PAROXYSMAL HYPERTENSION ASSOCIATED WITH TUMOR OF THE SUPRARENAL

By Arthur M. Shipley, M.D.
of Baltimore, Md.

This report has to do *with paroxysmal hypertension* associated with *tumors of the medulla of the suprarenal body*. The patient whose case is reported was referred to me by Dr. Maurice C. Pincoffs, who reported the point of view of diagnosis and clinical aspects before the Association of American Physicians on May 8. Portions of the tumor after removal were used for experimental work by Dr. William H. Shultz, and the three of us will publish a full report of all phases of the case later.

We are not concerned in this report with tumors of the suprarenal cortex. The medulla of the suprarenals is a part of the chromaffin system which is not confined to the suprarenal body. The two portions of the suprarenal, cortex and medulla develop from entirely different tissues; the cortex develops from the mesoderm. "The immediate anlage of the suprarenal medulla and the anlages of the remainder of the chromaffin organs lie in the sympathetic ganglions, which, in turn, are derived from the cells of the neural crest." These primitive cells of the ganglions are called sympathogonia or the sympathetic formative cells. In early fœtal life these cells migrate laterally toward the suprarenals. "During the migration, portions of the embryonic tissue may become split off; these develop as separate organs at varying distances from the aorta in the region of the renal arteries or the inferior mesenteric artery to form the organs of Zuckerkandl."

The first report of a tumor of the medulla of the suprarenal body was by Berdez,[1] in 1892. That these tumors may be associated with hypertension was pointed out by Neusser,[2] in 1898, who reported two tumors of the adrenals described by him as carcinoma. Vaquez,[3] in 1904, associated hypertension with increase of epinephrin in the blood. No one has proven, up to the present, that an increase of epinephrin is found in the blood in patients with hypertension. Many clinical observations in patients with chromaffin cell tumors of the suprarenal glands indicate that this is true, but the proof is not forthcoming.

Oppenheimer and Fishberg[4] give three varieties of tumors derived from the medulla of the suprarenal.

1. Sympathoblastomas, made up of immature sympathoblasts.

2. Ganglioneuromas, consisting of relatively mature sympathetic ganglion cells.

3. Paragangliomas, which is the type of tumor with which we are concerned in this paper. These are rare tumors and Rabin[5] was able to find only thirty cases in the literature, and in an excellent article in the *Archives of Pathology* for February, 1929, he discusses these cases and reports one of his own.

These tumors of the medulla of the suprarenal body have been given different names—perithelioma, paraganglioma, chromaffin cell tumors and pheochromocytoma. They were formerly considered as types of sarcoma, but it is now known that the majority of them are benign and encapsulated. Of the thirty tumors of medulla of the suprarenals many had associated with them hypertension, instability of the vasomotor system or glycosuria. Only three of them, however, showed paroxysmal hypertension. We mean by this that at irregular intervals the blood pressure will rise sharply 100 or more points above the normal and these rises will be accompanied by heart consciousness, rapid pulse, flushing, nausea or headache and that after a few hours' interval the pressure will return to normal.

We have been able to find in the literature only three cases of paroxysmal hypertension associated with chromaffin tumor of the suprarenal. The first case reported was by L'abbé, Tinel and Doumer.[6] This patient had attacks of paroxysmal hypertension associated with œdema of the lungs and in one of these attacks she died. Autopsy disclosed a tumor of the medulla of the left suprarenal.

The second case was reported by Oberling and Jung.[7] This patient was a woman, twenty-eight years of age, with a normal pregnancy and delivery in 1922. In 1927, close to term in a second pregnancy, she was found by her physician to have a pressure of 250/190, with well-marked albuminuria and severe headaches. The following day in hospital her pressure had fallen to 180/150, and in the ensuing few days the pressure was quite variable between about 170/110, and 220/155. She delivered normally, but went into a state of shock two hours after delivery with a pressure of 130/120, and a pulse of 150. She died in this condition a few hours later. At autopsy a kidney-sized, encapsulated tumor was found replacing the left adrenal. The histological structure identified it as a paraganglioma.

The third case was reported by Dr. Charles H. Mayo.[8] This patient was having attacks of paroxysmal hypertension and exploratory laparotomy was done, because it was thought that some pathology of the splanchnic nerves might be responsible for the attacks and because there was abdominal pain. A tumor was found that was retroperitoneal, behind the tail of the pancreas and impinging upon the upper pole of the left kidney. Doctor Mayo reported in addition to the tumor which was removed that the left suprarenal body was twice its normal size and that the right one was apparently slightly enlarged. The patient recovered and the symptoms disappeared. The microscopic diagnosis was retroperitoneal malignant blastoma.

Another case was reported which was not confirmed by either operation or autopsy, but it seems probable that the clinical diagnosis of paraganglioma was correct. Vaquez and Donzelot[9] reported this case in 1926. A young man, thirty-seven years of age, who showed very striking attacks of paroxysmal hypertension. The authors, on purely clinical grounds, were led to the belief that this was a case of suprarenal paraganglioma, similar to the one reported by L'abbé, Tinel and Doumer. The patient left their service, however, and later came into the care of Laubry,[10] who reported the outcome in a separate article in 1927. Laubry, accepting the clinical diagnosis of Vaquez, subjected the patient to deep X-ray treatment over the adrenals with the result that the attacks diminished and finally disappeared entirely and had been absent for six months at the time of his report.

Case Report.—The subject of this report came to see Doctor Pincoffs because of "attacks with palpitation of the heart." She was twenty-six years old, had been married one year, with no pregnancies. She had always been very active with a sanguine temperament. At this time a sister had a mass in the upper chest, which interfered with breathing and caused distention of the neck vessels.

Ten years before, when she was at school, she suffered at about weekly intervals with attacks of flushing and warmth in the right arm, associated with a sudden feeling of being shaky and nervous. She thought these attacks were brought on by playing basketball. They were brief in duration and after a few months they disappeared. After three or four years the attacks returned, but somewhat different in nature. They would begin with a hot, flushed feeling in both arms followed by a sensation of tightness and compression over the heart, which would beat forcibly. There was a feeling of difficulty in breathing and of swelling of the neck. After some time, nausea would appear and if she forced herself to vomit, some relief of symptoms would be obtained. The vomitus contained whatever might be in the stomach.

At first the attacks were infrequent, but gradually the interval between them shortened. They occurred at any time, but rarely late at night. She could not make out that any particular act of hers precipitated the attacks. They had a tendency to recur at about the same hour each day. She usually had at least one attack daily and sometimes, when the paroxysm was a light one, there would be a severe attack in the evening.

When she came in the hospital for study, the attacks were increasing in violence and frequency and severe occipital headache was an increasingly troublesome symptom. She had been in the habit of going off to herself and sitting quietly through the attacks. Afterward she felt entirely well. During the attacks there would be some apprehension, because of the symptoms, especially the sense of constriction and difficulty in breathing, the forceful heart action and a shaky, nervous feeling.

In addition to these symptoms there were frequent attacks of diarrhœa and vomiting, without fever. Her habits were negative, except for excessive cigarette smoking. During the preceding year she had had swelling in both parotid regions a number of times, which came on suddenly, was painless and without fever. This swelling would persist several weeks. In the first attack it was diagnosed mumps.

The physical examination was negative. The chest was clear. The heart was normal in position and size, sounds clear, good rhythm, pulse rate normal, blood pressure 120/90. Abdomen negative. Blood count normal. Wassermann negative. Stool normal. Two specimens of urine were examined, both showed a trace of albumen and one a definite reduction for sugar, confirmed by fermentation.

The patient was next observed in an attack. It was found that as soon as symptoms were complained of the blood pressure was already 190/98. It rose gradually to 219/110, and in the next half hour fell to 176/76. During the height of the attack there was marked pulsation of the vessels of the neck, the jugulars were prominent, the hands, feet, knees and nose were quite cool to the touch, the face a little flushed, there was marked tremor of the hands, the respirations were shallow and increased to 36, and the pulse rose gradually to 110, and fell to 76, with the fall in pressure.

A number of similar attacks were observed. It was proved that between the attacks the pressure was always normal. In one paroxysm the systolic pressure rose above 260, beyond where the instrument used could register it. Irregularities developed in the pulse toward the end of the attack. These were studied with the electrocardiograph and showed short runs of both auricular and ventricular tachycardia.

She remained in the hospital eight days under observation and in addition to the examinations described above, a number of fruitless studies were made which added nothing to our knowledge of the nature of the attacks.

Because of the foregoing history and examinations, a diagnosis of tumor of the suprarenal was made by Doctor Pincoffs. The thing that immediately concerned us was to determine which gland was involved. We had found two patients with similar symptoms in the literature and in both, the tumor was on the left side. The most careful palpation and percussion gave us no help and X-ray examination showed nothing unusual on either side. It would be difficult to remove either suprarenal through one incision, unless a mid-line incision were used and a transverse cut through the rectus muscle and lateral abdominal wall were made toward the side of the tumor. We were

afraid of a prolonged operation, because of the great hypertension during attacks and the rapid fall in blood pressure at the end of the attacks. We decided to guess as to the side of the tumor and if we guessed wrong to close that incision and to operate later through another approach.

Accordingly, June 14, 1928, a high left rectus incision was made and the left kidney and post-peritoneal region carefully explored. The left suprarenal was normal in size, consistency and shape and no evidence of any post-peritoneal tumor on the left side was found. There was a little accessory spleen in the peritoneal folds just lateral to the spleen. This was definitely splenic tissue and was about the size of a marble. The right side of the abdomen was then explored by palpation and a large, somewhat kidney-shaped tumor mass was felt just above the right kidney, between it and the liver, on a plane a little anterior to the kidney and mesial to it. It had some range of motion, was behind the peritoneum and was not attached firmly to either kidney or liver. It had about the consistency and movability of an enlarged thyroid in Graves's disease. It could not be reached through the left rectus incision and so it was decided to close the abdomen and wait until healing had taken place and then to approach the tumor through a different incision. The patient made a good operative recovery, although she continued to have almost daily attacks of paroxysmal hypertension. In one of these attacks she developed considerable dyspnœa, cyanosis and a very high blood pressure and it seemed, for a time, that she had developed a pulmonary infarct. These symptoms rapidly cleared up, however; no physical signs in the chest persisted and there was no spitting of blood.

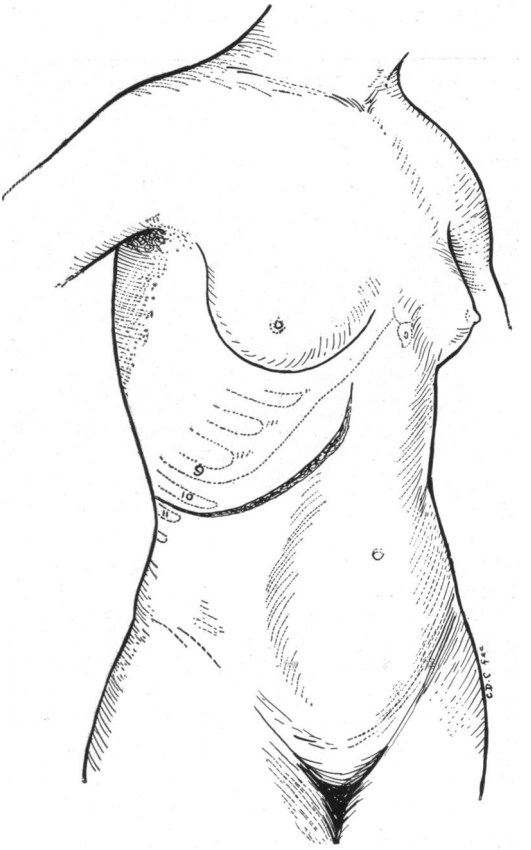

FIG. 1.—Incision to expose the suprarenal body.

Thirteen days later on, the patient was operated on the second time. She was placed on the operating table with her body tilted, so that the anterior axillary line on the right side was uppermost. A short incision was made parallel to the costal margin, extending from the outer border of the sheath of the right rectus muscle to the end of the eleventh rib. (Fig. 1.) The peritoneum was opened through this incision and the tumor palpated. It was found that it could be reached best by lengthening the incision intercostally between the tenth and eleventh ribs. This was done. This exposed the lower margin of the right lobe of the liver. Some difficulty was had in retracting the edges of the wound. Accordingly, both the tenth and eleventh ribs were cut across by an osteotome and this allowed a wide separation of the ribs. The hand of an assistant was used to retract the liver upward and this brought into view the ascending colon and its hepatic flexure, the right kidney and the tumor mass. (Fig. 2.) The parietal peritoneum lateral to the ascending colon was incised for a considerable distance and the colon mobilized and packed off to the left. This pre-

vented the small intestines from pushing into the operative field and brought the tumor directly into view. It was smooth, almost as large as the patient's kidney and lay immediately above the kidney and in contact with it below and tucked up very close to the under surface of the liver; above laterally it lay against the posterior abdominal wall and mesially it was in close contact with the ascending vena cava for several inches. It was quite firm in consistency, although not of stony hardness, smooth and was surrounded by a somewhat loose outer covering of areolar tissue containing a considerable number of large vessels. Between the mass and the kidney there was a strip of fatty tissue containing vessels that were quite large. The outer covering of the tumor mass was incised and this gave a very good exposure of it. There were a number of large vessels running from

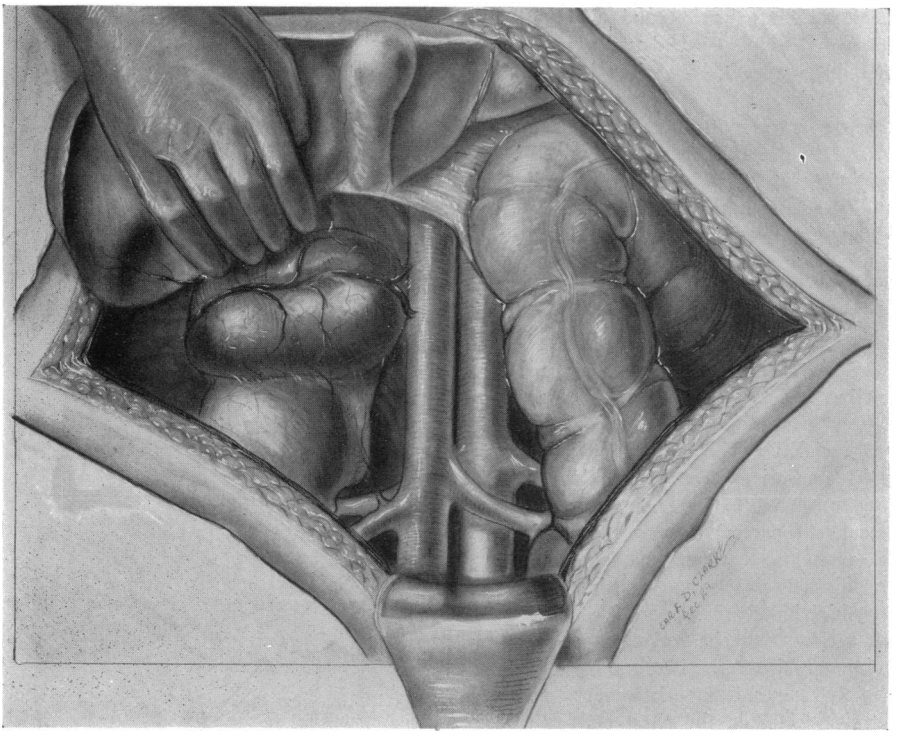

FIG. 2.—The tumor exposed.

this outer layer of loose connective tissue to a dense, smooth capsule intimately adherent to the tumor. The tumor, however, could be separated from its bed and a number of clamps were applied wherever veins were visible. No definite pedicle could be made out. The blood supply was abundant and came into it from a number of directions. The tumor was separated from the surrounding structures and considerable hæmorrhage was encountered in two localities; one below the tumor and between it and the kidney. This hæmorrhage was not difficult to control. The chief return blood supply went from the tumor mass directly into the ascending vena cava at about the level of the middle of the tumor and considerable difficulty was encountered in finding room enough between the tumor and the vena cava to apply clamps. After the tumor (Fig. 3) was removed there was some bleeding in this area and a good deal of anxiety was felt in controlling it, as it was feared that the vena cava would be torn. Altogether, the patient lost about eight ounces of blood. The clamps were tied and two cigarette drains were left in position. The duodenum was not seen; it was kept in mind because of its position behind the peri-

toneum and its relationship to the upper pole of the right kidney and to the right suprarenal. The patient's blood pressure varied sharply during the operation and she was infused on the table with normal salt solution. The wound was closed and she left the table quite shocked.

During the operation a careful record of blood pressure was kept by Doctor Pincoffs. She had no attacks of hypertension just previous to operation nor did any occur during or after operation. Her highest systolic pressure on the operating table was 152, and three other readings of 140, 130 and 138 were made in the early stages of the operation. As the operation progressed the blood pressure steadily dropped until just after the tumor was removed, when it was 88/62. After this the systolic varied between 94 and 110, and just as she left the table was 75. The anæsthetization, preparation, operation and dressing occupied one hour and twenty-five minutes. The patient left the table badly shocked and the blood pressure remained very low for several hours after operation. Her condition during this time was critical; well-marked grayish cyanosis, respirations rapid and shallow. She was given a transfusion of about 400 cubic centimetres and stimulated with an ampoule of caffeine sodium benzoate. At the most critical period she spat up a small quantity of frothy sputum containing some bright red blood. She then began to improve and later in the afternoon her condition had improved markedly. By the following morning her condition was good. Throughout convalescence, her blood pressure remained low. The day following operation it was 116/74, the next day 118/64 and from that time until July 10, it ranged between 95/65 and 110/70. She stood this low blood pressure very well and had no attacks of hypertension during her stay in the hospital after operation, and reports herself, ten months later, as entirely well and free from attacks.

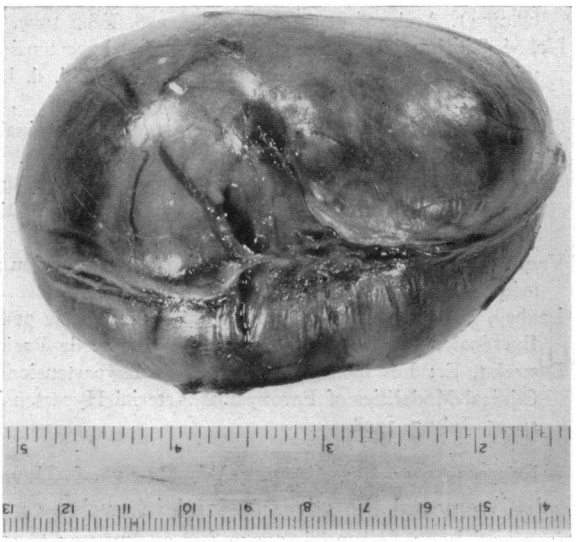

FIG. 3.—The tumor after removal.

The only post-operative complication was a rise in temperature and moderate pain in one leg, twelve days after operation. There was very little swelling or tenderness. It was diagnosed thrombo-phlebitis and treated accordingly. In a few days, these symptoms had disappeared.

The pathologist's report, made by Dr. Hugh R. Spencer, is as follows:

Gross.—The tumor weighs 115 grams, size 9 x 7 x 3.5 centimetres. It is completely encapsulated. On one side there is an orange-yellow row of tissue, which resembles adrenal cortex. It is soft. The cut-surface is gray in places while in other places it is red and appears hæmorrhagic. Some very small spaces (cysts?) are seen deep in the gross. The yellow tissue mentioned above, on section appears to be adrenal cortex with a very small gray portion, which resembles medulla and which appears to be continuous with the main portion of the tumor. All the yellow tissue is not more than one centimetre wide and two millimetres thick and extends as a narrow strip along one side for almost the entire length. At one place a small orange-yellow mass is found deep in the tumor. This mass is only two to three millimetres in diameter and resembles cortex.

Gross Diagnosis.—Tumor of Medulla of Adrenal.

Microscopic.—Frozen section as stained with scarlet-red (Herxheimer) shows no fatty material in tumor cells. Fatty material is found in abundance in cells of cortex. Tumor tissue fixed in a solution of chrome salts assumes a yellowish color. Sections show a tumor composed of oval and polygonal cells arranged in alveoli separated by capillaries. The nuclei are of various shapes, some are hyperchromatic.

Microscopic Diagnosis.—"Paraganglioma."

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DISCUSSION: DR. GEORGE W. CRILE of Cleveland, Ohio, remarked that he had removed the adrenal gland in twelve cases of hypertension. These cases had been followed, some for as long as twelve or ten years.

On the operating table there would be a fall in the blood pressure. This fall would sometimes persist for a few days, or a few weeks and then after that period the blood presusre would run an irregular course. As a whole, he was unconvinced that he produced any results. This report has no bearing on the case that was reported by Doctor Shipley; it is offered only to record a warning that we cannot put too much faith—as Doctor Shipley does not infer—in the fact that this tumor had a certain effect on the blood pressure.

DR. ROBERT TALBOT MILLER, JR., of Baltimore, Md., reported a case which possibly has some analogy to the condition described by Doctor Shipley; although the analogy is not quite clear.

It concerned a man of sixty, a very active and intelligent man who had been in the best of health. For a period of a year and a half to two years he had been suffering with attacks of precordial pain and distress and anxiety and was a picture of possible angina pectoris. He was submitted to very careful study and put into the hands of a very skilfull internist. The study

was made with the utmost detail. The internist concluded he was suffering from functional angina pectoris. He observed that with each attack the man had an extremely rapid and quite a marked rise in blood pressure, which persisted throughout the attack. He confirmed the previous findings, but was unable to find any reason for these attacks. He found, however, in the right lobe of the thyroid an adenoma, perhaps three cubic centimetres in diameter. The man was utterly miserable and the situation was explained to him. The internist suggested that the adenoma be removed with the hope that it would relieve his condition and he consented.

Doctor Miller took out a normal right lobe of thyroid containing the adenoma. The man was convalescent and out of bed in a little while and since that time has not had an attack. He has apparently recovered completely and is leading an active life.