant in the carotid body of man or the rat, but can be regularly demonstrated in those of the pig and cow. Furthermore, neither epinephrine nor any related vasopressor substance has been demonstrated in the carotid body or tumors derived therefrom. Boyd,[7] in a recent review of the subject, definitely rejected the idea that the carotid body be included in the paraganglionic system. Because of the inconstancy of the presence of chromaffin cells, because epinephrine has never been demonstrated and, most important of all, because of the difference in embryologic development, we will not consider tumors derived from the carotid body as paragangliomas.

There has been less dispute concerning the inclusion of the argentaffin tumors of the appendix and intestine with paragangliomas. Masson,[8] after studying 50 cases of carcinoid of the appendix, confirmed Huebschmann's [9] suggestion that argentaffin cells are chromophilic, but pointed out several reasons why these tumors should not be catalogued with the paragangliomas. First, the argentaffin cells are not derived from the neural crest, but are of entodermal origin. Masson wrote: "All the argentaffin cells enclosed in the nerves result from intranervous budding from the glands of Lieberkühn. The budding epithelia then separate from their gland matrix, migrate into the nerves of the mucosa and differentiate." Further, the argentaffin cells often contain lipoid substances and these are not seen in paraganglion cells. De Castro[10] has shown that the chromaffin reaction sometimes obtained in the carotid body does not depend upon the presence of epinephrine as the reducing substance, but rather on the action of the lipoids contained in these cells. The same might apply to the lipoids of argentaffin cells and the positive chromaffin reaction.

Lewis and Geschickter [11] included argentaffin tumors in their series of paragangliomas, but Geschickter now considers their exact origin to be less certain. For the reasons stated by Masson,[8] in addition to the fact that no epinephrine or similar substance has ever been demonstrated in these tumors, we prefer not to include argentaffin tumors with paragangliomas.

Some early writers have compared the coccygeal body with the

carotid body and so have included it in the paraganglionic system. Because it has nothing in common embryologically with paraganglion cells, we shall not consider it here.

CHROMAFFIN REACTIONS

Bennett,[12] in describing the suprarenal medulla of the cat, presented an excellent survey of the history and the significance of the chromaffin reaction. Henle [13] reported that a dark brown color appeared in the suprarenal medullary cells if they had been subjected to the action of chromic acid or potassium dichromate. Following the identification and synthesis of epinephrine shortly after 1900, it became known that the hormone could be easily oxidized and that the oxidized epinephrine was brown. Hartman and Blatz [14] used the chromaffin reaction to indicate the presence of epinephrine in the suprarenal medulla. Ogata and Ogata [15] thought that the brown color was caused by a precipitate formed by the interaction of epinephrine and chromium compounds. For the following decade the chromaffin reaction was used to indicate the amount of epinephrine in the tissues. In 1930 Gerard, Cordier, and Lison [16] showed clearly that the brown color could be produced by mixing epinephrine with strong oxidizing agents other than chromium compounds. This reaction, then, was not really a demonstration of chromaffinity, but a nonspecific reaction between epinephrine (and related compounds) and strong oxidizing reagents such as solutions of potassium iodate. The term chromaffin reaction is apparently a misnomer since the reaction depends on an oxidation reaction and not on chromium affinity. Organic substances which form these complex compounds with oxidizing agents include epinephrine, hydroquinone, resorcinol, aniline, polyphenols, and many others.

Bennett [12] stated that some of these compounds must be present in all tissues of the body and must account for the light brown color seen in all tissues fixed in dichromate. The much darker color of the suprarenal medulla and paraganglia merely indicates a greater concentration of these fuscogenic substances.

Because the chromaffin test is nonspecific, one should not classify a tumor as a paraganglioma simply because of the presence or absence of a positive reaction. Of greater importance are its origin from cells which have been derived from the neural crest and the presence in it of cells capable of secreting a pressor substance. In a practical sense, then, when one is attempting to classify a tumor suspected of being a paraganglioma he should consider the site of origin and the histologic resemblance to paraganglion cells of the suprarenal medulla. The histologic appearance may vary greatly and may be of little help in

classifying and identifying these tumors. We shall consider as being typical paragangliomas only those tumors which arise in the suprarenal medulla, or in association with the sympathetic ganglia, or in the sympathetic plexuses. The discussion will thus be limited and the statistics presented will be at variance with those by authors who have employed the term in a less restricted fashion.

Report of Cases

Case 1

A Negro housewife, 43 years of age, was first admitted to the Detroit Receiving Hospital on December 31, 1945, because of vaginal bleeding and weakness of 5 days' duration. The positive physical findings included pale mucous membranes, soft cervix with patulent os, and a large nodular uterus. Serologic tests for syphilis were negative and the hemoglobin value was 7.0 gm. per 100 cc. of blood. The clinical impression was complete abortion, multiple leiomyomas of the uterus, and secondary anemia. Treatment consisted of pituitary preparations and multiple blood transfusions. She responded well and was discharged on January 11, 1946, to return to the out-patient department. The blood pressure was not elevated. She was readmitted to the hospital on May 30 in order that definitive treatment for the uterine tumors could be carried out. At this time the blood pressure was 110/70 mm. Hg. The remaining physical findings suggested only multiple leiomyomas of the uterus and secondary anemia. On June 5 supracervical hysterectomy and appendectomy were performed without incident through a midline incision. While exploring the abdomen a retroperitoneal tumor was palpated slightly to the right of the midline and at the level of the third lumbar vertebra. This mass was black, moderately firm, and measured about 6 cm. in maximum diameter. The peritoneum was incised and the mass was found to be attached by a small pedicle to the retroperitoneal tissue. The exact relation to the abdominal aorta was not determined. The postoperative course was uneventful and the patient was discharged on June 17 to the out-patient department. In the succeeding 5 months she was followed at regular intervals and her progress was very satisfactory.

The specimen consisted of a thinly encapsulated, firm neoplasm weighing 30 gm. and measuring 5 by 3 by 2.5 cm. The formalin in which the tumor was immersed was colored brown. Approximately 90 per cent of the tumor was blue-black, there being a small, light-pink area at one end. The demarcation between the pigmented and non-pigmented portions was abrupt. Numerous slit-like cavities were seen in the pigmented portion. The tumor was composed of irregular polygonal cells arranged in solid groups, which were separated one from another by a delicate connective tissue stroma and thin-walled capillaries. In sections prepared from the pigmented areas the neoplastic cells contained a granular pigment, which on low-power examination appeared black and with higher magnification appeared brown-black. Sections from the light areas were almost devoid of pigment. The capillaries, stroma, and alveolar pattern were more prominent in the pigmented areas. The Prussian blue reaction for the presence of

iron was negative. Dopa and chromaffin tests were not done on the fresh material. Staining with the Mallory-Heidenhain technic, as recommended by Gomori,[17] gave negative results. This is an azocarmine stain with which substances related to epinephrine appear as violet granules in the cytoplasm of chromaffin cells. The pigment was darkened by aqueous silver nitrate and bleached with hydrogen peroxide.

Anatomic Diagnoses. Paraganglioma, benign, retroperitoneal.

Case 2

The patient was a Negro male, 34 years old, who was admitted to Detroit Receiving Hospital because of headaches of several months' duration associated with dizzy spells, nausea, and vomiting. He stated that he had innumerable tumors over his entire body since childhood. His blood pressure was 180/140 mm. Hg. The remainder of the physical examination was negative except for the cutaneous nodules and hypertensive retinopathy. Routine laboratory studies revealed little of note. A calcific mass, apparently within the left kidney, and a similar mass in the right upper abdominal quadrant were demonstrated radiographically. The patient was discharged and re-admitted 7 months later. It was then that the diagnosis of paraganglioma was suspected, for it was learned that laughing or change in his position would precipitate an attack of the previously described symptoms. Confirmatory tests were done, including perirenal insufflation for roentgenographic study. His attacks continued and he died, apparently in shock, before surgical treatment for his disease could be performed.

Multiple, discrete, cutaneous tumors varying from 1 mm. to 4 cm. in average diameter were distributed universally. There was an equinovarus deformity of the left foot. Examination of the contents of the cranial cavity revealed mild fibrosis of the leptomeninges. In the right cerebral hemisphere there was an elongated softening of the white matter. There was also a small hemorrhage in the pineal body. The heart weighed 425 gm. with a ventricular ratio of 3.0 (normal, 1.6 to 2.0). The peritoneal cavity contained 500 cc. of clotted and unclotted, recently shed blood. Beneath the right leaf of the diaphragm there was a hematoma, partially organized, measuring 8 cm. in maximum dimension. Within the spleen there was a subcapsular hematoma 4.5 cm. in diameter. In the walls of the esophagus, stomach, duodenum, small intestine, and large intestine were numerous firm, yellow-white tumors varying in size from 2 mm. to 2 cm. In the medial pole of the right suprarenal gland there was an encapsulated, spherical tumor, 3.5 cm. in diameter, which was reddish brown and hemorrhagic, and weighed 19 gm.; the uninvolved portion of the suprarenal gland weighed 5 gm. The opposite suprarenal body was diffusely enlarged, measuring 7 by 3 by 1 cm. and weighing 16 gm. Serial sections revealed no nodular lesion. Between this suprarenal body and the

superior pole of the kidney there was an area of recent hemorrhage measuring 4 cm. in maximum dimension.

In the brain there were atherosclerosis, arteriolar sclerosis, and thrombosis associated with multiple areas of softening and glial proliferation. The subcutaneous tumors and those throughout the gastro-intestinal tract were composed of encapsulated masses of interlacing bundles of fibrillar connective tissue with elongated nuclei, and no definite nerve bundles were seen in the sections examined. The lungs showed diffuse pulmonary edema, purulent bronchitis, passive congestion, and confluent lobular pneumonia. Nothing remarkable was noted in the sections prepared from the gastro-intestinal tract save for the previously described neurofibromas. In the kidneys, definite arteriolar sclerosis was seen which was indistinguishable from that frequently associated with essential hypertension. In addition a recent intracapsular hemorrhage was noted.

The suprarenal tumor was composed of polygonal cells measuring about 35 μ in maximum dimension which contained large vesicular nuclei with one prominent nucleolus per cell. The cytoplasm contained very fine, densely packed granules which were stained purple with hematoxylin and very closely resembled those of the secretory cells of the normal suprarenal medulla. These cells were arranged in cords and nests which were surrounded by a delicate connective tissue stroma. The tumor was highly vascular, containing many thin-walled capillaries and sinusoidal spaces, often markedly dilated. Some of the tumor cells were smaller (15 μ), more pink, and had dense nuclei without nucleoli. A portion of the tumor was placed in Orth's solution in order to demonstrate possible chromaffinity of the cells. When stained with Schmorl's technic [18] the nuclei appeared deep blue-green while the cytoplasm of the tumor cells contained numerous, very fine, yellowish green granules. Confirmation of this positive chromaffin reaction was obtained by staining formalin-fixed tissue with Heidenhain's azocarmine according to Gomori's suggestion.[17] With this technic, the granules were violet, corresponding to the granules of the suprarenal medulla which was used as a control. An interesting incidental feature was that the nucleoli of the tumor cells stained brilliant red.

Anatomic Diagnoses. Paraganglioma, benign, right suprarenal gland; neurofibromatosis, skin and gastro-intestinal tract; heart disease, hypertensive, with left ventricular hypertrophy; pneumonia, lobular, bilateral; hemoperitoneum; hematoma, subcapsular, spleen, kidney; arteriolar sclerosis, generalized; encephalomalacia; talipes equinovarus, left; kyphoscoliosis, thoracolumbar spine.

Case 3

The patient was a Negro male, 33 years of age, who was admitted to the Medical Service of the Detroit Receiving Hospital with a chief complaint of constipation, gas on the stomach, nausea, vomiting, and hiccoughs of 3 days' duration. He had had epigastric pain, relieved by soda and milk, for 10 years. The vomitus had been bloody on two occasions during the week prior to admission. He had had malaria as a boy and there was an indefinite history of syphilitic chancre 11 years before admission. Physical examination revealed slight icterus, decreased expansion of the right chest, and flatness. There was no cardiac hypertrophy; the abdomen displayed only slight tenderness, some distention, and spasticity of the rectus muscle on the right side. No abdominal masses were palpated. Results of routine examination of the blood and urine were normal. The working diagnosis was cholecystitis with cholelithiasis, and the patient was treated conservatively. During hospitalization, he became progressively worse and expired 5 days after admission.

The principal positive findings at necropsy were in the abdominal cavity. Generalized peritonitis had resulted from perforation of two ulcers of the duodenum and stomach. In the left suprarenal gland there was a neoplastic nodule measuring 2.5 cm. in diameter, confined to the gland. The remaining viscera appeared normal.

The neoplasm was composed of cells which varied greatly in size from 10 to 30 μ and were arranged in poorly formed cords and nests. The cells were roughly elliptical in most areas, but spherical in others. The cell boundaries were indistinct. The nuclei of the tumor cells, for the most part, contained moderately dense, diffusely distributed chromatin. However, the nuclei varied greatly in size and shape and contained no nucleoli. Some of the cells with indistinct outlines appeared to be giant cells and contained from two to five nuclei. The cytoplasm of the tumor cells was abundant and contained many fine, densely packed, violet-staining granules. Some of the tumor cells had undergone hydropic change. The stroma of the tumor, for the most part, was delicate, fibrous, and sparse. However, in some areas there was a very dense fibrous stroma. There were many dilated, thin-walled capillaries throughout the tumor. There was a moderate amount of necrosis and hemorrhage. At one edge of the section a rim of compressed suprarenal cortical tissue was seen.

Anatomic Diagnoses. Ulcers, duodenal and gastric, with perforation, generalized peritonitis, and abscess formation; paraganglioma, benign, left suprarenal gland.

Case 4

A white female, 21 years old, was first admitted to the Detroit Receiving Hospital on December 6, 1937. She had known that she had high blood pressure for 6 years prior to admission. This hypertension had been discovered in 1931 as part of a general physical examination because of symptoms of nervousness, palpitation, and headache. During the succeeding years the symptoms became progressively worse

and were accompanied by nervousness and irritability. In 1934 a partial thyroidectomy was performed at another hospital, at which time there was moderate elevation of the basal metabolic rate. Following this operation her symptoms were somewhat relieved but later returned, and in 1937 she was hospitalized for a "nervous breakdown." At this time her basal metabolic rate was plus 72 and another thyroid operation was performed. She felt better for a short time, but her symptoms returned and she became progressively worse. At the time of admission to the Detroit Receiving Hospital she was complaining of palpitation, headache, flushed face, and nervousness. Physical examination revealed only minimal changes of the vessels in the optic fundus. A remnant of the thyroid gland was palpable. The heart was moderately enlarged to the left with a systolic blowing murmur over the precordium and an accentuated aortic second sound. Blood pressure at the time of admission was 194/132 mm. Hg. Repeated determinations of the blood pressure revealed that the systolic pressure varied from 150 to 240 and the diastolic from 100 to 150. Routine studies of the blood and urine were normal. The Kline test was negative. The basal metabolic rate was plus 16. Blood cholesterol was 192 mg. per 100 cc. of plasma. An electrocardiogram indicated sinus tachycardia with no definite evidence of myocardial involvement. An excretory urogram revealed a slight outward displacement of the right kidney, and in the position of the left suprarenal gland a definite area of calcification was evident. While on the ward her condition remained unchanged. Marked variations in blood pressure determinations were noted. On January 18, 1938, an exploratory operation of the left suprarenal area was performed and a retroperitoneal tumor was found, situated superiorly and mesially to the upper pole of the left kidney and extending posteriorly along the spinal column at approximately the level of the 12th thoracic vertebra. The anterior surface was covered by a complicated mass of veins of considerable size, some being 2 mm. in diameter. Intravenous fluids, including whole blood, were administered. The blood pressure fluctuated greatly; at one time the systolic pressure was 290 and a reading was unobtainable at another time. All of the tumor was removed except the extreme posterior portion lateral to the spine. At this point in the operation the patient stopped breathing, and quantities of rust-colored, frothy fluid exuded from the nostrils and throat. Despite supportive measures, she expired. Permission for necropsy was not granted.

The specimen was submitted in several pieces, having an aggregate weight of 20 gm. They were irregular, dark brown, and soft. The formalin in which the tissue had been immersed for 24 hours was discolored brown. The tumor cells were large, irregular, and contained hyperchromatic nuclei with abundant deep-staining cytoplasm. Many of the cells were vacuolated. There was a considerable variation in nuclear size and staining intensity. A few mitotic figures were seen. Some of the cells were multinucleated, containing two to four nuclei. Thick and thin-walled veins were present throughout the tumor. There was an incomplete, thick, fibrous capsule. A portion of the tumor was stained with Giemsa's stain and no olive-green granules were seen. This, then, would be a negative chromaffin reaction with the Schmorl method.[18] However, when the tissue was stained with azocarmine, there was a definite positive reaction, the cytoplasm of the tumor cells

containing gray-blue, coarse granules. The nuclei were red except the large vesicular ones which had prominent red nucleoli.

Anatomic Diagnosis. Paraganglioma, benign, retroperitoneal.

Case 5 *

The patient was a white woman, 50 years of age, who had suffered from dyspepsia for many years. During the past 2 years she developed a chronic, persistent hypertension with blood pressure of approximately 160/90 mm. Hg. There was a gradual onset of exertional dyspnea and ankle edema which were relieved by the administration of digitalis. Four days prior to hospitalization she was seized by an attack of nausea, vomiting, and severe pain in the right upper quadrant. At the time of admission to Woman's Hospital her temperature was 100.2°F.; pulse rate, 90 per minute; and blood pressure, 190/110 mm. Hg. There was tenderness on the right side of the abdomen associated with a poorly defined mass. The results of hematologic and urine studies were within normal limits. On November 21, 1936, 6 days after admission, a cholecystectomy was done. During the operation, the blood pressure fluctuated widely. The gallbladder was thickened and contained two large stones and a large amount of thick purulent material. Her postoperative course was satisfactory during the first 3 days. She then became apprehensive, nauseated, and vomited several times. Temperature, pulse rate, and respirations increased and she became comatose. She died 9 hours after the onset of these symptoms.

There was a fairly well developed growth of hair on the upper lip and chin, but no other signs of masculinization. The heart weighed 300 gm., but was otherwise normal. There was hemorrhagic edema of the lungs. The right suprarenal gland was diffusely enlarged and weighed 25 gm. The left suprarenal gland was replaced by a firm, encapsulated tumor which weighed 600 gm. and measured 11 by 10 by 8 cm. It was easily removed from the surrounding structures. On cut section, it was seen to be highly vascular, soft, and white in some areas and pink in others. The epinephrine content was ascertained according to the method of Folin, Cannon, and Denis [19] and it was found that 10.2 gm. of the tumor contained 24.6 mg. of epinephrine. This would indicate that the entire tumor contained about 1400 mg. of epinephrine.

In the sections prepared from paraffin-embedded tissue and stained with hematoxylin and eosin, the tumor cells were seen to be polyhedral with indistinct cell boundaries. The average size of the cell was 35 μ. The nuclei in most cases were large, vesicular, and nearly all of them had prominent nucleoli. Some cells appeared to be binucleated. The cytoplasm contained fine, violet-staining granules. The cells were arranged in cords and nests and were separated from one another by delicate connective tissue stroma with a rich capillary network. Some

* Reported with the permission of Drs. Earl G. Krug and D. C. Beaver.

of the capillaries were distended and contained very many white blood cells. There was a remarkable resemblance between the microscopic pattern of the tumor and the normal suprarenal medulla. There was no necrosis or hemorrhage. The capsule was incomplete. Many thin- and thick-walled veins were present. A portion of the tumor was fixed in a chromate solution and sections examined from this material revealed brown granules in the cytoplasm of the neoplastic cells.

Anatomic Diagnoses. Paraganglioma, benign, left suprarenal gland; hypertrophy, myocardial, mild; edema, hemorrhagic, lungs; gallbladder, absence of, acquired.

Review of the Literature

The three terms commonly used in the literature by which these tumors are designated are paraganglioma, pheochromocytoma, and chromaffinoma. For reasons previously stated, chromaffinoma seems objectionable. Pick,[20] in 1912, suggested that the term pheochromocytoma (tumor of dark-colored cells) be used for those tumors arising in the suprarenal medulla and that the extra-suprarenal tumors be called paragangliomas. Some authors have followed his suggestion, but since this separation is arbitrary and does not reflect a fundamental distinction, we prefer to designate all of these tumors as paragangliomas. This term seems most acceptable since it refers to the cells from which these tumors are derived.

Many excellent reviews of the literature have appeared during the past 15 years. Belt and Powell[21] collected all of the cases reported up to 1934. In 1941 Biskind, Meyer, and Beadner[22] contributed a compilation of the cases treated surgically which had been reported prior to that time. Rosenthal and Willis[23] reviewed all of the cases of paraganglioma associated with neurofibromatosis. Green[24] studied the incidence of chronic hypertension and analyzed 50 reported cases. McGavack, Benjamin, Speer, and Klotz[25] analyzed the reports of malignant paraganglioma. Mackeith,[26] in his article submitted for publication in May, 1943, stated that 165 of these tumors had been described. Since that time approximately 40 more cases have been added. The 5 cases described in this paper bring the total number of reported cases to about 210.

These tumors occur with equal frequency in the male and the female, chiefly during young adult life, and usually between the ages of 20 and 50 years. However, the age variability is great: one of Fingerland's[27] cases was that of a 71-year-old male, and Soffer, Mencher, and Colp[28] reported an active tumor occurring in a 7-year-old girl. The few reports of cases occurring in infants and very young children are

all highly atypical. The 1-year-old infant described by Neff, Tice, Walker, and Okerblad [29] displayed hirsutism, precocious development of the genital organs, and obesity. The tumor which occurred in the mediastinum of a 4-year-old boy, reported by Wahl and Robinson,[30] contained neuroblastic elements with widespread metastases and thus does not belong in the category of paragangliomas.

About 90 per cent of these neoplasms have occurred in the suprarenal glands and there is a slight, but definite, predilection for the right gland. All of the extra-suprarenal tumors have occurred in the abdominal cavity or retroperitoneal area except two. One of the two acceptable intrathoracic paragangliomas was reported by Philips [31] from the apex of the pleural cavity, apparently arising from the first left thoracic ganglion. The second was reported by Miller [32] as occurring in a paravertebral position in the right pleural cavity opposite the 6th interspace. Of those described as extra-suprarenal but intra-abdominal, 10 have occurred in the organ of Zuckerkandl, 3 in the retroperitoneal area (including our first case), one at the hilus of a kidney, and one at the celiac ganglion. Many others have been reported in the carotid body, the appendix, and the sacrococcygeal body, but these tumors are not included in this review. Waaler [33] has collected all of the extra-suprarenal paragangliomas reported up to 1945.

These tumors are multiple in about 10 per cent of the cases. In 18 reported cases they have occurred simultaneously in both suprarenal glands. The importance of this fact is emphasized in the report of Knake [34] in which is described an 11-year-old boy who had one suprarenal tumor removed but died 5 weeks later. A similar benign tumor was found in the opposite suprarenal gland at necropsy. In addition to those with bilateral tumors, other reports describe apparently benign but multiple tumors. One of Fingerland's [27] cases had a tumor of the right suprarenal gland and the organ of Zuckerkandl. The important clinical implications of these facts must be apparent.

The tumors have varied in weight from 5 gm. to more than 2 kg. One tumor described by Soffer *et al.*[28] weighed 2 kg. after much blood had been removed. Typically, the tumors are encapsulated, spherical or oval, and reddish brown. Many are hemorrhagic and necrotic, and have undergone cystic degeneration. Often a rim of suprarenal cortex can be seen at one edge of the specimen. In our case 1 the tumor was blue-black because of the high melanin content, but this is unusual.

In the tumors which develop the more typical and characteristic histologic pattern there is an unmistakable resemblance to the suprarenal medulla. The nuclei of the tumor cells are large, vesicular, and frequently have prominent nucleoli. The cytoplasm is abundant, mak-

ing each cell polygonal. Often fine granules can be seen in the cytoplasm, even in sections prepared from formalin-fixed tissues and stained with hematoxylin and eosin. Frequently the cells are arranged in cords and nests and are separated by a delicate connective tissue stroma. Usually, there is an abundant capillary network. When fixed in Orth's solution and stained by the Schmorl technic [18] the nuclei are blue and the cytoplasm often contains olive-green granules. When fixed in formalin and stained with azocarmine, as suggested by Gomori,[17] the nucleus usually is pale, the nucleolus a brilliant red, and the cytoplasm often contains bluish violet granules. However, many of the tumors are atypical and may pose a problem in histologic diagnosis. Some tumors are composed of small cells with dark, pyknotic nuclei and no demonstrable nucleoli. The cells may be fusiform or spindle-shaped. Great variation in size and shape may be present, including the formation of giant cells. The cytoplasm may be scanty and contain no granules. The reactions to the Schmorl [18] and azocarmine stains may be negative. The cells may contain a large amount of melanin. Ganglion cells may be present. The pathologist must then give special consideration to the clinical features of the case.

It is difficult to ascertain the real incidence of hormonal activity of these tumors. Before 1922, at which time the relationship of these tumors to paroxysmal hypertension was first clearly described,[4] most of the reports consisted of necropsy findings and about one-half of the tumors apparently were inactive. During the past 20 years many clinical as well as pathologic diagnoses have been made and, quite naturally, the percentage of hormone-producing tumors has increased. During the past 4 years about 30 cases have been reported, all characterized by symptoms of epinephrine production. It is interesting that of the 9 tumors associated with generalized neurofibromas, only 2 (including our case 2) have produced the suprarenal-sympathetic syndrome.

There is some confusion in the literature concerning the frequency with which these tumors are malignant. McGavack *et al.*[25] stated that only 8 cases of definitely malignant paraganglioma had been reported and that all of these were physiologically inactive, *i.e.*, did not produce the suprarenal-sympathetic syndrome. The following year Mackeith [26] stated that 17 malignant paragangliomas had been described and that some of them had been active. The reason for this disagreement is that Mackeith apparently accepted all of the cases reported as malignant, whereas McGavack critically analyzed all of the reported cases and accepted only about half of them. McGavack categorically stated that it is not possible to separate the malignant from the benign

tumors histologically, and that "all of the cases in which metastases did not occur should be classified as benign." On this basis, he accepted only 7 cases and added another. We would insist upon invasion in lieu of metastasis as a criterion of malignancy. We believe that Fein and Carman's [35] case is a typical example of a benign paraganglioma incorrectly diagnosed. This patient was a 27-year-old female; at necropsy an encapsulated tumor of the right suprarenal gland was found which was assayed and found to contain epinephrine. There was no cachexia and no local invasion by the tumor or metastasis. Furthermore, the photomicrographs revealed a pattern which is compatible with that of a benign paraganglioma although the diagnosis given is medullary carcinoma of the suprarenal gland (malignant pheochromocytoma). Many similar examples could be cited to account for the disparity between the figures of Mackeith and McGavack. Since McGavack's report, no acceptable malignant paraganglioma has been reported. The presence of multiple tumors does not constitute proof of malignancy. There have been 18 reported cases of bilateral paragangliomas. McGavack has accepted as malignant only 5 cases with bilateral tumors. The bilateral paragangliomas of the suprarenal gland reported by Knake [34] were clearly benign. Fingerland's [27] case in which tumors were found in the right suprarenal gland and the organ of Zuckerkandl was reported as one of benign neoplasm.

In summary, it can be stated that a paraganglioma which is locally invasive or has metastasized should be considered malignant. If there are multiple tumors and one or more of the nodules is located where paraganglion cells are never found normally (*e.g.*, lymph node or bone), it is a malignant neoplasm. If the tumor is well encapsulated but the cells appear to be anaplastic, the observer must be cautious in classifying it as malignant. If the tumors are multiple and all of them are situated where paraganglion cells are normally found (*e.g.*, both suprarenal glands, one suprarenal gland and the organ of Zuckerkandl), again one must be cautious in interpreting one tumor as being primary and the others metastatic.

For the 8 cases of malignant paraganglioma accepted by McGavack *et al.*,[25] the following features were observed: All occurred in the suprarenal gland; none was associated with paroxysmal hypertension or the suprarenal-sympathetic syndrome; the age range was from 30 to 68 years with an average of 45.5 years; 5 of the 8 were bilateral; the outstanding clinical features were loss of weight, cachexia, and pain at the primary and metastatic tumor sites. In McGavack's own case, the picture of cachexia was so extreme that diagnoses of Addison's and Simmond's diseases were considered. In 3 of

the 8, a palpable mass was present. The regional lymph nodes were involved in all. Other metastatic sites were as follows: Thoracic lymph nodes, 5; liver, 4; bones, 3; lungs, 3; pleura, 2; skin, 2; intestines, 1; kidney, 1.

In several of the reported cases increased pigmentation of the skin has been described. There are two possible interpretations of this observation. The more obvious is that the expanding tumor has produced pressure on the suprarenal cortex and that the increased pigmentation is a result of cortical deficiency. There is abundant evidence, both clinical and experimental, that deficiency of suprarenal cortical hormones causes deposition of melanin in the skin. At least 4 cases of paraganglioma have been reported in which clinical features of Addison's disease were present.[25] In 2 there was excessive loss of sodium chloride in the urine and a retention of potassium. But the disturbing fact is that in none of these cases could encroachment on the suprarenal cortex be demonstrated. In McGavack's [25] case, for example, there was stretching of the cortex on the side of the tumor, but the opposite suprarenal gland was uninvolved, and serial sections of all endocrine glands revealed no significant change. The cause for the development of Addison's syndrome remains obscure. The other possible interpretation of the increased skin pigmentation is that it is related to neurofibromatosis, it being well known that areas of deep pigmentation often precede the development of neurofibromas.

Before concluding a discussion of the relationship of paragangliomas to disturbed suprarenal cortical metabolism, mention should be made of LeCompte's [36] case of a 31-year-old white female who displayed the signs and symptoms of the androgenital syndrome. Since this syndrome is sometimes due to hyperfunction of the suprarenal cortex, it might be thought that stretching of the suprarenal cortex stimulated it to activity, an effect exactly the opposite of that suggested in the preceding paragraph to explain the production of Addison's syndrome.

Many causes and mechanisms of death have been described for patients with paragangliomas. Of those with malignant tumors the cause of death was attributed to the cancer. Patients with tumors which were nonfunctional and apparently produced no epinephrine died of unrelated causes. When the epinephrine-sympathetic syndrome was present, the cause of death was usually attributed to some effect which the tumor produced. Very often the anatomic changes at death are minimal and the possibility of acute epinephrine intoxication arises. Dolgin [37] reviewed the causes of death in some detail and cited the work of Raab [38] on the toxic effects of epinephrine-like substances.

Effects of Epinephrine

One of the most interesting aspects of these tumors, and certainly the one most widely discussed in the literature, is the physiologic change produced in the patient as the result of the production of an epinephrine-like substance. In this respect paragangliomas resemble the active islet cell tumors of the pancreas, the virilizing tumors of the ovaries and suprarenal cortex, the basophilic tumors of the pituitary body, and others. The first clear-cut description of the syndrome of paroxysmal hypertension was written in 1922 by Labbé, Tinel, and Doumer.[4] Following this report there was rapid advancement in knowledge of the activity of these tumors. For several reasons it was natural for the early workers to suspect that they produced a substance similar to epinephrine. The frequent occurrence of these tumors in the suprarenal gland, the histologic similarity to the suprarenal medulla, the chromaffin reaction, and the striking resemblance of the spontaneous attacks of headache, hypertension, sweating, and pallor to the known physiologic effects of epinephrine all pointed to production by the tumor cells of a substance similar to epinephrine. That a vasopressor substance is present in an active paraganglioma can be demonstrated by several methods. The one most commonly used has been the injection of a neutralized acid extract of the tumor into a lightly anesthetized dog and a comparison of the pressor effect produced with the action of a known quantity of epinephrine. Hyman and Mencher [39] prepared a solution from a patient's blood while she was having an attack of paroxysmal hypertension. By perfusion of this material through a rabbit's ear, they were able to demonstrate a pressor effect. That this substance was similar to epinephrine was further supported since the effect could be reversed by ergotamine. In several cases an elevated level of the blood potassium has been reported. The significance of this is apparent when one considers that the injection of epinephrine into a human being causes an elevation of blood potassium of as much as 87 per cent above normal.[26] Epinephrine in a crystalline form was obtained from a tumor by Kelly, Piper, Wilder, and Walters [40] in 1936. DeVries, Mandl, Rachmilevitz, and Ungar [41] used a colorimetric method (Ewins' [42] test in a buffered solution) in estimating the epinephrine content of the tumor to be studied. Mortell and Whittle [43] injected dogs intravenously with diluted fluid obtained from a cystic tumor which they encountered, and made direct measurements of the vasopressor effect. Furthermore, they cited Strömbeck and Hedberg's [44] description of a chemical method based on the decolorization of methylene blue. The latter had described a case of which, during the

paroxysms of hypertension, the blood contained one thousand times the normal amount of epinephrine and during the remissions showed an epinephrine content which was elevated thirty-fold. It is true that these methods are often indirect and leave much to be desired, but certainly they prove that epinephrine (or a substance closely allied to it) is often produced by these tumors.

It is usually stated that bio-assay of the tumor must be done shortly after it has been removed. However, nowhere have we found descriptions of decreasing vasopressor activity as the time interval between removal and determination of epinephrine increased. In Mortell and Whittle's case [43] there was no decreased potency at the end of 48 hours, when the tumor was stored in the ice box. Fingerland [27] reported 2 cases in which he tested the formalin, alcohol, and Bouin's solution in tumors which had been preserved for 6 years, and demonstrated a strong epinephrine reaction. Since epinephrine is readily destroyed by oxidation in alkaline solution, one should store material to be assayed in an acid solution. The amount of pressor substance contained in paragangliomas has been reported to vary from 6.7 to 2300 mg.[45] From the normal human adult suprarenal glands only about 8 mg. are recoverable.

Varied clinical effects may be produced by these tumors. The syndrome first described and the one most often seen and recognized is that of paroxysmal hypertension. More recently, excellent reports have been made of cases simulating chronic essential hypertension,[24,46] diabetes mellitus,[47] hyperthyroidism,[45,48] and adynamic ileus.[49] Some patients have exhibited signs and symptoms of several of these categories. Rodin [50] has described in great detail the ophthalmologic changes which occur with this disease. Mackeith [26] has discussed the electrocardiographic changes. In Mortell and Whittle's [43] case, electroencephalograms were taken during the paroxysms and were found not to be altered. Hyman and Mencher [39] measured temperatures of the peripheral skin and found them to be lowered, presumably because of vasoconstriction. In the 2 cases reported by McCullagh and Engel [48] an elevated urea clearance was demonstrated, which suggests increased renal blood flow; in one there was also severe polyuria, arousing a suspicion of diabetes insipidus.

Several tests have been devised which have been useful for studying a patient suspected of having a paraganglioma. All of them are similar in that they are attempts to provoke an attack. One of the first was suggested by Coller, Field, and Durant [51] and consisted of a subcutaneous injection of a minute amount of epinephrine. Roth and Kvale [52] have induced attacks with the use of histamine. The mechanism is thought to depend upon the fact that histamine is antagonistic

to epinephrine and causes a temporary reduction in the circulating amount of that substance. However, the effect is temporary and thus the tumor responds with a "rebound" liberation of a large amount of epinephrine. Among the other methods might be mentioned the immersion of the feet in cold water (cold pressor test), the injection of insulin, and hyperventilation (which is thought to cause the diaphragm to press on the tumor). All of these tests have been successful in some cases and unsuccessful in others, so that there is little to recommend one rather than another.

Perirenal air insufflation preparatory to radiographic examination has been advocated by Hyman and Mencher [39] and has been very useful in their hands. Others have hesitated to employ this procedure because patients with these tumors are unstable and disastrous results have ensued. It may be that the attempted perirenal insufflation for the patient of our case 2 had something to do with his demise. Scout films of the abdomen have been helpful in many cases, for calcification in the kidney region has been seen. Often these shadows have been misinterpreted as being tuberculous in origin.

Relation to Neurofibromas

In the second case of our series, an active paraganglioma of the right adrenal was associated with neurofibromatosis of skin and viscera. Suzuki [3] was the first to report the simultaneous presence of these two neoplastic diseases, and the literature now contains 8 previously reported cases. In only one of these was the paraganglioma active, producing the suprarenal-sympathetic syndrome.[53] Our case 2, then, is the second to be reported in which a paraganglioma, multiple neurofibromas, and paroxysmal hypertension have occurred together.

The co-existence of these two neoplastic conditions in a frequency of 1 to 23 suggests that the relationship is more than fortuitous. Nearly all authors reporting such cases have made this comment, but nowhere have we found a satisfactory explanation of this concurrence. As has been described above, the paraganglion cells are derived from the migrating undifferentiated cells of the neural crest. Harrison [54] has demonstrated experimentally that when the neural crest is divided from the neural tube, the motor nerves continue to develop, but are devoid of the normal sheaths (Schwann cells). This indicates that the sheath cells, like the paraganglion cells, are derived from the neural crest. Stout [55] recently reviewed the histogenesis of neurofibromas and stated that Schwann cells play the dominant rôle in the formation of these tumors. These accumulated facts suggest, then, that paragangliomas and neurofibromas are both derived from cells which have ultimately come from the neural crest. Several writers have reported

cases demonstrating tumors consisting of combinations of ganglioneuromas, neuroblastomas, and paragangliomas.[30,56,57] These have been accepted as being expressions of different degrees and directions of differentiation from common primordial cells. An extension of this concept might explain the concomitant occurrence of neurofibromas and paragangliomas.

Melanin Production

One of the cases reported by us (case 1) is a retroperitoneal paraganglioma which was deeply pigmented. In attempting to identify the pigment, four substances were considered: hemosiderin, lipochrome, chromaffin granules, and melanin. The first three were eliminated from consideration and the pigment interpreted as melanin because it was iron-free, not soluble in fat solvents, bleached with hydrogen peroxide, and darkened with 5 per cent aqueous silver nitrate. Baker [58] has shown that these are the only chemical reactions which are of much practical value in the identification of brown pigment.

Tyrosine, when oxidized in the presence of the enzyme tyrosinase, yields melanin.[59] It can also be used as the precursor of epinephrine.[60] The possibility of a similar source for melanin and epinephrine and the close chemical relationship of these substances make it seem reasonable that a neoplasm possessing the potential capacity to produce epinephrine might also produce melanin.

Millar [61] has reported a case of malignant ganglioneuroma of the 7th thoracic sympathetic ganglion in which the ganglion cells contained melanin. Masson [62] has traced the origin of melanomas of the skin to Meissner's corpuscles which are composed of modified Schwann cells. Hyperpigmentation of the skin occurs before the development of, and in association with, multiple neurofibromas. Thus it would appear that a tumor derived from the cells which have origin from the neuroectodermal cells of the neural crest (paraganglioma, ganglioneuroma, neurofibroma, and ordinary melanomas of the skin) is apt to produce melanin. We are well aware that the definitive histogenesis of all of these tumors is not finally settled, but we believe that the accumulating facts lend support to the opinion of a common origin for these diverse neoplasms.

Summary and Conclusions

On the basis of the origin and distribution of paraganglion cells, tumors arising in the carotid body, appendix, and coccygeal body have been excluded from the group of paragangliomas. The chromaffin reactions are not specific for paragangliomas.

The previously reported cases of paraganglioma, reviewed with regard to age and sex distribution, location of tumors, hormonal activity, and histologic appearance, exhibit a variability of cytologic pattern and a marked degree of pleomorphism, which is, nevertheless, consistent with a diagnosis of benign paraganglioma. A diagnosis of malignancy should not be made in the absence of invasion or metastases.

There are 9 cases in which paragangliomas have occurred concurrently with neurofibromatosis. This concomitance may depend upon different degrees and directions of differentiation of neural crest cells.

Of the 5 original cases of paragangliomas which are described, one tumor was retroperitoneal and contained a brown pigment which was identified as melanin. The close chemical relationship between melanin and epinephrine is probably significant in this connection.

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DESCRIPTION OF PLATES

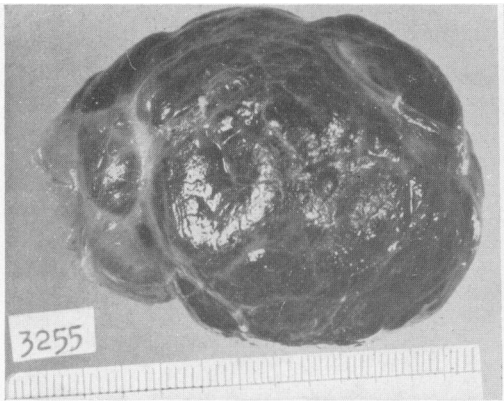
PLATE 192

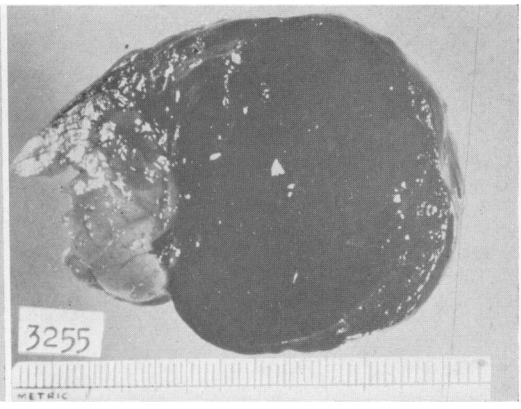
FIGS. 1 and 2. Case 1. External and cut surfaces of paraganglioma.

FIG. 3. Case 1. Pigmented area in tumor. Hematoxylin and eosin stain. × 240.

FIG. 4. Case 1. Photomicrograph of nonpigmented area in tumor. Hematoxylin and eosin stain. × 240.

1





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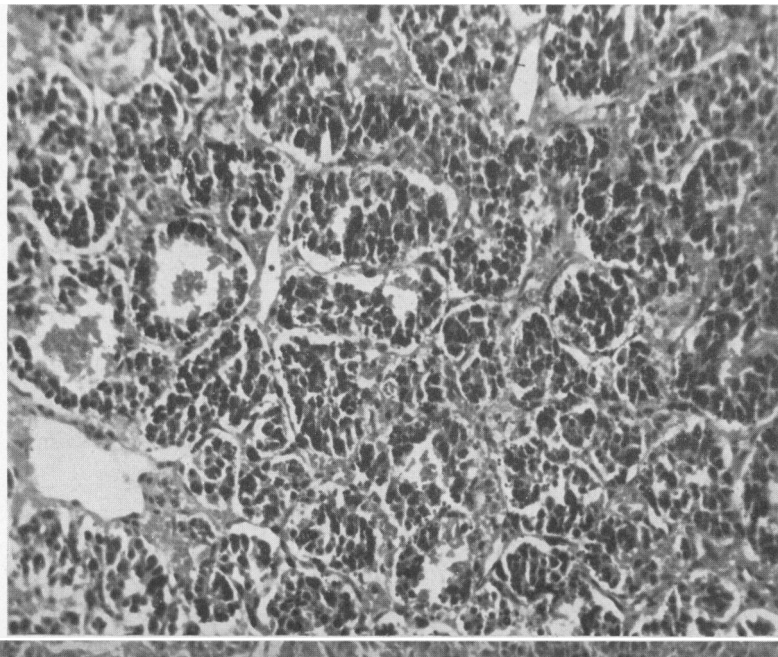

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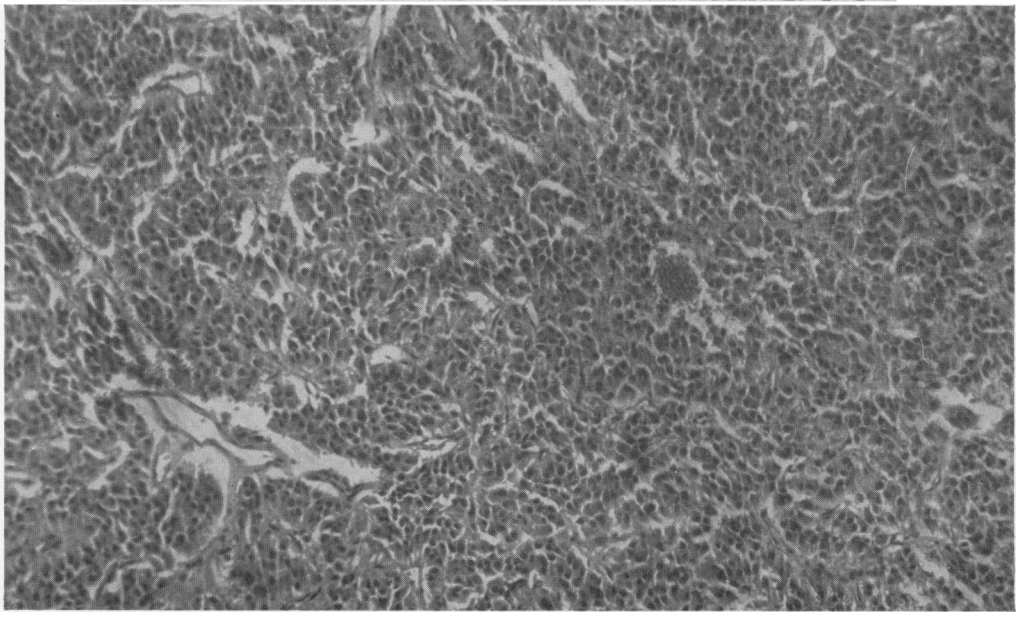

PLATE 193

FIG. 5. Case 2. Paraganglioma of right adrenal; diffuse hypertrophy of opposite adrenal.

FIG. 6. Case 2. Photomicrograph of representative area of the neoplasm. Hematoxylin and eosin stain. × 240.

FIG. 7. Case 2. Cytoplasmic granules and prominent nucleoli in tumor cells. Azocarmine stain. × 516.

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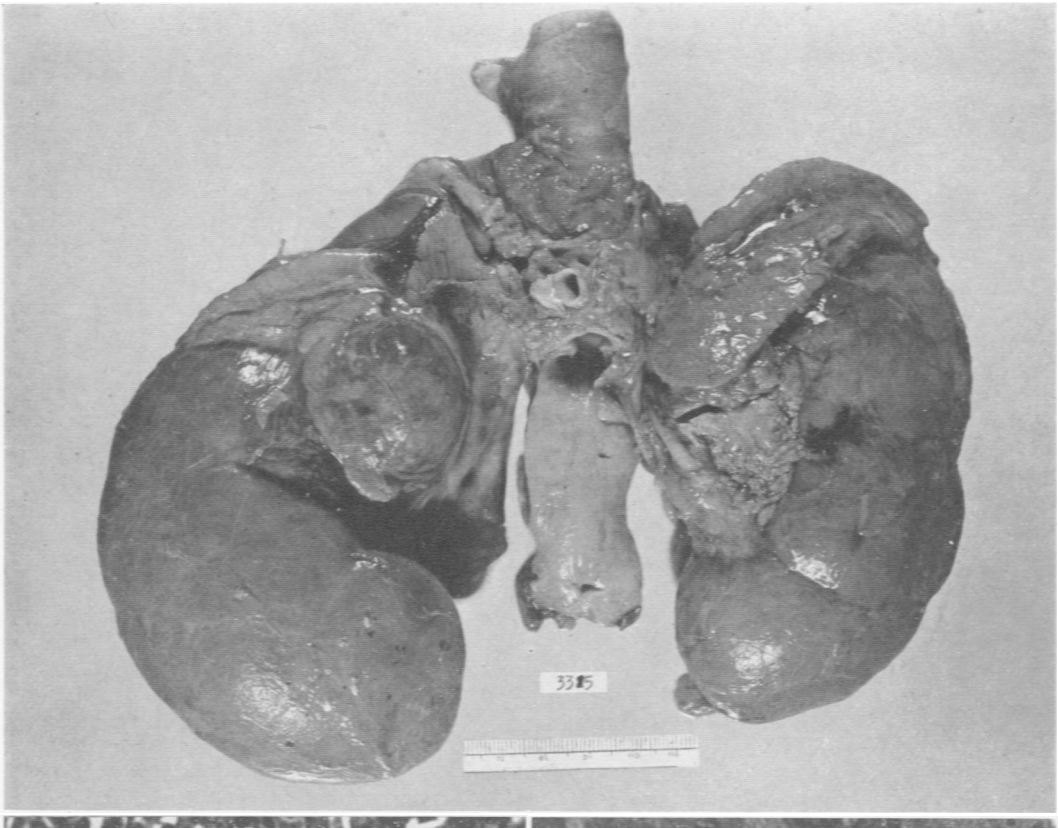

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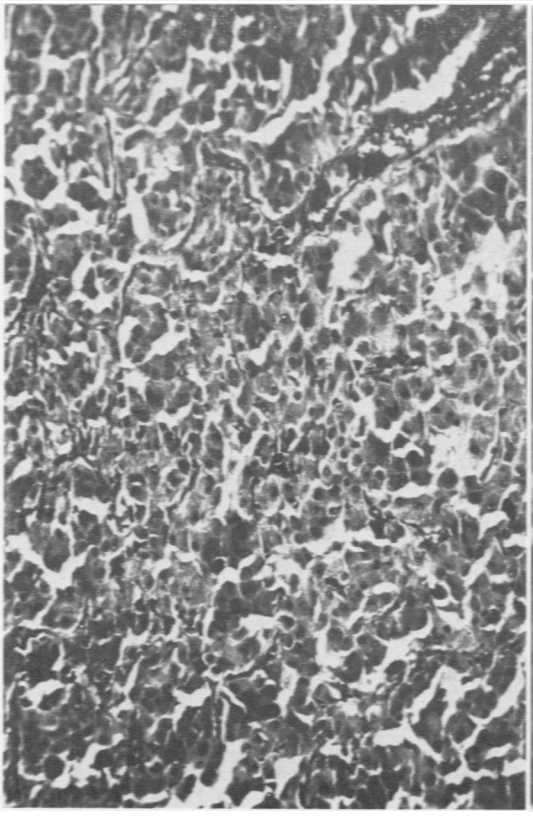

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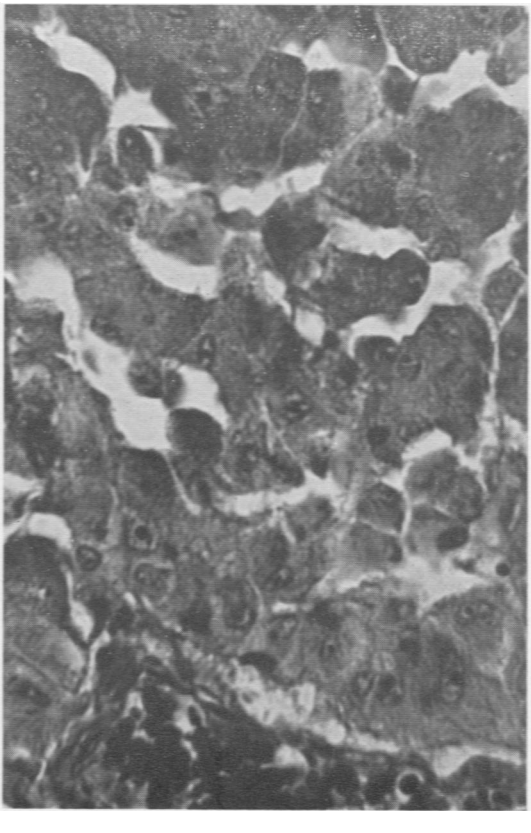
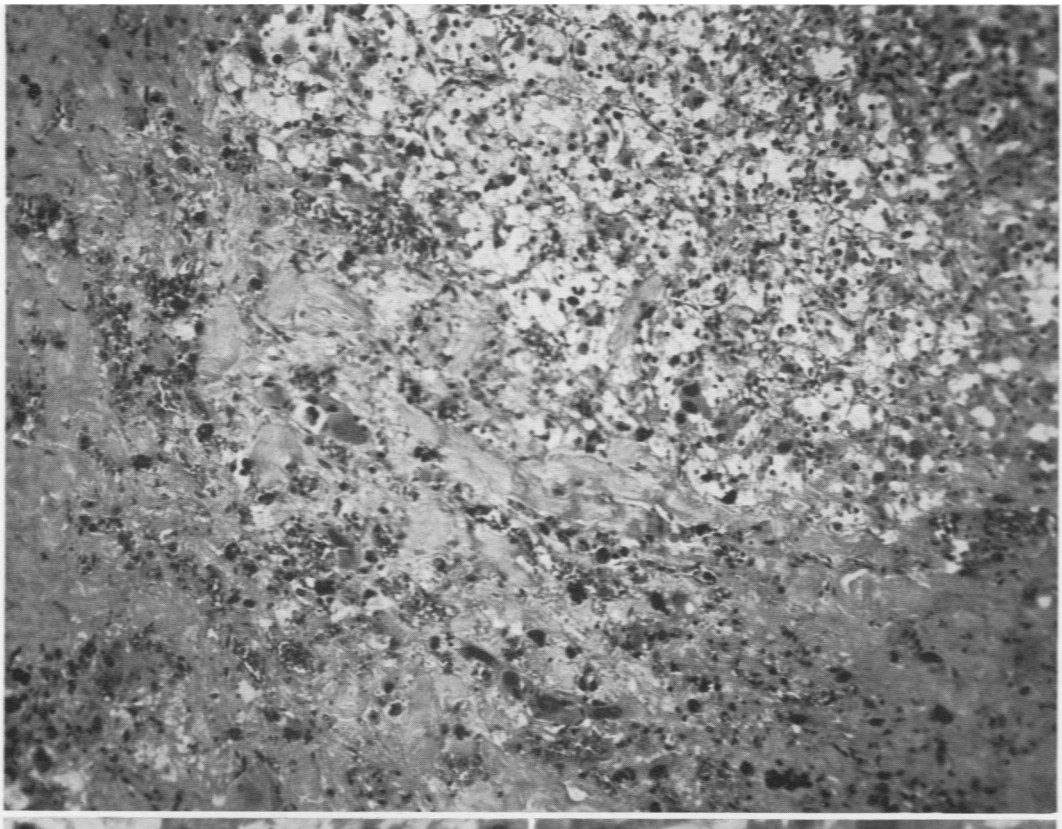


PLATE 194

FIG. 8. Case 3. Photomicrograph of neoplasm showing hydropic cell area at upper right and granular cell area at left. Hematoxylin and eosin stain. × 120.

FIG. 9. Case 3. Multilocular vacuolation of cytoplasm in hydropic area. Hematoxylin and eosin stain. × 516.

FIG. 10. Case 3. Granular cytoplasm in darker staining areas. Hematoxylin and eosin stain. × 516.



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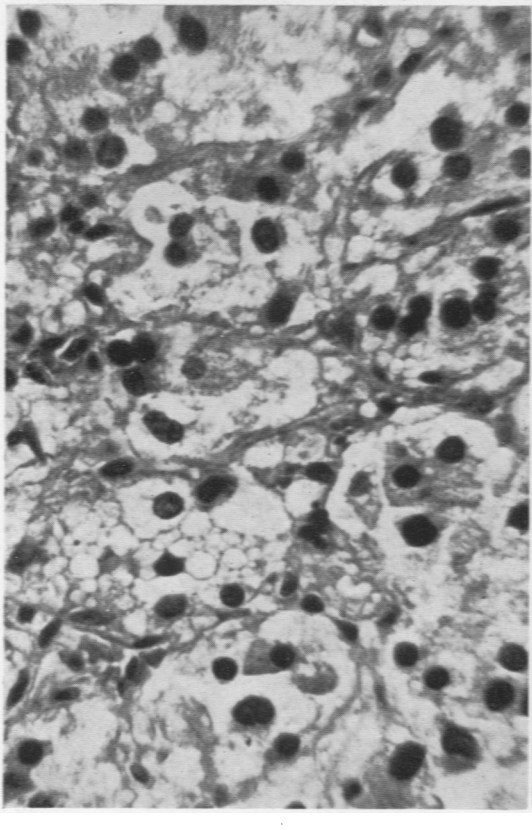

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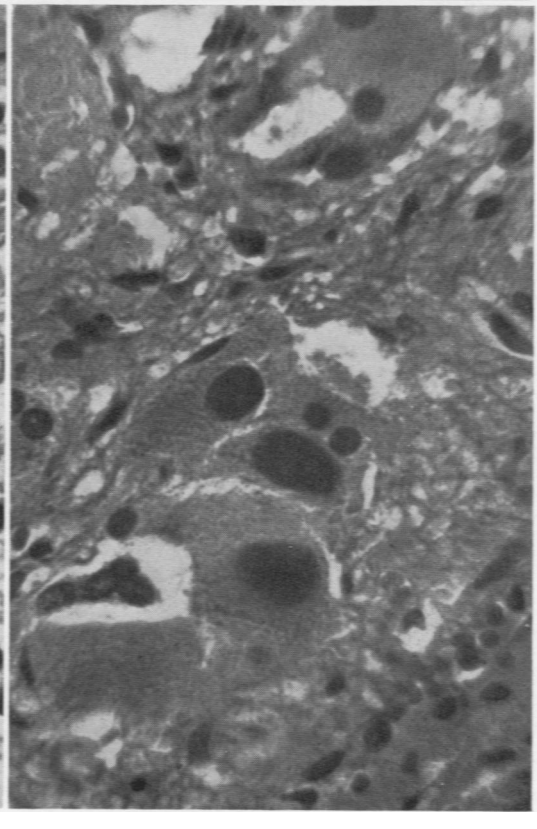

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PLATE 195

FIGS. 11 and 12. Case 4. Photomicrographs of representative areas. Many oval and spindle-shaped cells; some pleomorphism and prominent vascular spaces. Hematoxylin and eosin stain. × 125 and × 512.

FIG. 13. Case 5. Photograph of paraganglioma of left adrenal gland.

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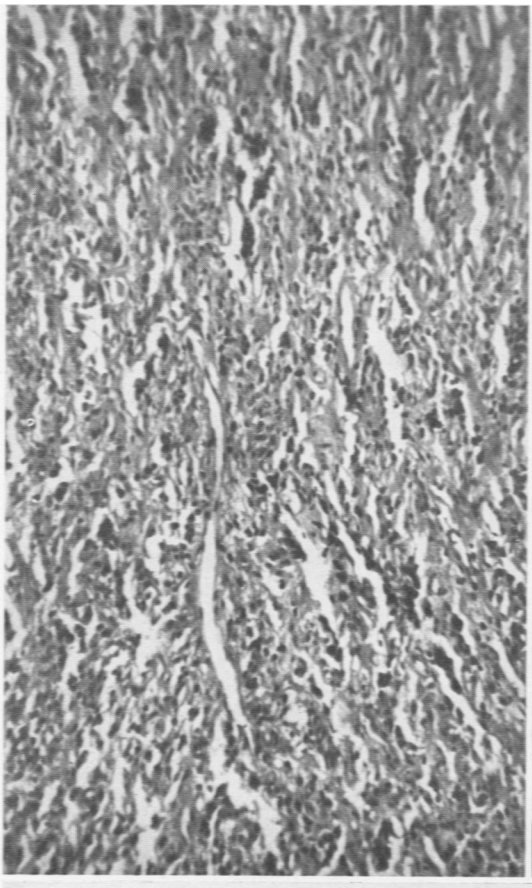
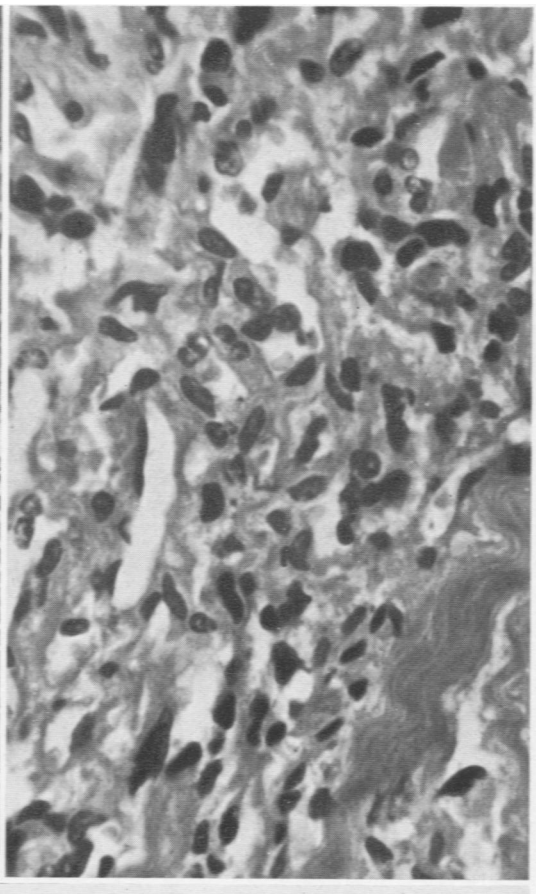


12



13

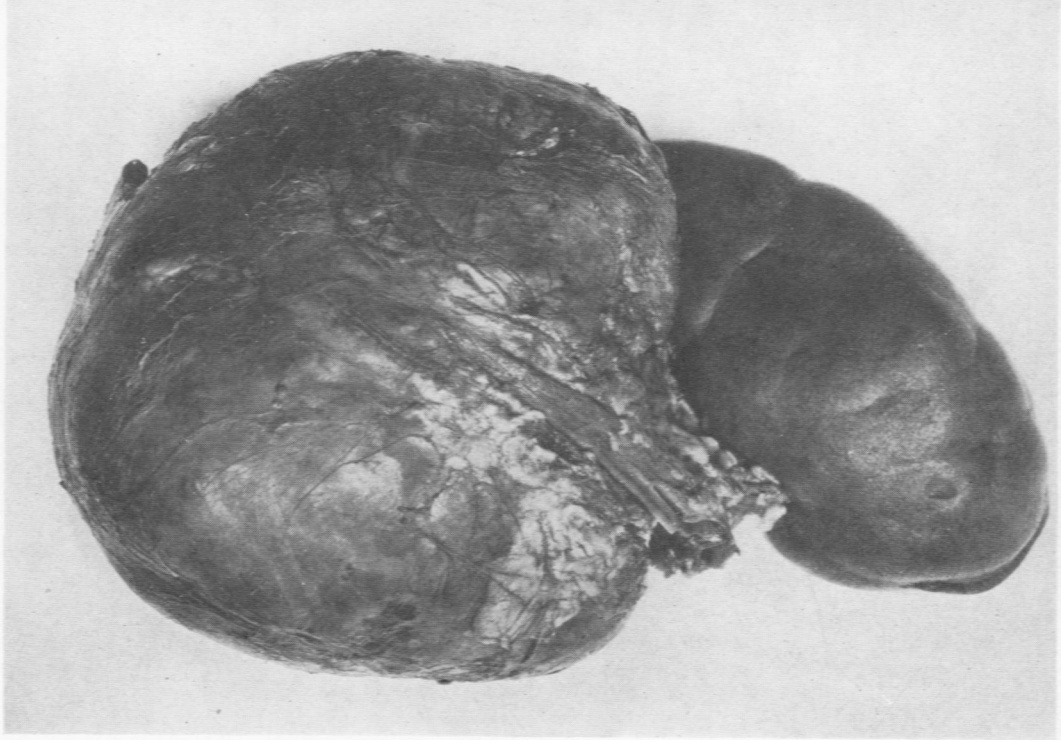


PLATE 196

FIG. 14. Case 5. Photomicrograph of representative area of the neoplasm. Hematoxylin and eosin stain. × 240.

FIG. 15. Case 5. Distinct granules in cytoplasm and wide sinus-like vascular spaces. Hematoxylin and eosin stain. × 512.

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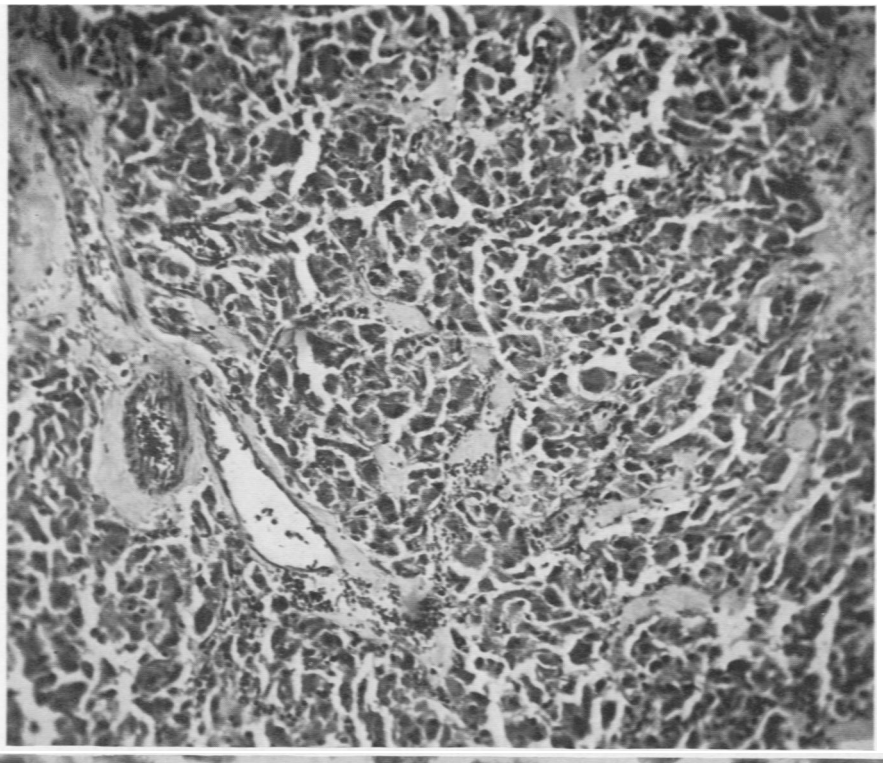

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