I wish to express my thanks to Professor Aubrey Lewis for his interest during this investigation and his helpful criticism in the drafting of the paper. My thanks are also due to Dr. O. W. Roberts, medical superintendent, Dulwich Hospital, for allowing me access to the case records, and to the physician-superintendents of numerous hospitals, as well as to Dr. the Hon. W. S. Maclay, Senior Commissioner, and Mr. F. W. Allen, of the Records Department of the Board of Control, and Mr. F. J. Spivey, of the Mental Health Department of the L.C.C., for their assistance with the follow-up of patients.

REFERENCES

Camargo, O., and Preston, G. H. (1945). *Amer. J. Psychiat.*, **102**, 168.
Clow, H. E. (1948). *N.Y. St. J. Med.*, **48**, 2357.
Dayton, N. A. (1940). *New Facts on Mental Disorders.* Baltimore.
Greeff, J. H. (1933). Quoted by A. L. Vischer in *Old Age.* London, 1947.
Lewis, A. (1946). *J. ment. Sci.*, **92**, 150
—— and Goldschmidt, H. (1943). *Sociol. Rev.*, **35**, 86.
Malzberg, B. (1940). *Social and Biological Aspects of Mental Disease.* New York.
Pollock, H. M. (1945). In O. J. Kaplan's *Mental Disorders of Later Life.* Stanford University.
Rowntree, B. S. (1947). *Old People.* London.
Sheldon, J. H. (1948). *The Social Medicine of Old Age.* London.
—— (1950). *British Medical Journal*, **1**, 319.

PHAEOCHROMOCYTOMA OF ADRENAL GLAND, WITH SUSTAINED HYPERTENSION

BY

H. J. C. SWAN, M.B., B.S., M.R.C.P.
Lecturer in Physiology, St. Thomas's Hospital Medical School

Phaeochromocytoma is an uncommon cause of human hypertension. However, the clinical result which follows successful diagnosis and treatment is in itself good reason why every effort should be made to recognize the condition as early as possible.

The association of an adrenal medullary tumour with hypertension was probably first recognized by Labbé *et al.* (1922), although the occurrence of such tumours had been noted earlier. The condition was the subject of an able review by MacKeith (1944), who collected 152 cases from the earlier literature. The usual clinical syndrome ascribed to phaeochromocytoma then comprised paroxysmal hypertension, sweating, and a number of symptoms referable to overaction of the sympathoadrenal system. MacKeith recognized that some cases might resemble malignant hypertension and others essential hypertension, but did not enter into details. Green (1946), however, recognized that phaeochromocytoma might occur not infrequently in patients with sustained hypertension, and there was little to distinguish such cases from essential hypertension. In a series of 51 cases selected from the literature for their completeness of data, Green showed that intermittent hypertension was present in only 14, sustained hypertension being found in the other 37. The problem in the diagnosis of this condition is therefore twofold: first, to recognize the possibility that phaeochromocytoma is the cause underlying a story of paroxysmal disturbances in a patient with normal blood pressure when seen; and, secondly, to differentiate between the rare phaeochromocytoma with sustained hypertension and the common essential hypertension.

The clinical features of phaeochromocytoma with paroxysmal hypertension have been adequately described in the literature. MacKeith's (1944) paper gives most of the symptoms. If the possibility of such a condition is considered a correct diagnosis should frequently be made.

The second, perhaps more common, situation in which hypertension is sustained presents a difficult diagnostic problem. This has led to the development, in recent years, of a number of pharmacological tests to differentiate phaeochromocytoma with sustained hypertension from that with essential hypertension. In spite of the successful application of certain of these tests —notably the benzodioxane test (Goldenberg *et al.*, 1947) and the histamine test of Roth and Kvale (1945) —some disadvantages still attend their general use. In 1950 Smithwick *et al.* emphasized certain clinical features, unusual in essential hypertension, which were to be observed in cases of phaeochromocytoma. In addition, their observations suggest that the response to simple routine investigations on patients with sustained hypertension should reveal a substantial number of those patients in whom the hypertension is due to phaeochromocytoma.

It now seems clear that phaeochromocytomata contain a mixture of adrenaline and *nor*adrenaline in varying proportions (Holton, 1949; Goldenberg *et al.*, 1949). The vascular responses to these substances in the human have been reported in the literature (Goldenberg *et al.*, 1948; Swan, 1949; Barcroft and Konzett, 1949). The relationship of *nor*adrenaline to phaeochromocytoma has been discussed in detail by Barnett *et al.* (1950). Therefore this aspect of phaeochromocytoma will not be considered here. Suffice it to point out that the symptom-complex may vary according to the pressor substance which predominates in the circulation, but that knowledge of the effects of very large amounts of the amines in man is lacking at present.

The present paper has been stimulated by the occurrence of a case of unsuspected phaeochromocytoma in this hospital. The patient was thought to be suffering from hypertensive vascular disease and was to be submitted to splanchnic sympathectomy for that condition. Details of the case are given below. The remainder of the paper is concerned with the diagnosis of phaeochromocytoma with sustained hypertension, the recent literature on phaeochromocytoma with paroxysmal hypertension having been summarized by Walton (1950).

Case Report

A 42-year-old Stock Exchange clerk was admitted to St. Thomas's Hospital on October 2, 1950. He had been a known hypertensive for eight years, but had come to hospital because of difficulty in using his right hand for one week. In 1941 he was called for service with the R.A.F. There is no record of the blood pressure at that time. In May, 1942, he complained of mild dyspnoea on exertion and frontal headache. The arterial blood pressure was found to be 170/110, and there was a cloud of albumin in the urine. Further investigation revealed red blood cells in the urine but no casts. The renal function was not impaired. The patient was invalided from the Service with the diagnosis of essential hypertension. On subsequent medical examinations by the Ministry of Pensions from 1943 to 1950 the arterial blood pressure varied between 180/115 and 210/130.

On admission the patient complained of tiredness, headache, and, as a major symptom, sweating. The latter symptom had troubled him from the age of 16, but at this time it had worsened considerably. The sweats were confined to the face and neck; the palms of the hands and the lower part of the body remained dry. Only rarely was axillary sweating noticed. When questioned about this symptom

after the diagnosis had been established the patient's wife recalled that frequently, on meeting a friend or in a similar situation, the patient had paled for a few moments, then, as his colour returned, beads of sweat would form on his forehead. Sweating also occurred without noticeable vasomotor changes. In addition he experienced frontal headaches of moderate severity. In the past year he had noticed some breathlessness on exertion, and at times had occipital headaches. In 1944 he had two "blackouts," and recently he had some difficulty in using his right hand.

On examination he was seen to be a thin, anxious person. His skin was moist, and at times beads of sweat appeared on the forehead. His mouth temperature was 99° F. (37.2° C.). No cardiac enlargement was discovered, but there was a loud first sound at the apex, with a soft systolic murmur. The aortic second sound was accentuated. The blood pressure in the right arm was 240/140. Examination of the arterial system revealed no abnormality. The optic fundi were considered normal. There was an indefinite weakness of the right hand. The diagnosis on admission was essential hypertension.

For the first week in hospital his temperature did not fall below 98° F. (36.7° C.) and fluctuated around 99° F.; the arterial blood pressure varied between 190/110 and 170/110 (Fig. 1). The blood urea on October 7 was 33 mg. per 100 ml., and there was no evidence of renal dysfunction.

The electrocardiogram was reported as indicating left ventricular strain. The heart showed slight left ventricular enlargement on screening. An intravenous pyelogram revealed no renal abnormality, but calcified opacities were noted above the left kidney. On October 11 a sedation test was performed. The response is shown in Fig. 2. As the ultimate prognosis was regarded as poor, a splanchnic sympathectomy was decided upon.

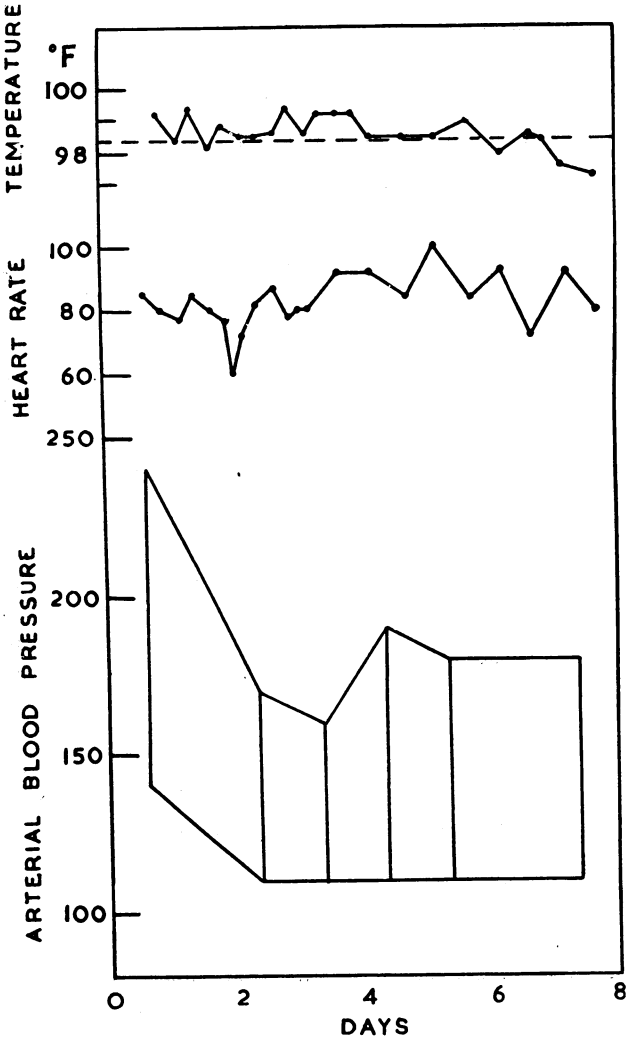

FIG. 1.—The mouth temperature, heart rate, and arterial blood pressure in the right arm recorded during the first week in hospital.

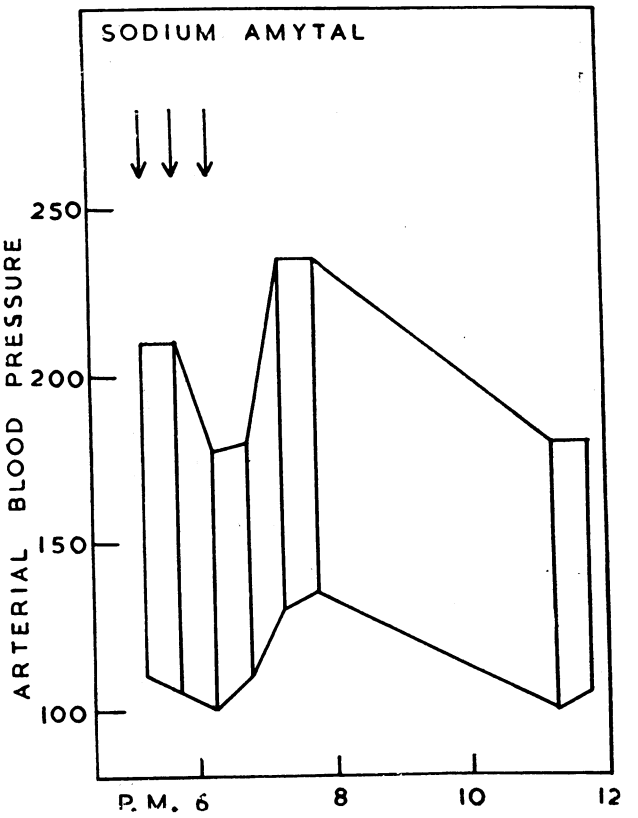

FIG. 2.—At each arrow 3 g. of sodium amytal was given. The arterial blood pressure response is shown.

On October 19 Mr. R. H. Boggon operated through a left lumbar incision. The anaesthetic (by Dr. W. D. Wiley) consisted of thiopentone (0.65 g.), gallamine triethiodide ("flaxedil") (160 mg.), gas, and oxygen. A tumour about 2 in. (5 cm.) in diameter was found in the left adrenal gland. On manipulation of this tumour the systolic blood pressure rose from 240 to 300 mm. Hg. Several large vessels running to the tumour were seen and ligated. The tumour was then removed. The blood-pressure changes during and after the operation, together with the measures taken to resuscitate the patient, are shown in Fig. 3. It was considered that the *nor*adrenaline infusion did much to prevent the occurrence of a fatal circulatory collapse (see Walton's (1950) case).

On the second post-operative day the patient developed abdominal distension and vomited several times. Continuous gastric suction through a Ryle's tube was instituted and 2 litres of glucose-saline was given intravenously. On October 22 the intravenous drip and gastric suction were discontinued and the patient improved steadily in the ensuing few days. During the first post-operative week the patient sweated continuously and to a greater extent than before his operation, but after the seventh day there was a notable diminution in sweating. Subsequently he developed a small venous thrombosis in the foot, but this cleared rapidly. A left-sided pleural effusion further prolonged his stay in hospital. On November 14 the blood pressure in the left arm was 125/80.

The tumour weighed 350 g. and was identified as a phaeochromocytoma of the adrenal medulla (Dr. J. L. Pinniger). "The tumour, which shows a well-marked alveolar arrangement in places, contains areas of necrosis

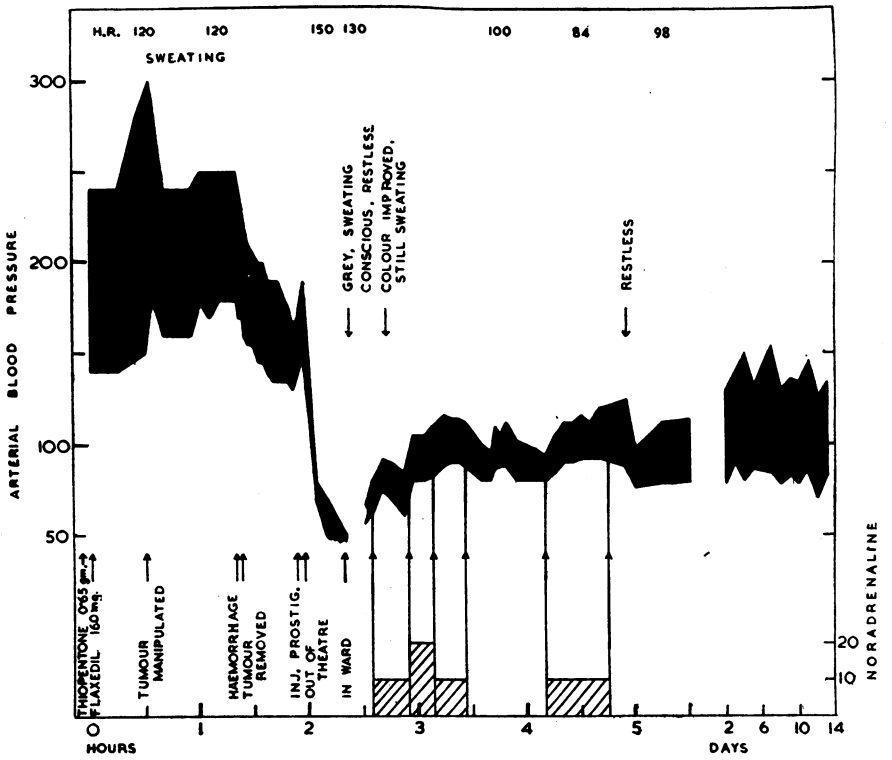

FIG. 3.—The arterial blood pressure during and after surgical removal of a phaeochromocytoma. The hatched squares indicate the rate of administration of L-*nor*adrenaline intravenously in μg. per minute. After 50 minutes the infusion of *nor*adrenaline was replaced by an infusion of saline, but as the systolic pressure fell below 100 mm. Hg the *nor*adrenaline was restarted. After a further infusion of *nor*adrenaline for 35 minutes, the pressure remained at a satisfactory level.

and of myxomatous degeneration. The cells and their nuclei show some variation in size."

A portion of the tumour was taken for assessment of adrenaline and *nor*adrenaline content. It was placed in a "deep-freeze" refrigerator at −4° C. Several hours afterwards it was realized that no HCl had been added to the tumour; 20 ml. of N/10 HCl was added 20 hours after the tumour had been removed, but the tissue was not melted or minced. Assay (Dr. Monica Mann) revealed 85 μg. of adrenaline and 875 μg. of *nor*adrenaline per g. of tumour tissue. Thus more than 90% of the biologically active substance present was *nor*adrenaline. The low amine content might have been due to the delay in acidifying or to the fact that a large amount of myxomatous, and therefore inactive, tissue was also present.

Comment on Case

From the patchy calcification, one is forced to conclude that the tumour had been present for a considerable time. It is of interest to note that the patient complained of sweating from the age of 16. He is known to have been hypertensive for at least eight years, and probably for longer; yet in spite of this duration of apparently severe sustained hypertension the arterial blood pressure reverted to normal levels after removal of the tumour. There was no evidence of arterial degeneration, and when last seen the arterial blood pressure was normal. However, Case 2 of Barnett *et al.* (1950) reverted to the hypertensive state one year after operation.

I have not as yet seen reported in the literature the use of *nor*adrenaline in the treatment of the post-operative collapse. In this case the blood pressure fell gradually for about 30 minutes after removal of the tumour. Just after he left the theatre (see Fig. 3) the blood pressure suddenly fell precipitantly. The patient was cyanosed and sweating freely: the respiration was shallow, the pulse rapid and thin. An infusion of L-*nor*adrenaline rapidly restored the blood pressure, and it was felt at the time that any reasonable blood-pressure level could have been obtained with this agent. The *nor*adrenaline caused the usual bradycardia and elevation of both systolic and diastolic blood pressures. The general appearance of the patient also improved remarkably. The tumour contained more than 90% *nor*adrenaline, and it is thought that the infusion acted as a temporary replacement of the tumour secretion which had been so rapidly removed; this allowed a more gradual restoration of the normal mechanisms of peripheral vasomotor tone.

Diagnosis of Phaeochromocytoma with Sustained Hypertension

The clinical features of a patient with phaeochromocytoma who exhibits sustained hypertension may in many respects be similar to those seen in essential hypertension. However, most of these patients present clinical features which may direct the physician's thoughts to the possibility that a tumour is present. Smithwick *et al.* (1950) point out that excessive sweating was a major symptom in 9 out of 10 cases of phaeochromocytoma observed by them, while the incidence in hypertensive vascular disease was but 2%. In my case the patient complained of excessive sweating for many years. The sweating is often generalized, and may continue for long periods. Its occurrence need not be related to any symptoms suggesting an outpouring of adrenal medullary substances. In addition to sweating, Smithwick *et al.* point out that a low-grade pyrexia often occurs. Those workers also noted an unduly high incidence of peripheral vasomotor phenomena in phaeochromocytoma. They commented on blanching of the fingers, discoloration of the skin of the hands and legs, and coldness of the hands and feet in 9 out of their 10 cases. Objective evidence of peripheral vasoconstriction may be obtained by the finding of a decrease in skin temperature and peripheral blood flow. In contrast these symptoms are rare in essential hypertension. Facial pallor was commented upon by the patient's wife in the case described above. In phaeochromocytoma with paroxysmal or sustained hypertension metabolic rate and fasting blood-sugar studies are of recognized value. It may be noted in passing that the finding of metabolic changes does not necessarily exclude the presence of a predominantly *nor*adrenaline-containing tumour, although the effect of *nor*adrenaline on metabolism is less than that of adrenaline. Undue lability of the arterial blood pressure would suggest the presence of a phaeochromocytoma. Wilkins *et al.* (1950) imply that the natural history of

the condition may be a progression from paroxysmal hypertension through "intermittent normotension" on to sustained hypertension. It would appear probable that a greater lability of blood pressure would occur in the intermediate stages of the natural course of that condition than in a case of essential hypertension. Hence observation of the day-to-day or hour-to-hour variations in blood pressure in the hypertensive patient would be of value.

Investigations directed to the cardiovascular system that can be easily undertaken may provide responses highly suggestive of phaeochromocytoma. The sedation test (Smithwick, 1948) performed in the above case did not give rise to the usual depressor response (Fig. 2). In the hypertensive subject a substantial fall in diastolic blood pressure commonly results, and, while an abnormal response in only one case is not significant, it is considered that the response of this patient to sedation was unusual and in the circumstances noteworthy.

Smithwick *et al.* (1950) found that in patients with hypertension due to phaeochromocytoma the responses to change in posture and to cold differed from the responses common in essential hypertension. For clinical purposes the cold-pressor (Hines and Brown, 1932) and postural tests are probably best combined as suggested by Smithwick (1948). Briefly, readings of blood pressure and pulse rate are taken at one-minute intervals for five-minute periods with the patient successively lying, sitting, and standing. The patient again lies down and a cold-pressor test is carried out in the horizontal position and, after an interval, with the patient sitting. In essential hypertension postural hypotension occurs only in 3% of cases and postural tachycardia in 15%. Of nine cases of phaeochromocytoma four had postural hypotension and five had postural tachycardia. A "negative" cold-pressor test is not common (22%) in essential hypertension, but seven of nine patients with medullary tumour had no significant rise in pressure to the cold stimulus. All of the above figures are taken from Smithwick *et al.* (1950). These results suggest that most patients with phaeochromocytoma would be distinguishable from those suffering from essential hypertension by the response to posture and cold. The tests can be performed simply, without complicated apparatus and without risk to the patient, and should also give further information on the vascular state in hypertensive disease.

Radiological studies have included intravenous pyelography, by means of which downward displacement of the kidney by the adrenal tumour may be seen. Barnett *et al.* (1950) reported three cases of phaeochromocytoma in which the tumour was demonstrated radiologically. Perirenal insufflation of air to demonstrate adrenal tumour may be dangerous and has resulted in fatalities. Calcification was present in the phaeochromocytoma removed from my case, and was noted on the lumbar skiagram.

Pharmacological Tests

The pharmacological tests suggested for phaeochromocytoma fall naturally into two groups. Certain substances cause a discharge of adrenal pressor substance into the circulation in patients suffering from phaeochromocytoma. Of these, histamine 0.025 mg. intravenously (Roth and Kvale, 1945), tetraethylammonium bromide (La-Due *et al.*, 1948), and methacholine chloride (Guarneri and Evans, 1948) have been put to clinical trial. Their administration to a case of phaeochromocytoma precipitates an attack of hypertension, but this effect is in itself not without risk. The histamine test has had a more extensive trial than either of the others. It is probably best suited for the production of an attack in patients with paroxysmal hypertension but normotensive when seen. The rise in pressure with histamine is in excess of the pressor response to cold in patients with phaeochromocytoma. The converse is true in essential hypertension. Wilkins *et al.* (1950) recommend that a suitable hypotensive blocking agent be available when the test is performed, as a very great increase in pressure has been observed in patients with phaeochromocytoma. Smaller doses (0.01 mg. i.v.) of histamine may prove safer and yet give evidence of the presence of the tumour. It seems likely that, while the histamine test is of value in cases with paroxysmal hypertension, if the hypertension is sustained the results may be difficult to interpret and the side-effects dangerous.

The mechanism of action of the histamine test is not at present clear. The general explanation is that a reflex overproduction of adrenal medullary pressor substance results in response to the sudden hypotension. However, tetraethylammonium bromide also causes a similar response: this substance blocks the efferent pathway of the postulated reflex at the junction of preganglionic fibre with the cells of the adrenal medulla (Morrison and Farrar, 1949). Histamine may act by a direct stimulation of the adrenal medullary tissue.

The second group of substances is probably of greater value in the diagnosis of phaeochromocytoma with sustained hypertension. These agents are known as the "adrenergic blocking substances." Nickerson (1949) deplores the use of "adrenolytic" in this connexion, pointing out that, in general, the latter term is an incorrect description of the action of these agents. Dibenamine (Spear and Griswold, 1948), dihydroergokryptine (Wilkins *et al.*, 1950), "regetin" (Grimson *et al.*, 1949), and piperidyl-methyl-benzodioxane (933 F) (Goldenberg *et al.*, 1947) have been used in their capacity as adrenaline-blocking agents in the diagnosis of phaeochromocytoma. Of these substances 933 F, now known as "piperoxane," has had the widest and most successful trial. In this test 0.25 mg. of 933 F per kg. body weight is injected intravenously. A moderate rise in blood pressure occurs in essential hypertension, while a distinct fall in blood pressure of up to 15 minutes' duration is noted in phaeochromocytoma. Recently Goldenberg and Aranow (1950) have reviewed the findings with this test. They record positive reaction to 933 F in 59 patients with proved phaeochromocytoma and only three false negative reactions. There were no known false positive responses to the test. This report indicates the effectiveness of the benzodioxane test for phaeochromocytoma.

However, reports have appeared stressing the severe side-reactions which the drug may occasion in essential hypertension. Drill (1949) noted an excessive rise in blood pressure with 933 F in essential hypertension. Green and Peterson (1950) reported an encephalopathy under similar circumstances, and on one occasion I have used tetraethylammonium bromide to prevent the development of encephalopathic manifestations. Rosenheim (personal communication, 1950) has observed acute pulmonary oedema in a hypertensive patient to whom 933 F had been given. Pentamethonium iodide was given to reduce the excessive hypertension, and venesection had to be performed. Wilkins *et al.* (1950) also remarked on the variability of the subjective response to 933 F and reported severe reactions to 933 F in 8%

of hypertensive patients. Nor does the action of 933 F appear to be straightforward. Prunty and Swan (1950) were usually unable to cause a reduction in the hypertension resulting from continuous infusions of adrenaline or *nor*adrenaline in normal subjects on injection of 933 F; in one subject only, undergoing an infusion of *nor*adrenaline, a slight fall in pressure was obtained. These workers considered that in their experimental investigation the excitatory effect of this drug on the cardiac output balanced or outweighed its inhibitory effect on the periphery. In essential hypertension the excitatory effect on the cardiac output may be considerable while the peripheral (inhibitory) response is slight, and thus a rise in arterial blood pressure occurs in susceptible hypertensive patients. Prunty and Swan did not dispute either the diagnostic value of 933 F in phaeochromocytoma or its blocking action on certain aspects of adrenergic activity. They considered, however, that its mode of action was complex and could not be explained as a simple blockade of circulating adrenaline-like substances. Morison and Lissak (1938) indicated that 933 F might accelerate the inactivation of adrenaline.

Piperoxane is the most effective pharmacological agent at present in general use in the diagnosis of phaeochromocytoma, but the physician should have a suitable hypotensive agent at hand lest he encounter a severe hypertensive reaction. Regetin has not had as extensive a trial as piperoxane, but Grimson *et al.* (1949) report responses similar to those obtained with piperoxane in patients with essential hypertension, and in a case of phaeochromocytoma.

Recently a different approach to the problem of diagnosis has been made by Engle and Euler (1950). These workers have demonstrated the presence of large amounts of adrenaline-like substances in the urine of patients suffering from phaeochromocytoma. The catechols are not found in quantity in normal subjects or in patients with essential hypertension. However, estimation of the catechols in the urine is not simple and requires some experience in the handling of biological preparations. Without doubt this method would prove most valuable if the technical difficulties could be overcome and the biological assay reduced to simple methods. Details of the estimation of the catechols are contained in Euler's (1950) review on *nor*adrenaline. The method of concentration from the urine has also been described (Euler and Hellner, 1950).

The following steps are suggested to aid in the early diagnosis of phaeochromocytoma with sustained hypertension. Particular attention should be given to the patient with sustained hypertension who complains of excessive sweating. If there is no complaint of the symptom a direct inquiry may be made, as the patient might consider that his excessive sweating was merely a personal extravagance. Inquiry should also be made into the occurrence of vasomotor disturbances—cold fingers, pallor, or numbness. If possible both cold-pressor and postural tests should be carried out on all hypertensive patients, but if facilities are limited these tests might be performed on hypertensive patients who complain of excessive sweating. Evidence of altered sugar metabolism and increased metabolic rate should be sought and an attempt made to visualize an adrenal swelling by means of low penetration *x* rays. A benzodioxane test would confirm the presence of a biologically active tumour. The presence of adrenal pressor substances may be demonstrated in the urine if facilities for their estimation are available.

Summary

A case of phaeochromocytoma of the left adrenal gland in which the tumour was successfully removed is described. The post-operative collapse which supervened was overcome by an infusion of L-*nor*adrenaline. The arterial blood pressure, which had been persistently elevated for at least seven years, reverted to normal levels. In retrospect certain clinical features are noted which might have suggested the post-operative diagnosis.

The diagnosis of phaeochromocytoma with sustained hypertension is discussed.

Acknowledgment is made to those mentioned in the text who were concerned in the management of the case. I have to thank Dr. J. S. Richardson for permission to publish the case records and for kindly reading the manuscript. Dr. R. S. Duff and Miss Weddell gave valuable assistance.

REFERENCES

Barcroft, H., and Konzett, H. (1949). *J. Physiol.*, **110**, 194.
Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. H., and Wilson, G. M. (1950). *Clin. Sci.*, **9**, 151.
Drill, V. A. (1949). *New Engl. J. Med.*, **241**, 777.
Engle, A., and Euler, U. S. von (1950). *Lancet*, **2**, 387.
Euler, U. S. von (1950). *Ergebn. Physiol.*, **46**, 261.
—— and Hellner, S. (1950). *Acta physiol. scand.* In press.
Goldenberg, M., and Aranow, H. (1950). *J. Amer. med. Ass.*, **143**, 1139.
—— Faber, M., Alston, E. J., and Chargaff, E. C. (1949). *Science*, **109**, 534.
—— Pines, K. L., Baldwin, E. de F., Green, D. G., and Roh, C. E. (1948). *Amer. J. Med.*, **5**, 792.
—— Snyder, C. H., and Aranow, H. (1947). *J. Amer. med. Ass.*, **135**, 971.
Green, D. M. (1946). Ibid., **131**, 1260.
—— and Peterson, E. M. (1950). Ibid., **142**, 408.
Grimson, K. S., Longino, F. H., Kernodle, C. E., and O'Rear, H. B. (1949). Ibid., **140**, 1273.
Guarneri, V., and Evans, J. A. (1948). *Amer. J. Med.*, **4**, 806.
Hines, E. A., and Brown, G. E. (1932). *Proc. Mayo Clin.*, **7**, 332.
Holton, P. (1949). *J. Physiol.*, **108**, 525.
Labbé, M., Tinel, J., and Doumer (1922). *Bull. Soc. méd. Hôp. Paris*, **46**, 982.
La-Due, J. S., Murison, P. J., and Pack, G. T. (1948). *Ann. intern. Med.*, **29**, 914.
MacKeith, R. (1944). *Brit. Heart J.*, **6**, 1.
Morison, R. S., and Lissak, K. (1938). *Amer. J. Physiol.*, **123**, 404.
Morrison, J. L., and Farrar, C. H. (1949). *Proc. Soc. exp. Biol. N.Y.*, **71**, 235.
Nickerson, M. (1949). *Pharmacol. Rev.*, **1**, 27.
Prunty, F. T. G., and Swan, H. J. C. (1950). *Lancet*, **1**, 759.
Roth, G. M., and Kvale, W. F. (1945). *Amer. J. med. Sci.*, **210**, 653.
Smithwick, R. H. (1948). *Amer. J. Med.*, **4**, 744.
—— Greer, W. E. R., Robertson, C. W., and Wilkins, R. W. (1950). *New Engl. J. Med.*, **242**, 252.
Spear, H. C., and Griswold, D. (1948). Ibid., **239**, 736.
Swan, H. J. C. (1949). *Lancet*, **2**, 508.
Walton, J. N. (1950). Ibid., **1**, 438.
Wilkins, R. W., Greer, W. E. R., Culbertson, J. W., Halperin, M. H., Litter, J., Burnett, C. H., and Smithwick, R. H. (1950). *Arch. intern. Med.*, **86**, 51.

A report in the *Daily Telegraph* of Thursday, February 22, notes that one London dentist has received fees totalling £20,516 net for less than a year's work under the National Health Service. The sum represents his gross salary for the period April 1, 1950, to February 15 this year, after deduction of superannuation and other special contributions, but 52% is reckoned by the Ministry of Health as likely to be expenses. Even so, this means that the man in question has an earned income of over £10,000, since he has not reported having any assistant. It is the highest income yet experienced in the area of the London Executive Council, which paid an average of £3,000 for the last 10 months to the 1,056 dentists under agreement in the county of London. In the same period 2,179 general practitioners received an average of £936.