PHEOCHROMOCYTOMA WITH DEMONSTRATION OF PRESSOR (ADRENALIN) SUBSTANCE IN THE BLOOD PREOPERATIVELY DURING HYPERTENSIVE CRISES

EDWIN BEER M.D., F. H. KING, M.D., AND M. PRINZMETAL M.D.
NEW YORK, N. Y.

FROM THE SERVICES OF THE MOUNT SINAI HOSPITAL, NEW YORK, N. Y.

THE following case report is placed on record to call attention to this clinical entity and to report some interesting observations made during the stay of the patient in the wards of the hospital and during the follow up after her discharge. Though Kohn described the chromaffin system in the abdomen about 40 years ago, judging from the literature, interest in neoplastic changes in this system has stirred the profession only recently. Case reports[1] of tumors derived from this system, both in the medulla of the adrenal and in the adjacent sympathetic nerves, though still exceedingly rare, are becoming more frequent during recent years, and every new case that is published is helpful to better understanding and earlier recognition of these curious growths, called paragangliomata or pheochromocytomata. To date only six cases of pheochromocytomata in the adrenal gland have been recorded, after successful removal of the growth. In addition, two cases have been reported in which the growths were outside the adrenal gland in the local sympathetic distribution (Mayo-Leriche Bauer). The case here recorded involved the left adrenal gland and operative removal of the large pheochromocytoma seems to have produced a complete relief.

Case Report.—A white female, single, age 26, was admitted to the Mount Sinai Hospital with the history of having nine years previously first noted the insidious onset of infrequent sensations of mild fatigue, throbbing headache and sweating at intervals. These symptoms were attributed to hyperthyroidism and she was subjected to subtotal thyroidectomy, without subsequent relief. Microscopic examination of the removed thyroid tissue proved it to be an adenocarcinoma. Sections obtained by request were examined by the pathologist at this hospital, who concurred in the diagnosis.

Her symptoms gradually increased in severity and about seven years ago she noted that the distal phalanx of the right index finger would, on occasion, suddenly become perfectly white, changing to a purple color which in turn would become replaced by an angry red. During the two years prior to admission, this phenomenon had extended to involve all the digits of both hands, and to a lesser extent the toes. For three years she had noted that the distal portion of the upper and lower extremities, as well as the tip of the nose, constantly felt cold, regardless of the season. Other cutaneous changes noted were a reddish-cyanotic discoloration of the skin around the ankles and a reddish-purple mottling and reticulation of the skin of the upper and lower extremities, most marked about the knee joint.

The patient complained chiefly of attacks in which the symptoms presented themselves in a fairly definite sequence. These episodes began with nausea and an intense, generalized headache. Her hair felt as though it were standing on end and being

Submitted for publication February 20, 1937.

pulled. This was soon followed by definite precordial throbbing with a subjective feeling of markedly exaggerated pulsations of the vessels of the neck. She was dyspneic and on occasions found herself gasping for breath. Her fingers then underwent the series of color changes already described. These symptoms soon abated, leaving her drenched with perspiration and utterly fatigued. Such attacks lasted about five minutes. Until about three months before entering the hospital, these episodes would occur once a week. After that they gradually increased in frequency and severity so that just before hospitalization, they were occurring almost every half hour. She had been informed by her physician two months previously that her blood pressure was 190-200. During the past four years, there had been a gradual loss in weight of 18 pounds, notwithstanding an excellent appetite.

The family history was of unusual interest. Both her mother and sister had had thyroidectomies; moreover, an older sister who had also had a thyroidectomy died at the age of 28, with a clinical picture strikingly suggestive of that presented by the patient herself, and which was believed to have been (according to the hospital record) a rare disturbance of the sympathetic system.

Physical Examination.—The patient was a thin, underdeveloped, young, white female, who appeared chronically ill and sweated profusely. The fundi showed a very slight thinning of the arteries with increased light reflex. There was a well healed collar incision at the base of the neck. The lungs were normal. The heart was not enlarged and its sounds were of good quality. The aortic second sound was louder than the pulmonic. A rough systolic murmur was present at the base. The radial vessels seemed, on palpation, to be moderately sclerotic. The blood pressure at the initial examination was 230/180. A slight fine tremor of the outstretched fingers was present. Abdominal examination was negative.

She continued to have attacks as previously described, in the hospital. At such times her blood pressure rose from 140/100 to 280/200. On the basis of this clinical picture, a presumptive diagnosis of an adrenal paraganglioma was made.

Laboratory Data.—The blood count was normal. Urine examination showed a normal concentration. Chemical examination of the blood showed the urea to be 25 mg., sugar 175 mg., cholesterol 425 mg., and sodium 138.3 milli-equivalents. The basal metabolic rate was, on three different occasions, plus 69, 39 and 27 per cent. The electrocardiogram showed a sinus tachycardia with a rate of 115 per minute, left ventricular preponderance, QRS of high voltage, slight depression of the R-T transition in leads 1 and 2, and upright T4. Oscillometric determinations showed diminished peripheral oscillations, there being only a flicker at the ankle level. There was a diminution of skin temperature of the peripheral portions of the body, as determined by dermotherm readings. The Janney test showed a fasting blood sugar of 65 mg. per 100 cc., with a rise to 240 mg. at the end of one hour, followed by a fall to 50 mg. at the end of three hours. The patient was given an insulin test, consisting of the injection of ten units of insulin while fasting, the fasting blood sugar being 105 mg. per 100 cc. One and one-half hours later, the patient went into profound hypoglycemic shock, the blood sugar at this time being 15 mg. per 100 cc. She, however, responded promptly to intravenously administered glucose. Epinephrine sensitivity was determined by the subcutaneous injection of two minims of adrenalin (1-1000), and there was an unusually high rise in the blood pressure, indicating an abnormal sensitivity. Investigation of the urine for hormones disclosed a slight amount of gonadotropic hormone but no estrin.

Demonstration of Pressor Substance in the Blood during Hypertensive Crises.—An investigation was undertaken to demonstrate the presence of a pressor substance in the blood. During an attack induced by exercise, at which time the systolic blood pressure was over 300, 200 cc. of blood were removed from the antecubital vein and its pressor effect compared with the blood of a control subject, by a modification of the Pissemski method of perfusion of the denervated rabbit's ear. This method had been found to be

sensitive to epinephrine in as high a dilution as 1 in 100,000,000. Not more than 35 minutes elapsed between the phlebotomy and the experiment.

A constant inflow pump was used. If the vessels constrict, the fluid in the manometric tube rises, and vice versa. The perfusion was started first with control plasma. After a base line was reached, the subject's plasma was substituted. A remarkable pressor effect resulted. This was repeated three times (Chart 1). The ear was then perfused with 1-300,000 solution of ergotamine tartrate. Following this procedure, it was again perfused with the two plasmas. The pressor effect had now disappeared (Chart 1). These observations demonstrated the presence of an active pressor substance in the circulating blood, which, in view of the reversal effect of ergotamine, is almost certainly adrenalin.

In view of the history and observations made on the Medical Service, it was evident that the patient was probably suffering from a pheochromocytoma of the adrenal medulla

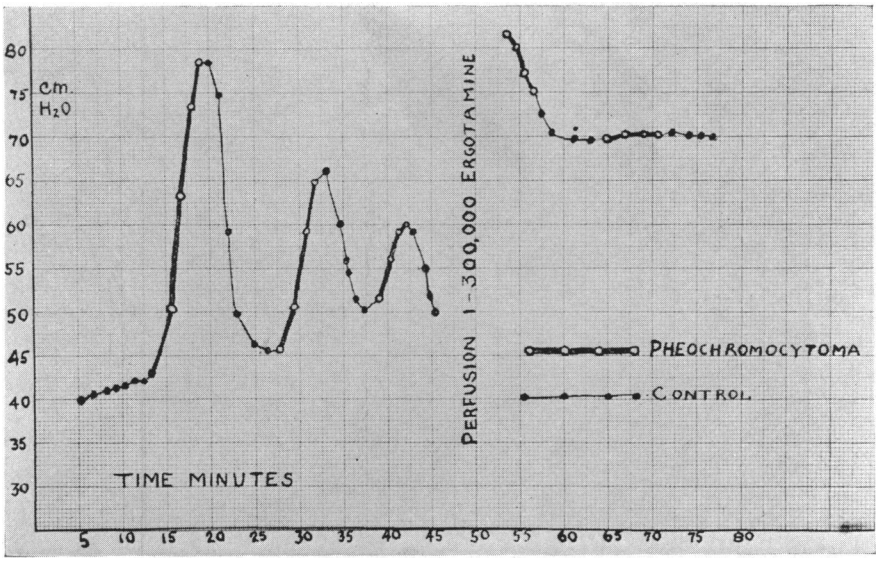

CHART 1.—Illustrating pressor effect of patient's plasma when perfused through denervated rabbit's ear and the reversal effect of ergotamine.

or adjacent sympathetic nerves. Before surgical removal could be attempted, however, it was necessary to determine which side was involved. One of the flat roentgenograms of the abdomen showed a diffuse but rather homogeneous shadow above the position of the left kidney; a retrograde pyelogram of this side showed that the left kidney had been pushed down, so that the pelvis was opposite the body of the third lumbar vertebra, and the upper calix showed definite pressure from above downward (Fig. 1). To outline the adrenal tumor, which was thought to be on the left side, a perirenal insufflation was undertaken by Doctor Mencher, which, in the anteroposterior and even better in the lateral view, outlined the left kidney and the large adrenal tumor situated directly above it, but separated from the kidney's deformed upper pole by a narrow linear gas band (Figs. 2 and 3). Studies of the right kidney showed it to be normal.

Operation.—May 29, 1935. Preoperative Diagnosis: Left adrenal pheochromocytoma. Anesthesia, avertin, supplemented by gas-oxygen. Intravenous glucose drip was begun before the operation. The kidney was readily located through a left lumbar incision. Above it, a very large, more or less spheroidal mass, occupying the region of the adrenal gland, was palpated and found displacing the kidney downward. The vascular pedicle of the kidney was seen to run into the capsule of the adrenal tumor, and a loop was

FIG. 1.—Retrograde pyelogram of the left kidney showing depressed kidney with compression of the calices in the upper pole.

FIG. 2.—Anteroposterior roentgenogram after perirenal insufflation, outlining clearly the large left adrenal tumor. Left kidney is surrounded with air and Gerota's fascia is filled with air.

FIG. 3.—Lateral oblique roentgenogram after perirenal insufflation, showing clearly the adrenal tumor, surrounded by the injected air, and below the adrenal tumor the much smaller kidney mass. Here again Gerota's space is full of injected air.

passed around the vessels, without tying them. Attempts to pull the renal pedicle toward the midline showed that it was impossible to separate the vascular structures from the adrenal tumor, and the ligature about the vessels was tied and the kidney removed, thus properly exposing the tumor, which ran up under the left leaf of the diaphragm. A number of vessels were tied during the delivery of the adrenal mass, which was about the size of a large grapefruit. The tumor was finally sufficiently liberated to afford access to its pedicle, which consisted of a very large vein, about one and one-half centimeters in diameter, which could be felt crossing the aorta, running into the vena cava.

Despite these manipulations, it was interesting to note that repeated blood pressures taken throughout the operation failed to show any rise, as one would have expected as the result of throwing adrenalin into the general circulation. During the operation at one time the systolic blood pressure dropped to 80. The operation was practically bloodless, and the wound was closed in layers in the usual way, with a small rubber drain. Following the operation, the patient was given a transfusion on the operating table.

The patient withstood the operation very well and, though somewhat shocked, made an uneventful recovery. The wound healed by primary union, except for slight retention.

Pathologic Report.—Macroscopic Examination: The specimen consisted of a globoid mass, weighing 290 Gm. and measuring 9 x 9 x 6 cm. (Fig. 4). The mass was well encapsulated. The capsule averaged 1 Mm. in thickness and its external aspect was rather smooth and even, except for scattered (1-3 cm. in diameter) projecting bosses. Along one edge of the specimen were a few fragments of yellowish brown tissue, which morphologically resembled adrenal cortex. In one portion immediately beneath the capsule was a nodule, the surface of which was dark brown-white. Its cortical rim was light yellow and bore a striking resemblance to minute adrenal glands. On section, the basic structures of adrenal gland, from which this mass presumably originated, were not distinguishable. Sectioned surface was fleshy in appearance and consistency. The surface, although rather smooth, consisted of irregularly sized lobules due to the presence of scattered smooth, delicate connective tissue strands. The surface further was irregularly mottled dull yellowish-pink, with innumerable flame-shaped rounded and less regular hemorrhagic zones (old and recent). In addition, there were several pea-sized and larger necrotic foci.

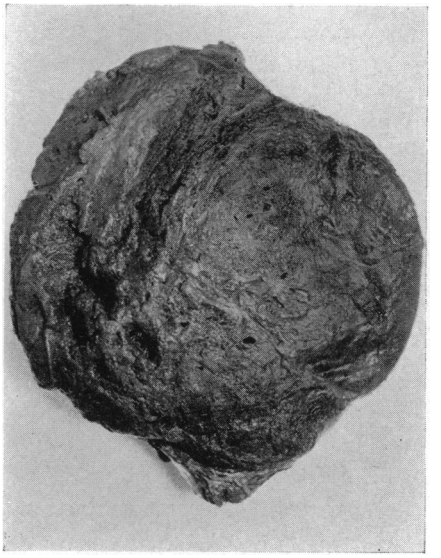

FIG. 4.—Gross appearance of cross-section of large adrenal tumor, which measures 9 x 9 x 6 cm. On the surface of the tumor are irregular projections made by the remains of adrenal cortex.

Microscopic Examination.—Sections stained with hematoxylin and eosin revealed the tumor to be composed of nests and anastomosing bands of round, spindle-shaped, and large polygonal cells, separated by very thin strands of connective tissue containing small blood vessels. Several areas of hemorrhage were noted, located mainly at the periphery. The cytoplasm of the tumor cells was granular and basophilic. The nuclei varied markedly in size and some of them appeared pyknotic. Sections of tissue fixed in Zenker's fluid showed a sparse distribution of brown colored pigment granules within the cytoplasm of the tumor cells, confirming the chromaffin nature of the growth. Between the cells and within the cytoplasm of some of them were noted ovoid bodies,

having a hyalin appearance and staining deeply with eosin. Stained with azocarmine, these bodies had a grayish-blue color and with phosphotungstic and hematoxylin they took a mahogany or light brown color. Only an occasional mitotic figure was noted. No ganglion cells were present. Sections stained for glycogen did not disclose this substance, nor was fat demonstrated after staining with sudan (Fig. 5). Sections of the removed kidney showed only mild arteriosclerosis. *Diagnosis:* Pheochromocytoma and kidney arteriosclerosis.

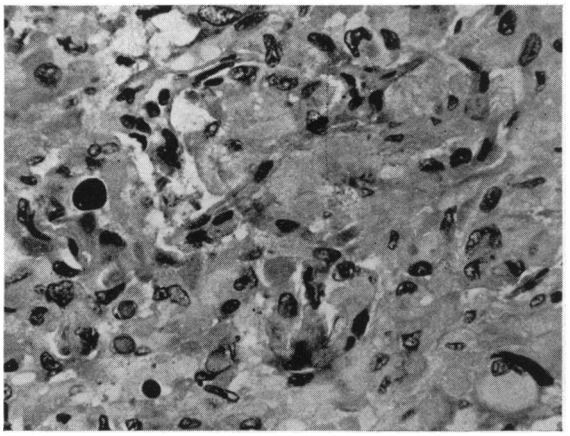

FIG. 5.—Histologic appearance of tumor (hematoxylin and eosin stain). Note deeply staining, hyalin-like body.

Further studies of the removed tumor were made by Doctor Frank, who was unable to demonstrate any gonadotropic hormone in the tumor tissue. A saline extract was made of the tumor tissue, which caused marked blanching when applied to a slightly scarified skin, showing that it contained an active constrictor element.

Postoperative Course.—The patient was considerably improved. There were no more systemic episodes and the blood pressure remained at 125/85. The previous cutis reticularis and discoloration of the skin above the ankles were no longer present. The tachycardia was much less marked. Her eye grounds still showed slight thinning of the vessels.

The laboratory procedures, done preoperatively, were repeated following the patient's return to the Medical Service, and the data obtained were as follows:

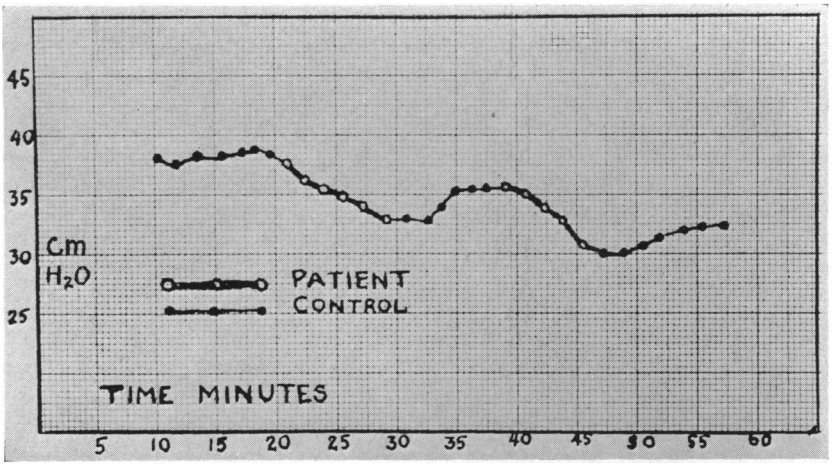

CHART 2.—Illustrating absence of pressor effect of patient's plasma following operative removal of tumor.

Postoperative Laboratory Data.—The basal metabolic rate on two occasions was minus 1 and 17. Chemical examination of the blood disclosed a fall of the urea to 11 mg. The blood sugar was 75 mg., and the total cholesterol had fallen to 270 mg. The blood count showed a moderate secondary anemia. The electrocardiogram was

unchanged. Oscillometric measurements still showed a diminution of peripheral pulsations, but they were more marked than preoperatively. There was an increase in peripheral skin temperatures, as determined by the dermotherm. The Janney test showed a flat curve for the blood sugar. It was no longer possible to demonstrate the presence of the pressor substance on repeating the perfusion experiment (Chart 2).

The patient had become very greatly improved when discharged, her blood pressure ranging between 125 and 135 systolic and 85 to 95 diastolic. Occasionally she is troubled with Raynaud-like symptoms in hands and feet, especially on exposure to cold. She has not had any attacks of the type described preoperatively.

COMMENT.—A matter of academic significance is brought up by this case. Although the majority of authors have expressed the opinion that the hypertensive crises in these cases are due to hyperadrenalinemia, several, in recent publications, have questioned this association. Some have actually doubted the causal relationship between the paraganglioma and the coexisting hypertension. Many previous authors have expressed regret over the lack of a reliable method of demonstrating the presence of adrenalin in the blood. This case would appear to be the first instance in which this pressor substance has been demonstrated in the blood biologically. The reversal effect of ergotamine makes it practically certain that the pressor substance is adrenalin. Moreover, the absence of this substance from the blood after the removal of the tumor establishes, beyond doubt, the causal relationship of this neoplasm to the hyperadrenalinemia and the hypertensive crises.

CONCLUSIONS

(1) A case of pheochromocytoma of the adrenal gland associated with hypertensive crises, relieved by successful operative removal of the tumor, is presented. This represents the seventh case successfully operated upon.

(2) This is the first instance of pheochromocytoma with hypertensive crises in which a pressor substance (adrenalin) has been demonstrated in the circulating blood during a crisis.

(3) No conclusions are drawn regarding the association of hyperadrenalinemia and essential hypertension.

(4) The value of perirenal insufflation in the preoperative demonstration of the tumor site is emphatically illustrated by this case.

REFERENCE

[1] Kelly, H. M., Piper, M. C., Wilder, R. M., and Walters, W.: Proc. Staff Meet., Mayo Clinic, January 29, 1936.