TWO CASES OF PHAEOCHROMOCYTOMA

BY

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Phaeochromocytomata are comparatively rare tumours, but the number of cases reported is increasing rapidly owing to clarification of the clinical picture and the diagnostic use of adrenolytic drugs.

Two cases are described here. In the first, as a result of radiological investigation, a malformed kidney was thought to be the cause of hypertension. An unsuspected phaeochromocytoma was present, however, and death occurred shortly after operation. In the second case the diagnosis was correctly made by clinical and biochemical methods, and the tumour was successfully removed.

Case 1

A man aged 24 was admitted to Cardiff Royal Infirmary complaining of attacks of headache, nausea, and vomiting, with blurring of vision of 16 years' duration. For this period he had suffered from postural giddiness. He had sweated excessively for the past nine years, and had had a dull pain in the right loin for five years. For two years before admission he had complained of dyspnoea and palpitation on moderate exertion.

He was well built and looked healthy. His pulse was normal in rate and rhythm. There was no cardiac enlargement either clinically or radiologically, or any signs of cardiac failure. The blood pressure was variable, ranging between 150/100 and 190/135 mm. Hg. It was found that moderate exertion, such as polishing a floor for 10 minutes, produced a rise of blood pressure from the lower levels to 180/135, and that this rise was associated with severe incapacitating headache. The pressure was raised both in the arms and in the legs. Apart from hypertension, the only abnormal physical sign was a slight resistance to palpation in the right loin.

The blood showed a persistent leucocytosis of about 15,000 per c.mm. The urine contained a trace of albumin, the blood urea was 20 mg. per 100 ml., and the urea-clearance test gave a normal result.

Intravenous and retrograde pyelography showed a normal right pelvis, but failed to outline the pelvis of the left kidney. In view of this unilateral abnormality it was decided to explore the left kidney. At operation the kidney was found to be small (68 g.). The upper pole was reasonably well developed, but the lower pole was shrunken and fibrosed. The pelvis was practically obliterated. This kidney was considered to be congenitally deformed. As it was thought to be the possible cause of the hypertension, it was removed. During the operation the patient collapsed, the blood pressure fell, pulmonary oedema developed, and he died in a few hours.

At necropsy the heart weighed 415 g., and showed left ventricular hypertrophy. The lungs were grossly oedematous and microscopically showed bronchopneumonia. The right kidney was normal (170 g.). The right adrenal gland was replaced by a rounded encapsulated tumour about 8 cm. in diameter and weighing 220 g. (Fig. 1). On section it was found to be composed of a pink, firm peripheral zone about 2 cm. thick, and a pale-green central portion which was soft and gelatinous. Microscopically, it was a typical phaeochromocytoma with large irregular polyhedral cells containing brown pigment. The centre of the tumour was necrotic.

Biological assay of the tumour was undertaken within 24 hours of death, by the effect of an extract on isolated rabbit gut, on frog's heart, and on the blood pressure of a cat. It was concluded that the tumour contained a mixture of *noradrenaline* and adrenaline in the proportions of 10 to 1.

Case 2

A married woman aged 29 was admitted to Bridgend General Hospital on May 11, 1950, from the antenatal clinic because of hypertension and albuminuria. She had been pregnant twice before. Since January, when she was four months pregnant, she had suffered from severe frontal and occipital headaches associated with throbbing pain in the temples, sweating, and coldness of the hands and feet. The attacks usually occurred on rising in the morning and on retiring to bed at night, and could be brought on by exertion. They were often severe enough to cause retirement to bed for a few hours or for the rest of the day. Bending or other changes of posture did not precipitate an attack.

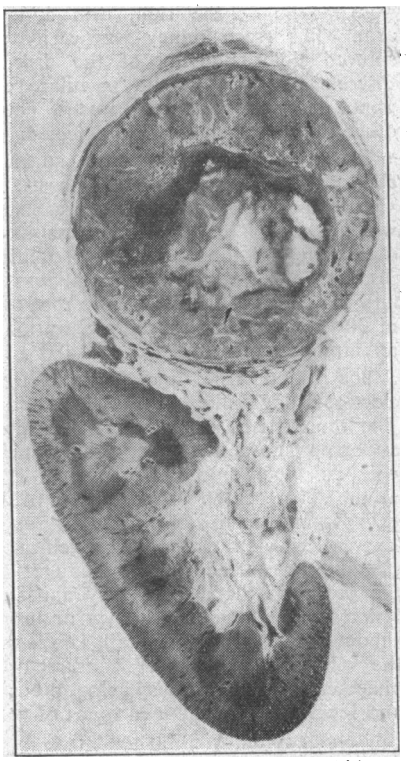

FIG. 1.—Tumour and right kidney. Case 1.

The patient also complained of vomiting a small amount of bile-stained fluid every morning since her pregnancy began. She had not experienced pain in the epigastrium, chest, or lumbar region, dizziness, vertigo, tingling of the feet, cramps in the legs, attacks of sneezing, or urinary symptoms, all of which have been described in cases of phaeochromocytoma.

There had been no significant illness during childhood except for bilious attacks, which had ceased at the age of 14. During the sixth month of her first pregnancy in 1947 she developed swelling of the face and ankles, which was associated with headaches. She was admitted to hospital, where her blood pressure was found to be 170/120. The urine contained albumin, and the blood urea was 51 mg. per 100 ml. Two days later her blood pressure was recorded as 210/150. A diagnosis of chronic nephritis was made, and the pregnancy was terminated with the delivery of a macerated foetus of 3½ lb. (1.6 kg.). The patient then lost her sight for a period of two months, and on recovery was discharged from hospital; her blood pressure was then 140/100.

Two years later she was again pregnant, but experienced no trouble until the birth of a premature stillborn hydrocephalic male child. Her blood pressure was then 134/104.

On admission for her present confinement the blood pressure was 180/120. Two days later it was 140/90, but during that evening she complained of headache, perspired freely, and her blood pressure rose to 180/130. Labour was induced, and on May 19 a macerated foetus weighing 5¼ lb. (2.4 kg.) was delivered. For the next week attacks of perspiration recurred, and the blood pressure ranged between 150/90 and 180/146.

On the seventh day of the puerperium she was pale, cold, and sweating. Her face was puffy, but there was no oedema elsewhere. Her temperature was 99.4° F. (37.4° C.), and pulse 112 and regular. The heart was not enlarged; a systolic murmur was heard at the apex. The blood pressure

was 125/90 at the right arm and 140/110 at the left arm. The right kidney was easily palpable. The fundi showed slight blurring of the disk margins, with small discrete exudates in the macular regions. In the right upper temporal quadrant was a patch of pigment. No other abnormal signs were detected.

The urine contained albumin, sugar, red and white blood cells, and hyaline and granular casts. Culture of the urine yielded a growth of coliform organisms. The blood count was normal. The blood urea was 40 mg. per 100 ml.; the urea concentration and urinary dilution tests gave normal results. The fasting blood sugar was 140 mg. per 100 ml., and the glucose-tolerance curve rose to 230 mg. per 100 ml. in 30 minutes after the administration of 50 g. of glucose, remaining at this level for two and a half hours.

The blood W.R. and Kahn test were negative. The electrocardiographic tracing followed a normal pattern. The radiologist's report was: "Straight *x*-ray film of the abdomen shows that the right kidney is ptosed and lies with its upper pole at the level of L 3 and its lower pole at the level of the lower border of L 5. Diffuse uneven calcification the size of a grape is seen at the level of L 1–2. The lateral view shows this calcification to be situated at the anterior surface of the body of L 2. I.V.P. confirms the ptosis of the right kidney and suggests rotation. No lesion is seen in either kidney or ureters, and the bladder shadow is normal. The appearances are consistent with the clinical diagnosis of suprarenal tumour, such as a phaeochromocytoma, displacing the right kidney caudally and located by a contained focus of calcification." (Fig. 2.)

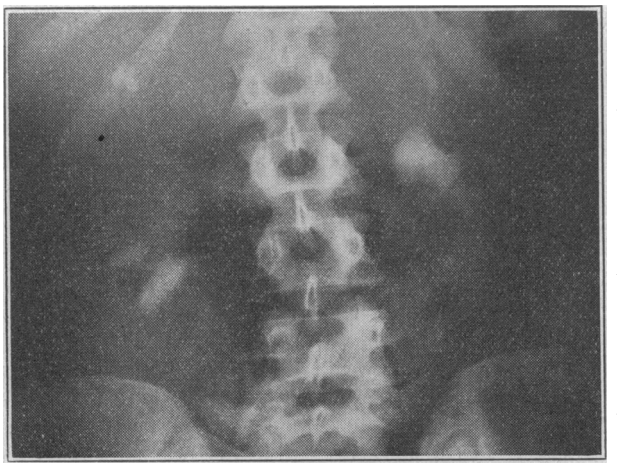

FIG. 2.—Case 2. Pyelogram showing focus of calcification in tumour and ptosed right kidney.

A diagnosis of pyelonephritis and phaeochromocytoma having been made, the former was treated with sulphonamides, and, using the Goldenberg technique, an attempt was made to confirm the diagnosis of an adrenal medullary tumour, using 933 F (2-1(1-piperidyl-methyl)1:4-benzodioxane hydrochloride). This drug is now marketed under the trade name of "piperoxane hydrochloride."

The dose of the drug was calculated from a weight and height table supplied by the makers (8 ml. of 0.2% solution), and was introduced into an intravenous saline drip after the blood pressure had stabilized at a high level. There was an immediate fall from 240/160 to 150/100. The effect lasted for about five minutes, when the pressure regained its former high level (Fig. 3).

It was decided that exploration of the right adrenal gland was justified. "Eucortone," 4 ml. daily for two days, was given pre-operatively.

Operation.—On June 29 Mr. D. B. Foster performed the operation, the anaesthetist being Dr. A. H. Musgrove. The patient was induced with thiopentone and gallamine triethiodide ("flaxedil") and maintained with gas, oxygen, and intravenous pethidine. A right thoraco-dorsal incision was made over the tenth rib and continued to the abdomen. The tenth rib was removed and the pleura opened. The diaphragm was incised and a tumour of the right adrenal was found. On the surface of the tumour were

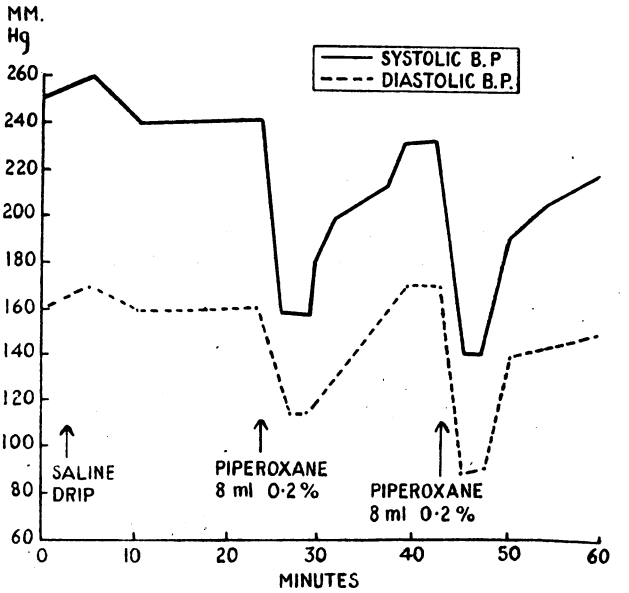

FIG. 3.—Case 2. Effect of piperoxane on blood pressure.

many large veins running to the diaphragm and to the inferior vena cava. The tumour was removed. The contralateral adrenal and both kidneys appeared to be normal.

During the operation the blood pressure was recorded every two minutes, and 5 ml. of 0.2% solution of piperoxane was given by means of an intravenous saline drip whenever the diastolic pressure exceeded 150 mm. Hg (Fig. 4). When the veins from the tumour were clamped and ligated, the blood pressure fell sharply from about 250/170 to 75/50. In order to minimize this fall 5 min. (0.3 ml.) of adrenaline hydrochloride solution 1:1,000 was repeatedly given into the drip. On return to the ward the blood pressure was 70/50.

Post-operatively the patient was given adrenaline in oil, 1 ml. intramuscularly every six hours for two days, and eucortone, 2 ml. daily for two days. The blood pressure

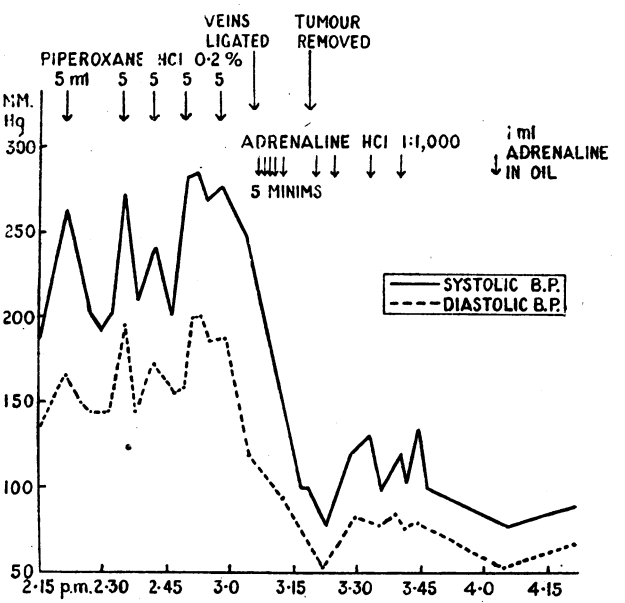

FIG. 4.—Case 2. Blood pressure during operation.

quickly rose to 110/70 and remained at this level until discharge from hospital on July 20. The fundi were then normal in appearance.

Repeated examination of the urine showed no abnormal constituents, the glucose-tolerance curve returned to a normal shape, and the calcification seen radiologically in the abdomen was no longer present.

The tumour was grey in colour, with a smooth, tough capsule, and measured 9 by 9 by 6 cm. (weight 360 g.). Internally it was soft and gelatinous, with a broad mottled haemorrhagic peripheral zone occupying the bulk of the tumour. At its centre was pale-green translucent material about 1.5 cm. in diameter and a bright yellow calcified body about 2 cm. in diameter (Fig. 5). It bore a very close resemblance to the tumour of Case 1 both microscopically and macroscopically.

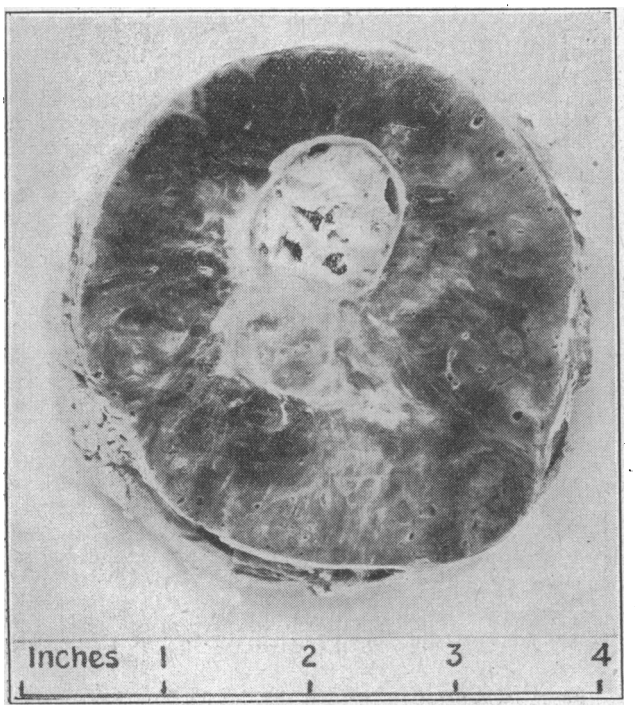

FIG. 5.—Case 2. The tumour.

Discussion

The diagnosis of a phaeochromocytoma may be very easy in the presence of paroxysmal hypertension accompanied by throbbing headache and sweating, but not every patient presents so obvious a syndrome. The hypertension may be sustained, the patient may be seen *in extremis* during the first paroxysm, or the condition may simulate Addison's disease (Cole, 1950).

Sweating is an important and well-recognized symptom. This would be difficult to explain on the previously held view that the sweat glands are entirely cholinergic. Most textbooks of physiology in fact still teach that this is so. However, Haimovici (1948) has shown that these glands in man have both a cholinergic and an adrenergic supply, and the sweating in phaeochromocytoma is thus explained.

The differential diagnosis includes a large number of conditions, and MacKeith (1944) has listed the following: essential hypertension, lead-poisoning, eclampsia, tabes dorsalis, aortic reflux, angina pectoris, thalamic tumour, hyperthyroidism, diabetes mellitus, peptic ulcer, chronic nephritis, polyarteritis nodosa, surgical shock, migraine, cerebral tumour, cardiac neurosis, and anxiety state.

In Case 1 a diagnosis of hypertension due to unilateral renal disease was made because of the exceedingly rare combination of a phaeochromocytoma and a congenital deformity of the contralateral kidney.

When the second patient was first seen the blood pressure was considered to be unequal in the arms; but this was not confirmed at subsequent examinations, and no doubt was the result of the rapid rise in the pressure, due to emotional causes, during the examination. Of particular value in the diagnosis were the palpable kidney, the paroxysmal hypertension, the cold sweating, the throbbing headache, the glucose-tolerance curve, and the *x*-ray findings.

The diagnosis of phaeochromocytoma has been made much easier by the use of adrenolytic drugs, of which the best known are "dibenamine" and those derived from dioxane, which were first investigated by Fourneau and Bovet in 1935.

Dibenamine (N,N-dibenzyl-beta-chloroethylamine hydrochloride) is structurally related to the nitrogen mustards. It has a prolonged action of 24 hours or more. Unfortunately we were not able to use it, since it is not at present available in this country, but it has been widely used in America (Spear and Griswold, 1948).

Of the dioxane derivatives the best known is 933 F. Structurally it somewhat resembles adrenaline and presumably acts by competing with adrenaline at the nerve-endings. Its effect lasts for a few minutes only.

Goldenberg *et al.* (1947) suggest its prophylactic use during the notoriously hazardous operations on these tumours. Of 64 patients operated upon before the use of adrenolytic drugs, 12 died (mortality rate 19%) (*B.M.J.*, 1949). In addition, several cases are reported of death during anaesthesia for other operations, or during parturition, when the tumour was unsuspected.

Bartels and Cattell (1950) consider that if a hypertensive crisis arises during any operation the adrenal areas should be explored, if this can be done conveniently, and adrenolytic drugs should be given, or the operation should be terminated. These authors are also of the opinion that collapse is not due to a diminution in the supply of adrenaline but is a result of left ventricular failure due to excess of circulating adrenaline, and may occur at any time before or during the removal of the tumour. They assert that the only measures necessary during the operation for removal of a tumour are the administration of an adrenolytic drug and the adoption of the Trendelenburg position. With this opinion we are in agreement, and it is probable that the administration of adrenaline and eucortone was unnecessary.

Summary

Two cases of phaeochromocytomata are described: the first was associated with a congenital abnormality of the contralateral kidney. Clinically the latter was thought to be the cause of the hypertension from which the patient was suffering.

In the second case the diagnosis was made clinically and was confirmed by the Goldenberg test, using piperoxane. Calcification in the tumour was demonstrated by radiography.

The blood pressure was recorded at frequent intervals during the operation for removal of the tumour in the second case and was controlled by piperoxane and adrenaline.

I wish to express thanks to Professor J. Gough and Dr. F. L. Dyson for help and advice; to Dr. S. D. P. Graham for the assay of the tumour; and to Dr. K. E. Barlow for the radiological report.

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A CASE OF ADRENAL PHAEOCHROMOCYTOMA

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The first case of chromaffin tumour of the adrenal medulla correctly diagnosed and successfully removed was reported by Shipley (1929). Between 1929 and 1947 these tumours have been successfully removed in some 44 cases (Hatch *et al.*, 1949). The object of this communication is to record the occurrence of a phaeochromocytoma with somewhat unusual features and its successful removal.

Case Report

The patient, a widow aged 66, had suffered irregularly from "peculiar attacks" for at least seven years. Each attack began with epigastric discomfort associated with eructation of gas and sometimes with retching. These symptoms were quickly followed by a feeling like an electric shock in the limbs, back of the neck, and back of the head. The patient felt warm during the attacks, although she had noted that her hands became blue. The attacks occurred in episodes, each lasting two to four months. There had been long free periods, the longest being nearly two years. During an episode there were four to seven attacks each week. For the past two years the attacks had been associated with "very rapid beating of the heart."

On examination the patient was found to be intelligent and co-operative. There was no cyanosis, oedema, or apparent rise in the jugular venous pressure. The pulse was 84 and regular, and the blood pressure 140/80 mm. Hg. There was clinical evidence of cardiac enlargement, the apex beat being in the sixth intercostal space in the anterior axillary line. The mitral first sound was split. Examination of the respiratory system revealed nothing abnormal. The liver edge was palpable 1 in. (2.5 cm.) below the right costal margin. A swelling, thought to be a palpable right kidney, was found in the right hypochondrium. Examination of her nervous system revealed nothing relevant.

The patient was seen during an attack on the day after admission. She appeared very apprehensive. The face was flushed, the limbs were trembling, and the hands were cold and cyanosed. The pulse was 150 and regular, and the blood pressure 270/170. Subjective symptoms lasted only 15 minutes. Within half an hour the blood pressure had fallen to 120/80, and the pulse rate had returned to normal. The variations in the blood pressure, spontaneous and induced, during the patient's pre-operative stay in hospital are shown in Fig. 1.

Investigations

An electrocardiogram obtained during her first attack in hospital showed sinus tachycardia, rate 150. The next day there was a sinus rhythm, rate 55. The standard unipolar limb and precordial leads were regarded as normal. The basal metabolic rate was − 10%, and the blood cholesterol 190 mg. per 100 ml. Radiography and fluoroscopic examination of the chest revealed moderate enlargement of the left ventricle; the lung fields were clear. An intravenous pyelogram showed good excretion on both sides, with normal calices and pelves. The right kidney appeared to lie rather low. The blood urea was 44 mg. per 100 ml.; W.R. negative; fasting blood sugar was 91 mg. per 100 ml., 105 mg. during an attack.

Injection of histamine, 0.05 mg., caused a rise in blood pressure, but did not produce tachycardia or any

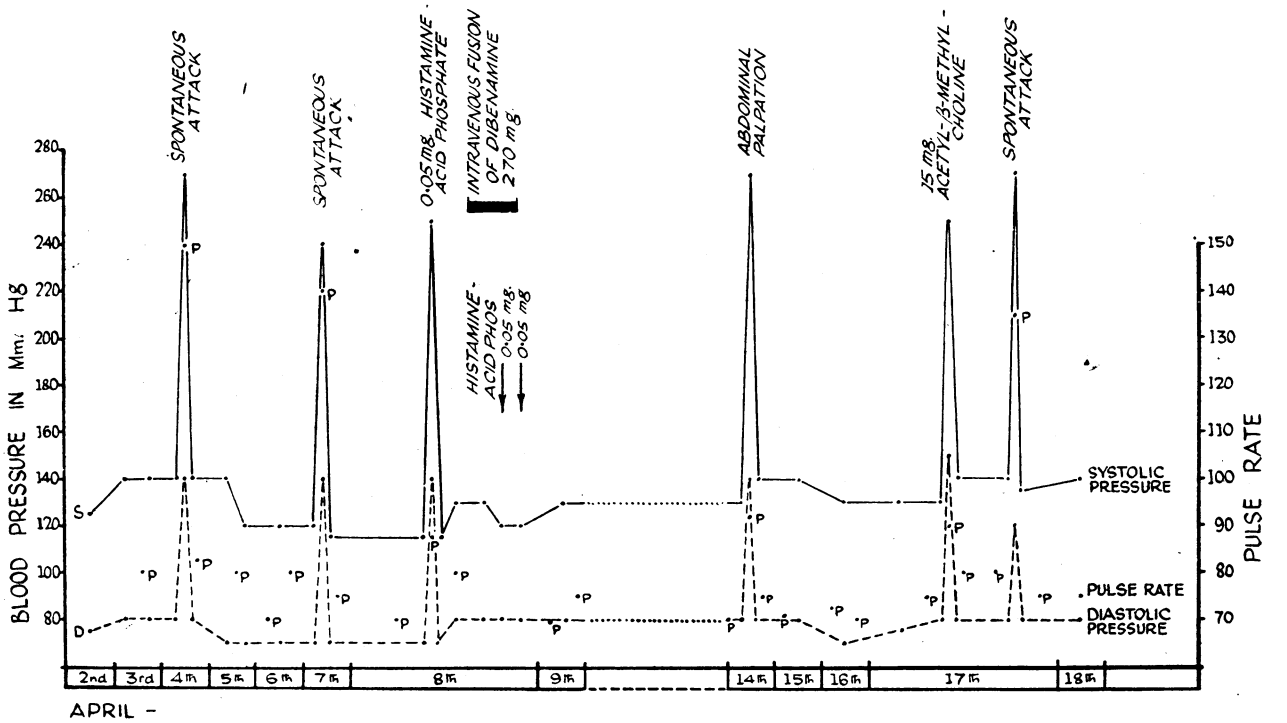

FIG. 1.—Blood-pressure readings and pulse rates before operation.