ESSENTIAL AND PAROXYSMAL HYPERTENSION, CONTRASTED BY CASE REPORTS *

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Articles dealing with essential hypertension are omnipresent in current medical literature. A number of cases of paroxysmal hypertension have been reported and another isolated example would add nothing to our knowledge of this subject. It is my intention to contrast essential and paroxysmal hypertension, hoping thereby to simplify their differential diagnosis.

Essential hypertension of the so-called benign and malignant phase is by reason of its secondary pathology one of the most frequently encountered lethal factors, accounting for approximately 11.4 per cent of all deaths.† Paroxysmal hypertension was the lethal factor in less than 0.1 per cent of the same series of cases. Paroxysmal hypertension is a clear-cut pathological-physiological entity representing the physiological response to neoplastic hyperplasia of normally functioning cells, the pheochrome cells of the adrenal medullary parenchyma. On the other hand, the causative factor of essential hypertension of the benign type is a matter of speculation, still resting on hypotheses, none of which is entirely tenable. In the second part of this paper (dealing with paroxysmal hypertension) a rather detailed consideration will be accorded the adrenal gland because it constitutes one of the many hypothetical etiological factors of essential hypertension, as well as being the actual site of the known causal pathology of paroxysmal hypertension.

PART I

ESSENTIAL HYPERTENSION OF THE BENIGN TYPE

Medical literature dealing with essential hypertension includes the life work of universally recognized specialists in all

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† A tentative figure based on incompletely classified forms of chronic cardiovascular disease encountered among 1105 autopsies performed by the author during his tours of duty.

branches of our profession. Almost all the valuable work now being accomplished on this subject is along medical, surgical and experimental chemical-physiological lines, and it would appear that too little attention is focussed on the data included in autopsy protocols.

The term essential hypertension has been generally accepted since Allbutt [1] in 1895 recognized the occurrence of isolated hypertension by following patients with increased blood pressure over periods of years. I would define essential hypertension as the manifestation of sustained high blood pressure without recognizable cause, although later secondary cardiac, cerebral and renal vascular changes occur. Naturally all individuals with essential hypertension of the benign type do not succumb to this ailment and the secondary vascular changes may merge into those of the senile form. Logically the term essential hypertension should be limited to the condition usually referred to as essential hypertension of the benign type.

In selecting the cases to be reported, 1 case essential hypertension of the benign type, the 2nd case one of paroxysmal hypertension, I was able to find records of 2 patients who presented much in common. Both were white males of the same age at the time of death (45 years); both were army officers, one a member of the Medical Corps, the other of the Veterinary Corps; and both died as the result of cerebral hemorrhage. I was enabled through the courtesy of the Office of the Surgeon General to secure the necessary data to prepare graphs illustrating the blood pressure readings of both officers from the time of their entry into the Service to death (Graphs 1 and 2).

Case 1. Essential Hypertension of the Benign Type

Clinical History: The patient, P. McN., was a white male, aged 45 years at the time of death. He was a moderate user of alcohol and smoked in excess, approximately 50 cigarettes daily. His father died at 60 years of age from cardiovascular disease with diabetes; his maternal grandmother died at 60 years from apoplexy; and a paternal aunt is reported to have had a blood pressure above 200 mm. Hg. for a number of years.

The past illnesses of the patient included mumps at the age of 22 years, complicated by orchitis. He had had mild influenza several times and several attacks of tonsillitis. The Wassermann and Kahn reactions were always negative.

In May, 1931, during the routine annual physical examination of this offi-

cer, a trace of albumin and hyaline casts were found in the urine. During 1932 the patient had repeated hematuria due to associated nephrolithiasis (see below). In December, 1932, he had severe epistaxis which required packing to control. The blood pressure readings are depicted in Graph 1.

The patient was admitted to the Walter Reed General Hospital, Washington, D. C., Nov. 14, 1933. At the time of admission he was ambulatory, afebrile and in fairly good general condition. The blood pressure on admission to the hospital was 220/140, and the pulse pressure 80 mm. Hg. The eyegrounds revealed marked angiosclerosis with scarring and recent small retinal hemorrhages. The blood count showed 3,830,000 erythrocytes; hemoglobin 75 per cent; total leukocyte count 8000; and the polymorphonuclears 69 per cent. The urea nitrogen was 20 mg. per cent, the blood sugar 108 mg. per cent. The basal metabolic rate was plus 2. The electrocardiogram showed left axis deviation and inverted T waves in lead I. Roentgenograms revealed widening of the aortic arch and left ventricular hypertrophy; the lungs were negative and the kidneys showed dense shadows in both renal areas. The specific gravity of the urine ranged from 1.006 to 1.027; all specimens of urine presented 1 to 2 plus albumin, sugar negative, many leukocytes and occasionally many erythrocytes. The urinary findings are in part accounted for by the complicating nephrolithiasis.

On Feb. 8, 1934, the patient complained of severe basal headache. On February 10 he had epistaxis. Muscular twitchings were noted and he became unconscious for one-half an hour. On February 11 the blood pressure was 270/170, and the pulse pressure 100 mm. Hg. A spinal puncture was made and clear fluid obtained. On February 23 at 12 midnight he had a convulsion and became unconscious for a short time. The blood pressure was then 235/143 mm. Hg. and flaccid paralysis of the right lower extremity supervened. A second convulsion accompanied by unconsciousness came on at 1.30 A.M. At 2.00 A.M. there was a third convulsion, and a fourth at 2.45 A.M. Flaccid paralysis of the right upper and lower extremities was noted. The left pupil was dilated and the right pupil was contracted to pin-point size. He remained unconscious until death, which occurred at 2.45 P.M., Feb. 24, 1934.

Postmortem Examination *

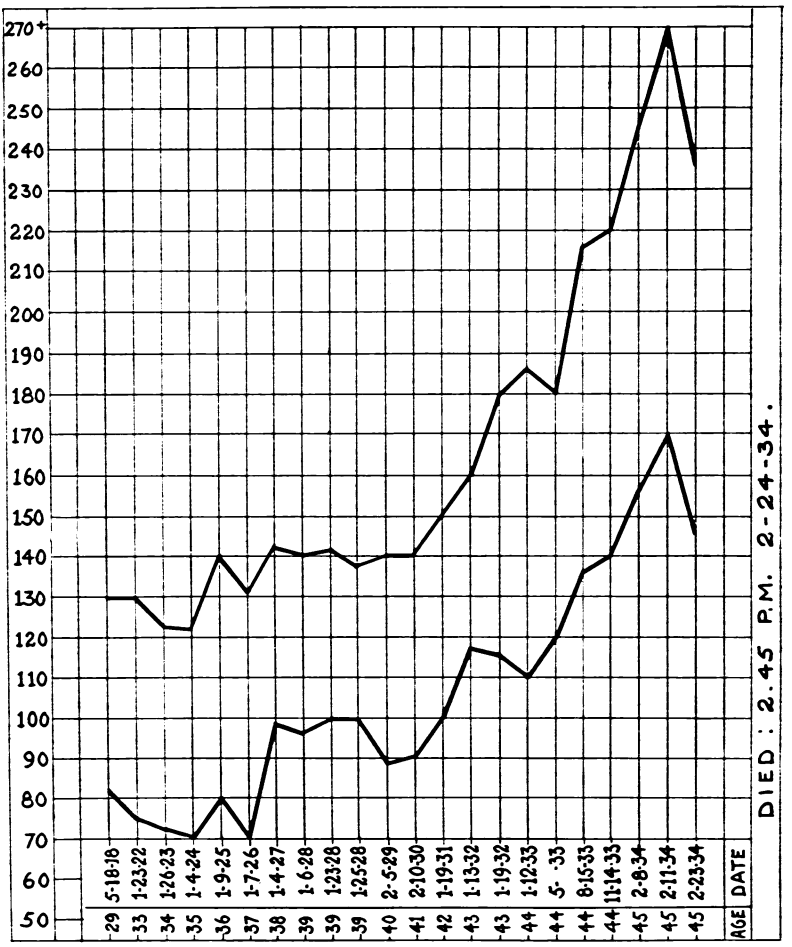
The body length was 175 cm., the weight approximately 61 Kg.

Heart: The heart weighed 550 gm. The wall of the right ventricle measured 7 mm. in thickness, the wall of left ventricle 2.8 cm. The aortic ring was 7.7 cm. in circumference. The coronary arteries showed moderate intimal thickening; the lumens were patent and the contents fluid blood.

Aorta: The aortic arch measured 6.5 cm. in circumference, the thoracic aorta 5.5 cm., and the abdominal aorta 4 cm. The aortic intima was diffusely thickened and presented plaques of fat imbibition, but no calcification or ulceration was observed.

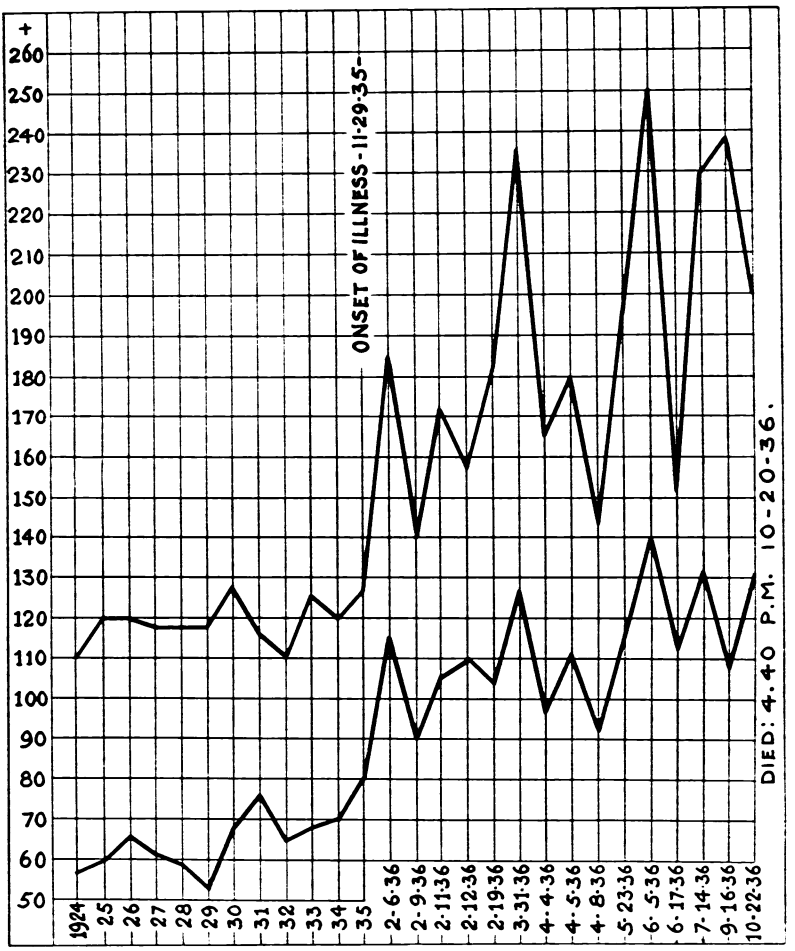
Adrenals: The adrenals were of normal size.

* A–1612, Walter Reed General Hospital, Washington, D. C.



GRAPH 1. Blood pressures, Case 1: essential hypertension of the benign type, death from cerebral accident (A–1612, W.R.G.H.).

The graph shows: (1) At no time was the pulse pressure within the normal limits indicated in Table I; from 1918, when the patient was 29 years old, to 1926 when he was 37 years old, the pulse pressures varied between 48 and 55 mm. Hg. (2) For a period of 3 years, 1926–1928 inclusive, the patient's diastolic pressure rose while the systolic pressure remained stationary and the pulse pressure dropped accordingly. (3) After 1929, when the patient was 40 years old, the diastolic and the systolic pressures rose concomitantly, fairly slowly at first, then with extreme rapidity up to the time of death which occurred Feb. 24, 1934.



GRAPH 2. Blood pressures, Case 2: paroxysmal hypertension, death from cerebral accident (A–2018, W.R.G.H.).

The graph indicates a normal blood pressure from the time of the patient's entry into the Service (1924) until the onset of the final illness, November, 1935, with the exception of a slight transitory rise during 1930 to 1931. After November, 1935, the blood pressure tracing resembles the temperature chart in a case of septicopyemia, marked by daily and hourly elevations and depressions. The final illness lasted approximately 11 months; death occurred Oct. 23, 1936 (the graph indicates the date of death as of Oct. 20, 1936, by error); cause of death, cerebral accident, hemorrhage into the optic radiation of the left hemisphere of the forebrain.

Kidneys: The right kidney weighed 110 gm., the left 120 gm.; combined renal weight 230 gm. The weight of the heart (550 gm.) divided by the combined renal weight (230 gm.) was 2.39 (ratio). The cortical surfaces of the kidneys were pinkish and granular; the renal cortices measured 5 mm. in thickness and the markings were preserved. The sinus fat was slightly increased. There were several mulberry-like calculi located in the calices of both kidneys and an impacted calculus was lodged in the lumen of the right ureter.

Microscopic examination of the renal tissue revealed moderately advanced nephrosclerosis of the benign type involving the interlobular and interlobar arteries. The afferent glomerular arterioles were not involved.

Brain: The brain weighed 1610 gm. The convolutions were flattened. The left lateral ventricle was distended with clotted blood due to a "blow-out" hemorrhage involving the posterior cornu of the left internal capsule with extensive spread through the adjacent parietal and frontal lobes of the forebrain and rupture into the left lateral ventricle. The hemorrhage was single. The vertebral arteries, the basilar artery, the circle of Willis and the cerebral branches all presented thickened parchment-like walls with encircling atheromatous bands.

Anatomical Diagnoses: (1) Eccentric hypertrophy of the heart, weight of heart 550 gm.; (2) atheromatosis of the aorta, moderately advanced; (3) coronary arteriosclerosis, moderately advanced without obstruction; (4) cerebral arteriosclerosis, advanced; (5) cerebral hemorrhage, massive, source of hemorrhage the left lenticulostriate artery, with destruction of the posterior cornu of the left internal capsule and rupture into the lumen of the left lateral ventricle of the brain; (6) renal arteriosclerosis, benign type, moderately advanced (microscopic finding); and (7) nephrolithiasis, bilateral, with impacted calculus in the lumen of the right ureter.

Comment

The blood pressure readings of the above case, from May 18, 1918, to death, were secured and are incorporated in Graph 1.*

* Through the courtesy of Major E. S. Cooley, U. S. Army, Office of the Surgeon General, Washington, D. C.

Study of the graph brings out the following points. (1) At no time was the patient's pulse pressure within the normal limits indicated in Table I. From 1918 when the officer was 29 years old, to 1926 when he was 37 years old, his pulse pressure varied between 48 and 55 mm. Hg. (2) For a period of 3 years, 1926 to 1928 inclusive, the patient's diastolic pressure rose while the systolic pressure remained stationary and the pulse pressure dropped accordingly. (3) After 1929, when the officer was 40 years old, the diastolic and the systolic pressures rose concomitantly, fairly slowly at first, then with extreme rapidity up to death, which occurred February 24, 1934.

TABLE I

Data on Body Weight and Blood Pressure of 256 Army Officers

Decade	Number of cases	Body weight	Systolic blood pressure	Diastolic blood pressure	Pulse pressure
		lbs.	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*
3rd	37	150	120	74	46
4th	51	160	122	77	45
5th	97	166	124	79	45
6th	64	161	132	81	51
7th	7	158	138	84	54
Averages:	256	159	127	79	48

NOTE: The ages vary from 24 to 64 years, the retirement age of army officers. The diastolic pressures present a fairly uniform rise with an increase of 10 mm. Hg. in 40 years, an average increase of 0.25 mm. Hg. per year, diastolic blood pressure.

The results of the annual physical examinations of 256 army officers for the year 1939 were made available for study * and are found to include valuable data relative to the blood pressure readings of a group of white males who are under constant medical supervision and whose lives and pursuits are fairly uniform. Of the total 256 officers 14, or 6 per cent, classify as obese, body weights averaging 90 Kg.; 6, or 2 per cent, present evidence of essential hypertension, not regarded as of sufficient severity to justify retirement; and 3, or 1 per cent, present some of the physical manifestations of the senile type of general arteriosclerosis. However, for the purpose intended, to supply workable averages, no cases were excluded and the body weights and the blood pressures of the 256 army officers are listed in Table I.

* Through the courtesy of Lt.-Colonel D. H. Mebane, Medical Corps, U. S. Army, Chief of the Medical Service at the Tripler General Hospital, Honolulu, Hawaii.

Part II

Paroxysmal Hypertension

The Adrenal Glands

In order to comprehend the pathology of the adrenal gland one must be reasonably cognizant of the histogenesis, anatomy and pathology of that organ.

Histogenesis: Quoting Maximow [2]: "The cortex develops from the celomic mesoderm on the medial side of the wolffian ridge, and the medulla from the ectodermal tissue from which the sympathetic ganglion cells also arise." Quoting Bailey and Cushing [3]: "The cells of the ganglionic crest . . . migrate into the visceral areas to form the anlage of the sympathetic nervous system. When they reach their final stations they differentiate into the neurons of the sympathetic ganglia, the capsular cells of these ganglia, and into the *chromaffine* cells of the adrenal medulla and analogous structures."

Anatomy: The adrenals are wedge shaped organs located on the upper poles of the kidneys. At birth the adrenals are relatively large, approximately one-third of the renal weight; during adult life the combined adrenal weight, ranging from 10 to 20 gm., is approximately one-thirtieth of the combined weight of the kidneys. The adrenals are located in a mesh of nerve fibers derived from the celiac ganglia, splanchnic, vagi and phrenic nerves. The adrenals receive their blood supply from three sources: from the inferior phrenic arteries, directly from the abdominal aorta, and from the renal arteries. The adrenal arteries break up into arterioles which course throughout the fibrous capsules of the adrenals; the adrenal arterioles reflect any degree of arteriolarsclerosis which may be found during the microscopic examination of the renal tissue. The arterioles in the adrenal capsules divide into capillaries which course inward between the lines of cortical cells to form the anastomosing capillary mesh of the formatio reticularis; the capillaries then reunite to form the sinusoids of the adrenal medulla. In the adrenal medulla the sinusoids join to form one large vein on either side, emptying into the inferior vena cava on the right and into the renal vein on the left, almost directly

below the eustachian valve of the heart. The walls of the two adrenal veins have a tunica media composed of longitudinally arranged fasciculi of smooth muscle fibers. In hypertension, chronic or due to any cause, the muscle fasciculi of the adrenal veins hypertrophy. Nervous stimuli to the adrenals pass: (1) to the chromaffin cells through the multipolar sympathetic neurons located in the substance of the adrenal medulla; and (2) to the longitudinal bundles of smooth muscle cells forming the walls of the adrenal veins, exciting a shortening of the veins with a pulling or suction action on the soft vascular tissue of the adrenal medulla, directly aiding the withdrawal of the secretory product (epinephrin) into the lumen of the sinusoids and veins, to be poured almost directly into the right atrium of the heart.

At birth the glomerular zone of the adrenal cortex is well developed; during adult life it gradually undergoes sclerosis, and at senility is hardly recognizable. Approaching senility the fascicular zone of the adrenal cortex undergoes nodular hyperplasia, at times quite marked though of no pathological significance. In essential hypertension the adrenal cortex is usually deep and the cells rich in lipoids. At birth the adrenal medullary parenchyma is sparsely represented though gradually increasing in relative volume as age advances. In cases of long continued hypertension from any cause the adrenal medullary parenchyma is increased in amount; the chromaffin cells show augmented physiological activity, manifested by the presence of numerous hyaloid cell inclusions located: (*a*) within the bodies of the large basophilic cuboidal and cylindrical cells palisading on the thin walled sinusoids of the adrenal medulla; and (*b*) within the capsules and in the bodies of the sympathetic neurons.

Physiology: The adrenal cortical parenchyma is indispensable for the continuance of life; adrenalectomized animals die after passing into a state of hemoconcentration with cationic imbalance; and there is marked increase in sodium elimination and potassium retention. Quoting Anderson and coworkers [4]: "Cushing's syndrome is an expression of the overproduction of cortin; studying the urine excretion of sodium and potassium and the blood level of these electrolytes, and comparing the findings with those of a patient with Addison's disease, it is reasoned that since some patients with Addison's disease are helped by a high sodium and

low potassium intake, then patients with Cushing's syndrome should be benefited by being placed on the opposite regimen, namely low sodium and high potassium intake." These authors state that this form of treatment proved effective in 1 case; the blood pressure decreased and there was a loss in weight.

Physiology of the Medulla: Epinephrin is the secretory product of the adrenal medullary parenchyma. The most delicate biological reaction, positive to a 1:800,000,000 concentration, fails to demonstrate any increase in the amount of epinephrin in the circulating blood. Quoting Rogoff and Marcus [5]: "Intravenously injected epinephrin disappears from the circulation so rapidly that it is rarely detected beyond the point of its pressor action and not after one complete circulation of the blood." The above observer believes that the concept that hypersecretion of epinephrin causes persistent elevation of blood pressure is untenable.

The normal physiological action of epinephrin may possibly be regarded as a direct action on the auriculoventricular node of the conductive system of the heart, located above the base of the septal cusp of the tricuspid valve. In paroxysmal hypertension resulting from adrenal medullary tumors of the pheochrome cell type the liberation of epinephrin during the episodes or crises exceeds all physiological and experimental bounds.

The correlation between the physiological functions of adrenal and thyroid is illustrated by 2 cases coming to autopsy. In 1 case, a white female,* aged 74 years, the thyroid weighed 55 gm., being five or six times the usual weight in senility, and it was rich in colloid. The adrenals presented complete bilateral destruction of the cortical parenchyma and most of the medullary portions by tuberculous caseous-nodose lesions. (2) In a 2nd case, a white male,† aged 48 years, there was complete replacement of the thyroid parenchyma by neoplastic tissue, carcinoma solidum. The combined weight of the adrenals was 45 gm., over twice the normal maximum weight of these organs. Another case,§ which illustrates the physiological function of the adrenal cortical parenchyma, was that of a white male, aged 39 years: the thyroid weighed 32 gm. (normal); the kidneys were polycystic, combined weight

* A–1802, Walter Reed General Hospital, Washington, D. C.
† A–1803, Walter Reed General Hospital, Washington, D. C.
§ A–2213, Walter Reed General Hospital, Washington, D. C.

7620 gm.; the combined adrenal weight was 26 gm., and the adrenals showed marked cortical hyperplasia regarded as the effort to maintain the cationic balance between the blood plasma and the blood and tissue cells of the patient.

Pathology: The pathology of the adrenal gland may be divided into: (*a*) lesions primary in the adrenal itself, cortical and medullary portions; and (*b*) lesions primary in the adrenal retroperitoneal rests, the organs of Zuckerkandl, and adrenal rests in the substance of the kidneys, the primary foci of Grawitz tumors. Adrenal cortical cell rests are sometimes encountered attached to the epididymes of the testes, but I have no record of primary tumors of adrenal tissue in this location. Limiting the discussion of adrenal neoplasia to that primary in the medullary parenchyma. the 1105 autopsies forming the basis of this study furnish two examples: (1) a neuroblastoma * having as its chief cell a unipolar neuroblast, a cell midway in its developmental position between the undifferentiated cells migrating from the ganglionic crest of the embryo and the highly differentiated chromaffin cells and sympathetic neurons of the adrenal medulla; and (2) a 2nd case,† a pheochromoblastoma, in which the chief cell was a variant of the highly differentiated chromaffin cells of the fully developed adrenal medullary parenchyma. As would be expected from their respective developmental positions, the neuroblastoma was highly malignant, widely metastasizing and without physiological activity, while the pheochromoblastoma was relatively benign, showing only local invasion and extension and presenting a very highly developed physiological activity manifested by episodes of hypertension of the paroxysmal type.

Abstracts of Reported Cases of Paroxysmal Hypertension

The medical literature includes reports of a number of cases of paroxysmal hypertension and the following case reports will be briefly abstracted.

Belt and Powell [6] described a syndrome characterized by paroxysmal hypertension and periodic tachycardia, pallor followed by a flushing of the skin, glycosuria, headache, nausea and vomiting, and pulmonary edema. The case reported is that of a Jewess aged

* A–1718, Walter Reed General Hospital. Washington. D. C.
† A–2018, Walter Reed General Hospital. Washington. D. C.

45 years. The patient died during a crisis accompanied by marked pulmonary edema. Autopsy revealed an adrenal tumor weighing 1000 gm. The chemical examination demonstrated 0.2 gm. of epinephrin per 100 gm. of tissue. The technic of the colorimetric estimation of epinephrin was that of Folin, Cannon and Denis.[7]

Labbé, Tinel and Doumer [8] report the case of a female, aged 28 years, who suffered from attacks of nausea and vomiting, three to four attacks a week. During these attacks the systolic blood pressure rose to 280 mm. Hg. Glycosuria was noted. The hypertension varied from day to day and from hour to hour. Pulmonary edema developed and the patient died. The left adrenal was replaced by a tumor mass about 6 cm. in diameter.

Labbé, Violle and Azérad [9] report a case of "paroxysmal sympatheticotonia" in a male patient aged 29 years, who died as the result of cerebral hemorrhage.

Mayo [10] reports the case of a female aged 30 years. The chief symptoms were nausea and vomiting, and cough with blood tinged expectoration. The crises were marked by paroxysmal hypertension during which the systolic blood pressure varied between 300 and 180 mm. Hg. The patient was operated upon and a pheochrome tumor (paraganglioma) was removed. The tumor mass measured 6 by 4 cm. and was located retroperitoneally mesial to the left kidney. The patient made a complete recovery.

Rabin [11] reports the case of a Polish woman aged 45 years. The clinical course was marked by episodes characterized by nausea and vomiting with rise in blood pressure up to 226/180 mm. Hg. Coma developed and the patient died. At autopsy an adrenal medullary pheochromocytoma was found which yielded 1.5 mg. of epinephrin per gm. of tissue.

Burgess, Waterman and Cutts [12] report the case of a Jewess, aged 25 years, who complained of palpitation associated with pallor and constipation. At the onset of the crises the pulse rose to 144 per minute; bradycardia accompanied by extrasystoles developed. Headache was severe. The pyelogram demonstrated a downward displacement of the right kidney. The blood sugar was 125 mg. per cent, and the non-protein nitrogen 31 mg. per cent. The Wassermann test was negative. The patient was operated upon and died almost immediately from pulmonary edema. During operation a tumor mass 9 cm. in diameter, soft and hemorrhagic,

was removed from the upper pole of the right kidney. The microscopic diagnosis was pheochromocytoma primary in the medulla of the right adrenal. No metastases were found.

Geschickter [13] reports a "benign paraganglioma" of suprarenal medullary tissue in a woman aged 53 years. Geschickter states: "In paragangliomas of the suprarenal glands, hypertension, hypotension, and vasomotor instability are not infrequently observed . . . the suprarenal cortex may be invaded and destroyed. . . ."

Ewing [14] classifies adrenal tumors as cortical and medullary. Medullary tumors of the adrenal are subgrouped as focal hyperplasia, neuroma ganglionare, neuroblastoma, and chromaffin cell tumors. He states that medullary chromaffin cell tumors form large masses. The sinuses are invaded but there are no metastases. The structure is composed of groups of round, oval and polygonal cells, most of which are small. Giant cells with single or multiple nuclei occur. Pigment is irregular in distribution. Homogeneous acidophilic cell inclusions are usually present.

Shipley [15] reports the case of a young married woman, aged 26 years, who complained of attacks characterized by cardiac palpitation, nausea and vomiting. Severe occipital headache was an increasingly troublesome symptom. Her blood pressure varied from 120/90 on admission, to 190/98, rising quickly to 219/110 and falling rapidly to 176/76 mm. Hg. The diagnosis of adrenal tumor was made but the side was not determined. The patient was operated upon, first on the left side, and the left adrenal was found to be normal; on the right side a tumor mass primary in the right adrenal was discovered and removed. The day following the second operation the patient improved. During convalescence the blood pressure remained low, 116/74 mm. Hg. Ten months later she reported herself to be free from previous symptoms. The mass removed weighed 115 gm. A small amount of cortical adrenal tissue remained extending over one side of the neoplasm. Microscopic sections showed the tumor to be composed of oval and polygonal cells arranged in small alveoli separated by capillaries. The diagnosis was paraganglioma.

In my opinion the term paraganglioma should be limited to tumors arising from retroperitoneal rests of adrenal medullary tissue, while neoplasia primary in the adrenal medullary parenchyma should be designated as pheochromocytoma or pheochromo-

blastoma, depending on the degree of differentiation manifested by the tumor cells.

Kelly and his associates [16] suggest the following reasons for the paroxysmal nature of the hypertension associated with pheochrome cell tumors of adrenal medullary tissue: (*a*) periodic hemorrhages into the substance of the tumor mass; (*b*) any unusual exertion, such as bending, expressing epinephrin from the neoplastic tissue; and (*c*) emotional reactions such as are believed to stimulate an increased output of epinephrin. They are of the opinion that the complete absence of signs of arteriosclerosis is of particular interest; this is evidence against the conception that epinephrin plays any part in the production of arteriosclerosis and essential hypertension. I do not entirely concur with the foregoing assumption; although epinephrin probably does not play a primary rôle in essential hypertension, still I believe that a secondary physiological function is maintained by the adrenal medullary parenchyma in essential hypertension. They report the case of a married woman, aged 37 years, who complained of episodes during which the blood pressure rose from 90/70 to 280/160 mm. Hg. During these episodes extreme cutaneous pallor developed and the patient was nauseated. The attacks lasted about 15 minutes. The pulse was not appreciably accelerated. The blood sugar was 118 mg. per cent. Indefinite resistance and tenderness were elicited above the right kidney, which was palpable. The patient was operated upon and a tumor mass was located cephalad to the upper pole of the kidney. The mass was 10.5 cm. in diameter and weighed 240 gm. On chemical examination the neoplastic tissue yielded approximately 300 mg. of crystalline epinephrin. Postoperatively the convalescence was uneventful and no further episodes occurred.

Evans [17] reports the case of a girl, aged 12 years, who died during an episode of paroxysmal hypertension. Autopsy revealed a pheochrome cell tumor primary in the medullary portion of the left adrenal.

Wells and Boman [18] note that the characteristic symptoms of 13 patients completely disappeared following surgical removal of benign tumors composed of epinephrin-producing cells such as are normally present in the adrenal medulla. They state that during severe attacks there may be failure of the left ventricle of the heart, manifested by cyanosis, coughing with blood tinged sputum.

and that the sudden transient spasm of the arterioles of the body accounts for many of the manifestations of this condition. The attacks tend to increase in severity and frequency. They report the case of a female, a school teacher aged 30 years. The initial symptom was a pounding of the heart like a sledge hammer. During these attacks the blood pressure rose to 180/140 mm. Hg. and then dropped suddenly. The patient died during anesthesia for attempted appendectomy. Autopsy demonstrated a tumor primary in the right adrenal and weighing 20 gm. Chemical examination of the neoplastic tissue showed 1 per cent of epinephrin.

The 12 cases of pheochrome cell tumors, including the following case, may be classified as follows: females, 10 (2 Jewesses); males, 2; average age 34 years. Two of the tumors were primary in retroperitoneal rests of adrenal medullary tissue (paragangliomas); 5 were primary in the right adrenal medulla and 2 in the left; in 3 of the cases abstracted the side involved is not indicated. In 3 cases transient glycosuria was noted. The 2 male patients died as the result of cerebral hemorrhage. Three of the patients died during crises as the result of marked pulmonary congestion and edema. Four of the female patients were operated upon; 1 died immediately following operation, and 3 made complete postoperative recovery without subsequent episodes.

Case 2. Paroxysmal Hypertension

Clinical History: The patient, A. D. M., was a white male, a veterinarian of the Medical Department of the U. S. Army. There were no previous illnesses other than the usual diseases of childhood. He used no alcohol and smoked in moderation. The family history revealed no chronic cardiovascular disease. The patient was admitted to the hospital Nov. 15, 1929, stating that he had passed a large tarry bowel movement. On admission to the hospital he was pale and anemic in appearance. The blood pressure was 108/60 mm. Hg. He was treated on the basis of an emergency duodenal ulcer and was discharged on March 17, 1930.

The patient had enjoyed good health from March, 1930, to November, 1935. On Nov. 29, 1935 he caught cold, complained of headache and was nauseated. He was hospitalized, placed on the Sippy regimen, and discharged later improved. On December 7th he suddenly felt cold and his head ached. Within a few hours he became delirious for about 48 hours, and after complete consciousness returned he remarked that his vision had become hazy. The blood counts, the Wassermann reaction, the spinal fluid examinations and the results of blood chemistry were all negative. The blood pressure on Jan. 5, 1936 was 172/118 mm. Hg.

The patient was transferred to the Walter Reed General Hospital, Washington, D. C., on Feb. 4, 1936. At this time he was 45 years old. On admission

the pupils were equal and reacted to light and accommodation. The blood pressure was 154/96 mm. Hg. On February 7th, after an enema, the patient became nauseated and complained of severe headache; following catharsis (castor oil) the headache subsided and he felt better. On March 4th nausea and vomiting recurred accompanied by severe headache. A spinal tap was made; the spinal fluid was clear, pressure 20 mm. Hg. A brain tumor was considered as a possibility. On March 16th the urine became bloody; the clinical record states that "hypernephroma must be considered." On March 19th the urine was free from blood. On March 23rd the case was considered as one of "undoubtedly essential hypertension with renal arteriolarsclerosis." On March 27th hematuria occurred again and epididymitis (left) developed. By April 18th the patient's condition improved; he had gained in weight and was out of bed in a wheel-chair. On May 8th the headaches returned and became increasingly severe; he was nauseated and vomited frequently. The clinical record on June 5th notes: "The patient remarked that he felt better after saline infusions." On July 13th another crisis developed; the clinical notes state: "The distressing spells are coming on more frequently; the attacks arise when the patient is constipated and are initiated by headache, nausea and vomiting. The subjective symptoms are relieved by saline infusions and by castor oil. During the attacks the extremities are cold." On October 22nd an attack began; the patient vomited and became restless and irrational. There was involuntary urination. The blood pressure registered 200/130 mm. Hg. The urea nitrogen was 15 mg. per cent. The patient closed his right eye with difficulty. The next day right hemiplegia developed; the pulse became feeble and the respirations stertorous. The patient died at 4.40 P.M. on Oct. 23. 1936. The duration of the final illness was approximately 11 months.

The variations of the blood pressure readings are depicted in Graph 2. Throughout the final illness there was no elevation of temperature except during the last 2 days when the temperature rose to 102° F. The pulse varied between 80 and 110 beats per minute. At no time during the final illness were abdominal pain and tenderness elicited.

Laboratory Data: A roentgenogram on Feb. 6, 1936, showed that the cardiac shadow was normal in size, shape and position; the lungs were essentially normal. On August 31st flat plates of the abdomen were negative. No pyelograms were made. Some of the specimens of urine revealed 2 plus albumin, sugar negative, many leukocytes and erythrocytes, but no casts. The blood count on February 5th revealed: erythrocytes 3,960,000; hemoglobin 70 per cent; total leukocyte count 10,000; polymorphonuclears 68 per cent; eosinophils 3 per cent.

Postmortem Examination *

The body was that of a poorly nourished white male, aged 45 years. The body length was 176 cm., the weight approximately 55 Kg. The voluntary musculature was fairly well developed. The pupils were equal at 3 mm. The neck and chest were of normal contour. The anterior abdominal wall was flat. No edema of the feet or ankles was present.

* A–2018, Walter Reed General Hospital, Washington. D. C.

Thyroid: The thyroid weighed 29 gm. On microscopic examination the acini were large and the colloid homogeneous. The epithelium was of the cuboidal and flat types. There was no lymphocytic reaction. No thymus rest was encountered.

Lungs: Microscopic examination of the pulmonary tissue revealed an acute bronchiolitis and peribronchiolitis.

Heart: The heart weighed 385 gm.; the subepicardial fat was scant in amount. The wall of the left ventricle measured 2.2 to 1.5 cm. in thickness. The aortic ring was 7.3 cm. in circumference; the mitral ring 10 cm. The valves were normal. The coronary arteries and the aorta presented moderate intimal thickening, but no lime salt deposits or ulceration were present. The thoracic aorta measured 5.3 cm. in circumference and the abdominal aorta 4 cm.

Stomach and Intestines: Normal in appearance. The colon contained large masses of hard fecal material.

Spleen: The spleen was small, weighing 50 gm.

Adrenals: The left adrenal weighed 7 gm. and was normal in size and contour. The retroperitoneal fat surrounding the left adrenal included small aberrant groups of adrenal cortical parenchyma. On microscopic examination the cells of the left adrenal cortex were rich in lipoids and the medullary portion showed no alteration from the normal.

Tumor Mass Replacing the Right Adrenal: A tumor mass, 12 by 9 cm. in diameter, weighing approximately 200 gm. (section of the inferior vena cava is included in the gross specimen illustrated in Figure 1) was present in the right adrenal. The mass shelled out easily from the surrounding fat but was firmly united to the wall of the inferior vena cava and to the thickened overlying parietal peritoneum. Neoplastic tissue appeared in the lumen of the cava in the form of a nodule about 0.5 by 2 cm. The outer surface of the tumor was coarsely nodular, the consistence firm, and the cut surfaces brownish gray. After remaining in Kaiserling I the neoplastic tissue assumed a darker brown hue. The free surface of the parietal peritoneum overlying the tumor mass presented innumerable nodules varying in size up to 0.25 cm. The cut surfaces of the peritoneal nodules had the same gross appearance as the cut surfaces of the primary growth. Similar nodules were found on the under surface of the right leaf of the diaphragm

cephalad to the right adrenal tumor mass, and attached to the free surfaces of both leaves of the mesentery of the small intestine.

Microscopic Examination of the Newgrowth: The growth is very cellular; the cells are arranged in groups (alveoli), round to oval in contour, and are located in close proximity to thin walled blood channels (Figs. 2–4). The cells are quite pleomorphic, fusiform, cylindrical and pear shaped, and in some instances are united to the supporting fibrillary scaffolding by stem-like protoplasmic processes. The cells vary greatly in size and shape. The cytoplasm of the cells is amphophilic and finely granular; some of the cells contain unstained vacuoles and in other cells there are acidophilic hyaloid inclusions. The nuclei of the tumor cells are mostly small, circular in outline and eccentric in position; the linin network is poorly differentiated. A few cells present larger oval, hyperchromatic nuclei and scattered cells have two or more nuclei. Many of the neoplastic cells present an atypical nuclear division; the nuclear chromatin is divided into from 6 to 50 hyperchromatic bodies, oval, rod and dumbbell shaped and massed in the central zones of the dividing nuclei. In scattered areas throughout the newgrowth the neoplastic tissue contains a dull brown, coarsely granular pigment; the pigment gives a negative iron reaction with potassium ferrocyanide and is consequently regarded as melanin. In sections stained by Bielschowsky's method the fibrillar stroma includes no argentaffin fibrils; the tumor cells are silver-positive, and the cytoplasm of the cells appears as a fine silver gray dust including coarser particles of reduced silver.

Kidneys: The right kidney weighed 145 gm., the left 140 gm.; combined renal weight 285 gm. The weight of the heart (385 gm.) divided by the combined renal weight (285 gm.) equals 1.35, as compared with the cardiorenal ratio of 2.39 in the case of essential hypertension reported above.

Urinary Bladder: The wall was thickened and the trabeculae prominent. No cellule formation was present. The bladder mucosa was studded with innumerable pale gray, slightly raised points the size of the head of a common pin. The trigone was low and narrow and the ureteral orifices normal. The microscopic picture presented by the bladder mucosa indicated a chronic follicular cystitis.

Left Testis: The epididymis was thickened and indurated and cross sections revealed numerous small abscesses.

Brain: The brain weighed 1440 gm. The contour was normal and the pia normal. Sectioning the brain showed an area of recent hemorrhage about 2 cm. in diameter located in the optic radiation of the left hemisphere of the forebrain. The hemorrhage was surrounded by a wide zone of edema with innumerable points of secondary capillary bleeding.

Pituitary: The pituitary was normal in size and contour. The basilar artery, the circle of Willis and the cerebral arteries presented normal walls. The contents were fluid blood.

Anatomical Diagnoses: (1) Chromaffin cell tumor (pheochromoblastoma) primary in the medullary portion of the right adrenal; neoplastic invasion of the lumen of the inferior vena cava; implantation metastases on the free surface of the overlying parietal peritoneum and on the contiguous peritoneal surface of the right leaf of the diaphragm; small implantation metastases on the free surfaces of both leaves of the mesentery of the small intestine, but no other distant metastases. (2) Cerebral hemorrhage, single, optic radiation of the left hemisphere of the forebrain. (3) Cystitis (urinary bladder), chronic, follicular; and (4) epididymitis, subacute, suppurative (left testis).

Comment

The blood pressures in the above case are charted from 1924 to 1936 inclusive and are incorporated in Graph 2. The graph indicates that during 1930 there was a slight rise in both the systolic and the diastolic readings. The initial hospitalization of the patient was Nov. 15, 1929; the blood pressure of that date was 108/60 mm. Hg. From the onset of the final illness, Nov. 29, 1935, to death, which occurred Oct. 23, 1936, there were abrupt alterations in the blood pressure marked by daily and hourly changes, making the blood pressure graph resemble a temperature chart in a case of septicopyemia. The final illness was subacute in nature and the duration was approximately 11 months.

In explanation of the constipation and headache, two of the more prominent and distressing subjective manifestations, Wiggers,[19] in referring to the effect of epinephrin on muscle, writes that excitatory effects result on the pyloric and ileocolic sphincters.

Inhibition of contractions and tonus occurs in the gastrointestinal tract. In reference to headache, he states that increase in intraventricular pressure is believed to be the most common cause of headache. Intracranial and intraventricular pressure are simultaneously increased as a result of an increase in arterial pressure or reflex dilatation of the cerebral vessels. The headache so frequently associated with great hypertension becomes explicable on the grounds that increased arterial pressure *per se* increases brain volume and perhaps also increases the secretion of cerebrospinal fluid by the choroid plexus.

The episodes characterizing cases of paroxysmal hypertension associated with pheochrome cell tumors primary in the adrenal medullary parenchyma are, in my opinion, wholly explicable on the ground of the accumulation, in the substance of the newgrowth, of the secretory product (epinephrin) of the tumor cells. In any newgrowth there is not the normal physiological nerve control of the parenchyma and the normal mechanical removal of the secretory products by sinusoids is lacking; therefore the secretory products (if such be formed) will accumulate until large amounts gather and are "spilled over" into the capillary system of the neoplasia.

Almost all of the case reports illustrating paroxysmal hypertension (including that of the author) note some degree of tachycardia; some of the case reports indicate bradycardia. The pulse rate, in my opinion, indicates the amount of epinephrin "spilled over" during the episodes. (1) If the amount of epinephrin liberated be very great, sufficient to escape complete oxidation during its passage through the lungs, bradycardia will result. (2) If the amount of epinephrin liberated during the episodes be entirely or almost completely oxidized during its passage through the pulmonary circulation, tachycardia will result. Marey's law, quoted from Howell,[20] reads as follows: "Marey (La Circulation du Sang, Paris, 1881) gives the two following laws: (1) Whatever increases or diminishes the *force* with which blood is driven from the heart toward the periphery will cause the velocity of the blood and the pressure in the arteries to vary in the same sense. (2) Whatever increases or diminishes the *resistance* offered to the blood in passing from the arteries to the veins will cause the velocity and the arterial pressure to vary in an inverse sense. That is, an increased

resistance diminishes the velocity in the arteries while increasing the pressure, and *vice versa*." The slowing of the pulse after the intravenous administration of adrenalin is probably accounted for by secondary reflex vagus excitation because it does not occur (experimentally) after preliminary vagus section.

Starling [21] states: "The point of attack of adrenalin appears to be in the muscular or glandular tissue, since its effects may not only be obtained after destruction of the cord and sympathetic plexuses, but even obtained (and in an exaggerated degree) after time has been allowed for the peripheral (post-ganglionic) fibers to degenerate as a result of extirpation of the corresponding ganglia."

Referring to the transient glycosuria noted during or immediately after episodes of paroxysmal hypertension, I believe the glycosuria to be strictly renal in type, due to the sudden increase in pressure in the "arterial mirabile" of the kidneys (glomerular tufts of the renal corpuscles, including the afferent and efferent glomerular arterioles). Starling states that adrenalin acts directly on the liver cells, inciting a rapid discharge of glycogen with resulting hyperglycemia and glycosuria. In the 12 cases of paroxysmal hypertension cited, transient glycosuria was noted only in 3, and the highest blood sugar estimation was 125 mg. per cent, within the normal limits.

Summary and Conclusions

The main object of the foregoing discussion of essential hypertension and paroxysmal hypertension, with reports of contrasting cases, is to assist in the differential diagnosis between two conditions which may be said to be similar yet entirely different from one another. The early recognition of the physiological response to pheochrome cell tumors primary in the adrenal medullary parenchyma is of great therapeutic importance by reason of the complete cure afforded by surgical intervention in a fairly high percentage of cases, contrasting with the poor prognosis offerable individuals with essential hypertension even of the benign type.

The following are the more apparent differential points dis-

tinguishing the two conditions (essential and paroxysmal hypertension) as exemplified by the case reports:

	Essential Hypertension	Paroxysmal Hypertension
(*a*) Family history	Often strongly positive for chronic cardiovascular disease	Usually negative
(*b*) Previous illness	Previous hospitalization for cardiovascular disease may be listed	Usually irrelevant
(*c*) Present illness	Marked chronicity	Course relatively short and marked by episodes increasing in frequency and severity
(*d*) Special examinations		
X-Ray	Left ventricular cardiac hypertrophy. The aortic arch may be widened	Heart not necessarily enlarged; aorta may be normal
Electrocardiogram	Left axis deviation and T wave negativity may be noted	Not necessarily altered from normal except during episodes
Blood pressure	See Graph 1	See Graph 2
Pyelogram	Negative	Downward displacement of kidney on the side of the adrenal tumor mass may be noted
Blood counts	Slight secondary anemia	May be normal
Urine examinations	Traces of albumin with hyaline casts may be reported	Normal except during episodes when there may be transient renal glycosuria
Retinoscopy	Marked retinal angiosclerosis with hemorrhages	Retinal hemorrhages may be noted
(*e*) Causes of death	Cerebral accident; coronary accident; uremia; intercurrent disease. Death usually during the fifth or sixth decade of life	Cerebral accident which may be atypical in location. Congestive heart failure (left ventricular failure). Death during the fourth decade of life, at 34 years average of cases listed

Other conditions which must be ruled out in arriving at the recognition of pheochrome cell tumor primary in the adrenal medullary parenchyma include: (1) Hypertension associated with renal arteriolarsclerosis, the so-called malignant phase of essential hypertension; (2) renal hypertension associated with the secondary contracted kidneys seen in chronic glomerular nephritis; (3) congenital and acquired forms of renal maldevelopment, in-

cluding polycystic kidneys; (4) neoplastic hyperplasia of the adrenal cortical parenchyma (hypernephroma and Grawitz tumors); and (5) brain tumors.

The reported case of paroxysmal hypertension was not diagnosed ante mortem, having been overlooked by competent observers; however, the consolation remains that the pheochromoblastoma found at autopsy was quite inoperable, due to the fact that (see Figure 1) it had invaded the lumen of the inferior vena cava and was not entirely benign in character, innumerable small implantation metastases already having made their appearance.

In the foregoing article the subject of essential hypertension has hardly been touched upon and it is my intention, in a series of subsequent articles, to report contrasting cases of essential hypertension of the so-called malignant type and nephritic hypertension, and to discuss and illustrate the more commonly encountered syphilitic cardiovascular reactions found at autopsy.

NOTE: I wish to express my appreciation to the Curator of the Army Medical Museum, Washington, D. C., for his assistance in the necessary microphotography.

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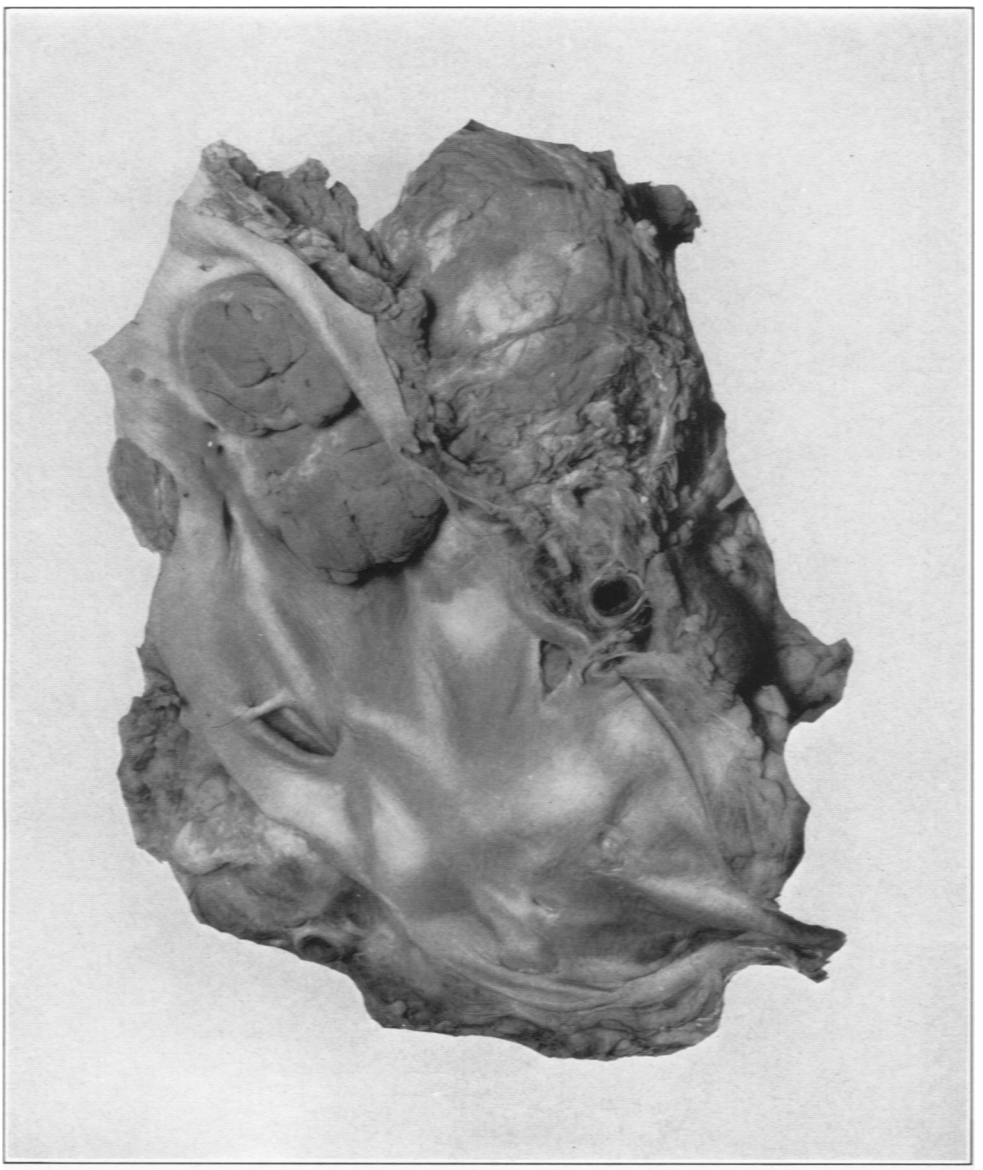
DESCRIPTION OF PLATES

PLATE 110

FIG. 1. Pheochromoblastoma primary in the medullary portion of the right adrenal (Case 2, A–2018 W.R.G.H.). Posterior aspect of the tumor mass. The inferior vena cava is opened longitudinally. The growth invades the lumen of the cava in the form of an ovoid nodule about 0.5 by 2 cm. The neoplastic tissue was firm in consistence, the cut surfaces brownish gray, changing to a darker brown after having been immersed in Kaiserling I.

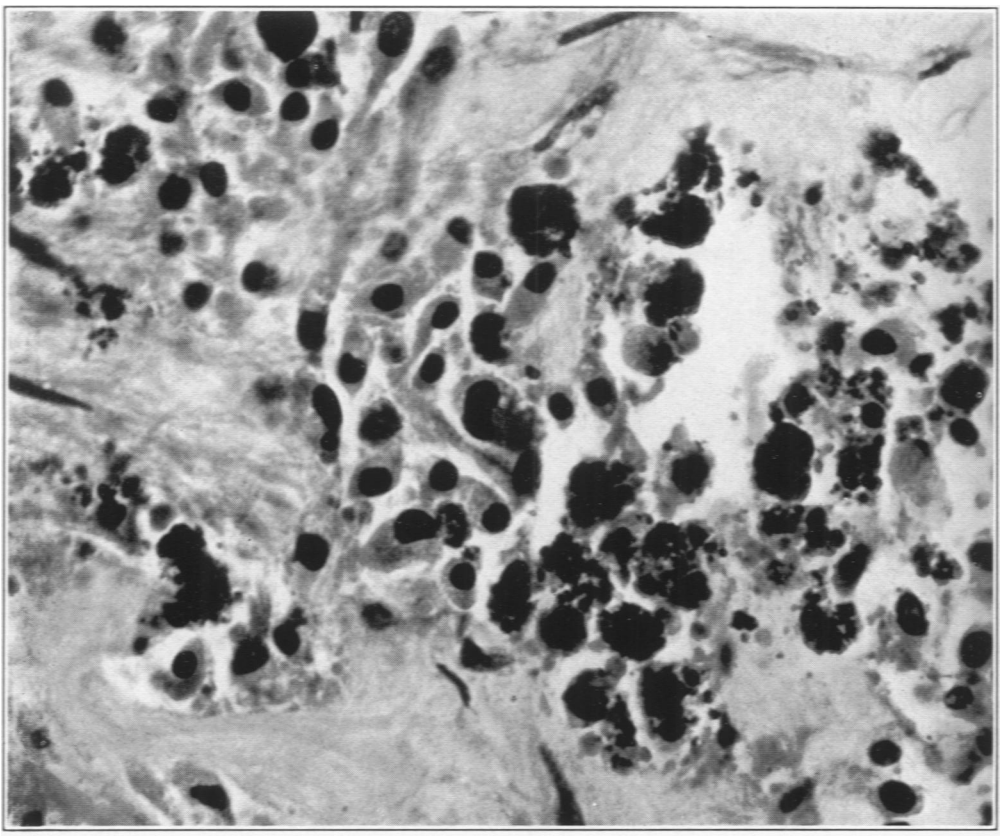


Foucar Essential and Paroxysmal Hypertension

PLATE III

FIG. 2. Pheochromoblastoma primary in the medullary portion of the right adrenal (Case 2). Microphotograph showing one of the scattered collections of iron-free pigment regarded as melanin. Hematoxylin-eosin stain. × 800.

FIG. 3. Pheochromoblastoma primary in the medullary portion of the right adrenal (Case 2). Microphotograph showing the irregularity in the size of the nuclei, the poorly differentiated nuclear detail, the tendency to eccentricity in nuclear placement, and the stippling of the cytoplasm of some of the cells. Hematoxylin-eosin stain. × 810.



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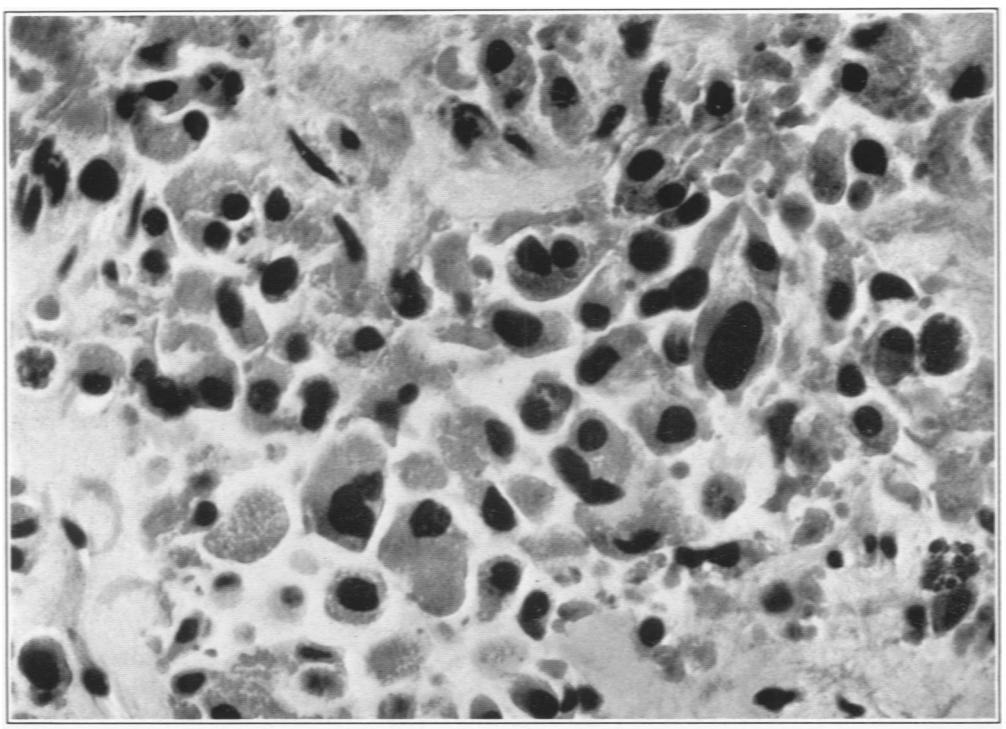

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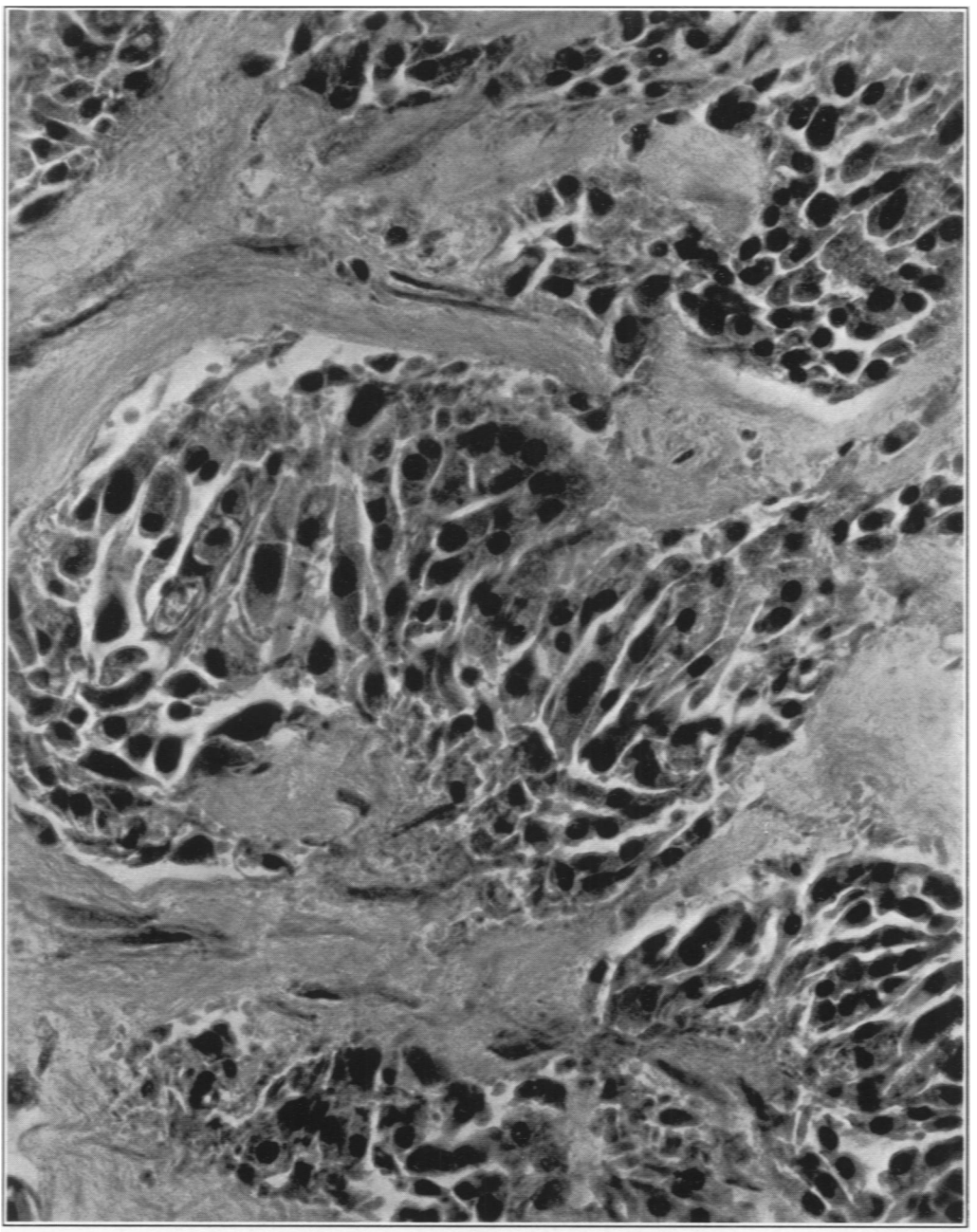
PLATE 112

FIG. 4. Pheochromoblastoma primary in the medullary portion of the right adrenal (Case 2). Microphotograph showing the alveolar arrangement of the tumor cells. The nuclei of the cells are hyperchromatic and the nuclear details are poorly differentiated. The interstitial stroma consists of delicate collagenous fibrils, glial-like in appearance. Hematoxylin-eosin stain. × 850.



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