Case ReportsADRENO-CORTICAL HYPERACTIVITY—
TWO INTERESTING CASESR. W. LOGAN, M.B., CH.B., B.Sc.
*Registrar in Biochemistry*N. L. McMILLAN, M.B., CH.B.
Surgical Registrar
The Victoria Infirmary, Glasgow

Adrenocortical hyperactivity presenting as, or complicating, a surgical emergency is comparatively uncommon; but the finding of two such cases in the same ward within one month must be a very rare event. The following account is a description of the presenting features, biochemical diagnosis and treatment of the two patients concerned.

The first patient is presented as having possible congenital adrenal hyperplasia and the other was shown to have bilateral adrenocortical carcinomata.

Methods

Urinary Steroid Estimations: 17-ketosteroids were estimated by the method of Moxham and Nabarro (1956) as were the total 17-hydroxycorticosteroids. 17-hydroxycorticoids (17,21-dihydroxy, 20-ketosteroids) were estimated by Kornel's (1959) method using the Porter-Silber (1950) colour reaction. To ascertain the proportion of the steroids which was hydroxylated in the 11-position, the method of Hill (1960) was utilised, the result being expressed in ratio form: 11-deoxy-17-ketogenic steroids. Pregnanediol

11-oxy-17-ketogenic steroids was determined by the technique of Klopper, Michie and Brown (1955), and pregnanetriol by that of Bell and Varley (1960). Patterson's (1947) qualitative test was used to detect the presence of excess dehydroepiandrosterone, and separation of the 17-ketosteroids into 3α and 3β fractions was effected by a method based on Haslam and Klyne (1952).

Where applicable, ACTH stimulation was achieved by the intravenous infusion of 75 units (B.P.) over an 8 hour period, and adrenal suppression by the administration of betamethasone 0.5 mg. four times daily for three days.

In addition to morphological examination of the adrenocortical tumour in the Pathology Department of the Victoria Infirmary, studies were carried out in the Department of Steroid Biochemistry of the University of Glasgow, to ascertain the histochemistry of the tissue, and to determine its biosynthetic ability and hydroxylating enzyme content.

Case No. 1.

On 28th April, 1962, a 57-year-old married woman was admitted because of severe colic which radiated from the right lumbar region to the right groin. The pain had been present for four days and had worsened prior to admission. Vomiting had occurred several times and general weakness was also evident. There was no upset of micturition although the urine had been dark for a few days, and no history of dyspepsia or upset of bowel function was elicited.

The patient's past history included three hospital admissions. The first was in 1957 because of menorrhagia, when a diagnosis of cystic hyperplasia was made, and she was noted to have a blood pressure of 185/100 mm. Hg. Her menstrual history until then had been normal, the menarche occurring at the age of 13. There were two children, born in 1941 and 1943, both of whom were in good health. In 1959 she was admitted because of menopausal metrorrhagia, and on account of her obesity a radium menopause was performed in preference to a hysterectomy. She was then hypertensive, blood pressure 190/110.

In 1961, pneumonia led to her third admission and treatment with intravenous fluids was necessitated, because of collapse and a fall in blood pressure to 115/80. At that time she was found to have a non-functioning right kidney due to what was possibly a ureteric calculus at the level of the 5th lumbar vertebra. A probably incomplete 24-hour collection of urine (creatinine 0.29 g/24-hrs.) yielded high normal 17-ketosteroids (13.4 mg./24-hrs.) and low normal 17-hydroxycorticoids (5.1 mg./24-hrs.). A further control urine collection was requested to confirm a tentative diagnosis of the adrenogenital syndrome, and determination of the response to intravenous ACTH and steroids was suggested; but unfortunately the patient left hospital before this could be accomplished.

Examination on present admission (28.4.62)

This revealed an obese woman (214 lb.) in a state of shock. There was moderate tenderness on the right side of the abdomen and over the right loin. The pulse rate was 128/min., of good volume; but the blood pressure was only 85/50. Temperature, 103.5°F. Respiratory and cardiac examinations revealed nothing of note. Urine: albumin present, no sugar or ketones. The centrifuged deposit contained 5 pus cells per high power field.

The general impression was that the patient had renal colic and an associated urinary infection together with adrenal failure.

Immediate treatment included intravenous fluids and sulphadimidine—1 g. 4-hourly (for 2 days). Urinary steroid assays were performed in view of the findings in 1961 and a summary of the relevant information is given in Table I.

A diagnosis of the adrenogenital syndrome was made on the basis of the result obtained on 28th April, 1962, taking into account the 1961 figures. Clinically the only feature suggestive of previous excessive androgen production was the presence of facial hirsutism, the high 17-hydroxysteroid result doubtless being due in part to the administered cortisone.

TABLE I
SUMMARY OF FINDINGS IN CASE I

Date	Procedure	Blood Pressure mm. Hg.	Urine				Plasma		Creatinine Clearance ml./min.
			Creati- nine g./ 24 hrs.	17-Ket- osteroids mg./24 hrs.	17-Hydroxysteroids mg./24 hrs.	Kornel Moxham and Nabarro	Urea mg./ 100 ml.	Creati- nine mg./ 100 ml.	
1957 1959 1961 28th April, 1962	Intramuscular cortisone 50 mg.	185/100 190/110 115/80 85/50	0.29 *1.45	13.4 43.8	5.1 39.7	55.0	177	5.4	
29th April, 1962	50 mg. t.i.d.	100-110/60-70							
30th April, 1962	50 mg. t.i.d.	120/80							
1st May, 1962	50 mg. t.i.d. + DOCA 5 mg. b.d.	130-140/80							
2nd May, 1962	DOCA 5 mg. b.d. + Cortisone 25 mg. t.i.d.	110/70					131	2.1	44
3rd May, 1962	Cortisone 50 mg. t.i.d. + DOCA 5 mg. b.d.	140/80	1.24	14.4	18.9		75	1.2	69
4th May, 1962	Cortisone 25 mg. t.i.d. + Aldosterone i.v. 0.5 mg. b.d.	110/70							
5th May, 1962	Cortisone 37.5 mg. t.i.d.	140/80							
9th May, 1962	Cortisone 50 mg. b.d.	140/80	1.55		22.6				
11th May, 1962	Cortisone 50 mg. t.i.d.	140/80	1.26	9.9	37.3				
15th May, 1962	Betamethasone 0.5 mg. q.i.d.	140/80	1.33	9.4	18.6				
19th May, 1962	0.5 mg. q.i.d. + Potassium citrate 20% 2 drams q.i.d.	155/100	1.10	1.4	4.8				
21st May, 1962	Patient Discharged from Hosp.								
27th May, 1962	Betamethasone 0.5 mg. q.i.d.	160/100	1.25	6.8	6.3				
20th July, 1962	0.5 mg. q.i.d.	155/100	1.03	2.6	2.0				
9th Sept., 1962	0.5 mg. t.i.d.	155/100	1.32	5.1	6.8				
23rd Sept., 1962	0.5 mg. t.i.d.	160/100					39	1.2	120
24th April, 1963	0.5 mg. b.d.	160/100	1.07	5.4	6.2				

*11-deoxy 17-ketogenic steroids

11-oxy 17-ketogenic steroids = 0.9:1

(normal range [in children] 0.06—0.57)

Pregnanediol 5.2 Pregnanetriol 0.2

Electrolytes (mEq./litre.):— Sodium 136: Potassium 4.3: Chloride 95: Carbon dioxide 18.7

One point of interest was the fact that both DOCA and intravenous aldosterone failed to maintain the patient's blood pressure, only cortisone and later betamethasone being effective. The suppression of the 17-ketosteroid production by the latter agent rendered the presence of an adrenal tumour very unlikely and the diagnosis of congenital adrenal hyperplasia a strong possibility (Soffer, Dorfman and Gabrilore, 1961).

Perirenal insufflation was unsuccessful and tomography failed to reveal any adrenal enlargement. An IVP in May, 1962, again demonstrated the absence of right-sided renal function; but in July, 1962, some restoration of function had occurred.

At present the patient is enjoying good health.

Case No. 2

For 19 days prior to admission on 22nd May, 1962, the patient, a young unmarried woman aged 25, suffered from a pain in her right loin and right iliac fossa. During the last four days the colicky pain intensified and on the day before entering hospital she vomited. At no time was she troubled by dysuria and there was no history of dyspepsia. She did admit, however, that she had experienced similar attacks of pain for about 4 years, and that the episodes occurred every 4-6 weeks, lasting from 4 to 21 days at a time. Apparently she menstruated from the age of 17 until 21, although the periods were irregular and scanty, varying in interval from 4 weeks to 9 months. Since the age of 21 there had been no further vaginal bleeding. Her only other complaint was that she was subject to migrainous headaches.

Some time previously she had been investigated on account of her amenorrhoea and the finding of a hypoplastic uterus was noted. At that time she was apparently given what proved to be an unsuccessful course of gonadotrophins. At the age of 22 she was treated at home for pyelitis.

She had twice before been examined by her own doctor as a suspected case of appendicitis; but with conservative treatment the pain had settled on both occasions.

On Examination: The patient was flushed and lay ill at ease. There was tenderness in the right iliac fossa and what appeared to be a mass in the right hypochondrium; but guarding made the latter finding difficult to demonstrate. Bowel sounds were present and there was no peritoneal irritation. Examination of the urine revealed no abnormality. The breasts were atrophic and there was present a moderate degree of facial hirsutism, although there was not a frankly male escutcheon. Moderate clitoral enlargement existed.

An IVP showed that renal activity on the left side was impaired, and that there was clubbing of the calyces on both sides. About this time a specimen of urine submitted to bacteriological examination yielded a heavy growth of *E. coli*, and a course of sulphonamides was given until the development of a skin rash led to withdrawal of the drug. A cholecystogram revealed a non-functioning gall bladder without demonstrating the presence of any calculi.

The temperature never rose above 99°F. during the period of the patient's stay in hospital and the blood pressure was 103/75 mm. Hg. Clinically the impression was of a young woman showing

TABLE II
URINARY STEROIDS IN CASE 2 FOLLOWING ACTH AND BETAMETHASONE

Day	Procedure	Creatinine g./24 hrs.	17-ketosteroids mg./24 hrs.	17-hydroxysteroids mg./24 hrs.	
				Kornel	Moxham and Nabarro
1.	Nil	0.48*	19.8	20.1	63.8
2.	Nil	1.18	52.8	49.7	149.8
3.	ACTH 75 units intravenously over 8 hours	1.04	45.5	55.9	126.2
4. }	Betamethasone 0.5 mg. x 4 per day	1.10	69.3	54.3	182.4
5. }		0.73	52.8	40.2	128.0
6. }		0.83	53.3	35.9	—

*Incomplete urine collection.

moderate signs of masculinity and repression of secondary female characteristics.

Laboratory Investigations: 24-hour urinary steroid outputs were—17-ketosteroids 45.7 mgs. 17-hydroxycorticoids 22.0 mgs. (Kornel). These findings suggested a diagnosis of (a) mixed adrenocortical hyperactivity due to an adrenal tumour or (b) possible congenital adrenal hyperplasia (with high Porter-Silber chromogens as in case 1).

Further investigations included (1) ACTH stimulation, (2) Betamethasone suppression and (3) Glucose tolerance test.

The GTT yielded a flat curve, probably due to defective absorption following a vasovagal attack after the test dose of glucose. The urinary findings in response to tests (1) and (2) are shown in the accompanying table II.

The ratio of $\frac{11\text{-deoxy } 17\text{-ketogenic steroids}}{11\text{-oxy } 17\text{-ketogenic steroids}}$ was raised (1.2:1) on urinary specimen (1) and Patterson's test for dehydroepiandrosterone was weakly positive. Fractionation of the 3 and 3 β 17-ketosteroids on the same urine, however actually yielded the normal percentage of 12.9 for the β components. Urinary pregnanediol excretion was 10.8 mg./24 hours and pregnanetriol 1.2 mg./24 hours. Since laparotomy was to be performed, perirenal insufflation was not attempted.

With the subsidence of pain, a large mass in the right hypochondrium could clearly be felt for a day or two prior to operation.

Operation (21.6.62). The usual preoperative course of ACTH was omitted on the assumption that the adrenal tissue was unresponsive, as had been shown by the result of the infusion test. Steroid cover was provided in the form shown below.

24-hours before operation — 100 mg. cortisone acetate i.m.
4-hours before operation — 100 mg. cortisone acetate i.m.

Before going to theatre a slow intravenous infusion was instituted, containing 200 mg. hydrocortisone hemisuccinate 500 mg. Anaesthesia began at 9.20 a.m., flaxedil, halothane, nitrous oxide and oxygen being used. Laparotomy revealed a huge tumour, presumably arising from the right adrenal gland. It was largely necrotic and cystic and was densely adherent to surrounding structures, particularly the underside of the liver. Attempted removal of the mass led to considerable haemorrhage, chiefly from the liver, and despite transfusion with blood and plasma, followed later by external and finally direct cardiac massage, collapse occurred and the patient died one-and-three-quarter hours after commencement of the operation.

Histology. The large tumour of the right adrenal gland weighed 1500 grams. Numerous sections were prepared from this for microscopic examination, and we are very grateful to Professor T. Symington of the Department of Pathology, Glasgow Royal Infirmary, for his co-operation in allowing us to use the photomicrographs. Normal adrenal architecture was absent in the sections examined and the tumour was malignant. The left adrenal gland, whilst being atrophic, contained what was probably a small primary carcinoma.

Enzymatic Studies. For these we are indebted to Dr. J. K. Grant of the Department of Steroid Biochemistry, the University of Glasgow. They demonstrated that the tumour responded very feebly *in vitro* to ACTH. The response involved both 11 β -hydroxylation and cortisol formation, and contrasted with the findings reported following ACTH *in vivo*.

Discussion

Case No. 1. For normal routine purposes, it has been standard practice in this laboratory to use a Porter-Silber reaction for determining 17-hydroxycorticoids. This procedure is known to give falsely high results if the patient is receiving certain drugs, notably—iodides, chloral hydrate or sulphamerazine (Marks and Leftin, 1954 and Lamp-Hintzen and Veld, 1955). Therefore the early treatment with sulphonamides rendered the elevated 17-hydroxycorticoid result suspicious; but determination by the method of Moxham and Nabarro confirmed the high 17-hydroxycorticoid levels. This finding raised the question of how a patient with congenital adrenal hyperplasia could be producing excess 17-hydroxysteroids whilst at the same time suffering from hypotension which responded only to cortisone.

To explain the absence of clinical signs compatible with the elevated 17-hydroxycorticoid figures it is necessary to consider the various types of enzymatic defect encountered in congenital adrenal hyperplasia.

The most common syndrome is that due to deficiency in the 21-hydroxylase system (Wilkins, 1962) whereby there are low amounts of cortisol produced (Wilkins, Gardner, Crisler, Silverman and Migeon, 1952) together with large amounts of 17-ketosteroids and pregnanetriol (Jailer, 1958). The clinical picture is one of simple virilism, with or without a sodium-losing syndrome.

FIG. 1.—Macroscopic view of the adrenocortical carcinoma removed from Case 2.

In the case described, however, the Kornel method for 17-hydroxycorticoids yielded results above the normal range, and as this is specific for steroids having the side chain

(Silber and Porter, 1954), there was obviously no gross defect in 21-hydroxylation. The even higher figure obtained by the borohydride/sodium bismuthate technique (Moxham and Nabarro) is understandable since this estimates four separate side chain groupings.

(Appleby, Gibson, Norymberski and Stubbs, 1955.)

FIG. 2.—Adrenocortical carcinoma in case 2. The trabecular arrangement of the cells and the presence of vascular spaces is shown. Most of the cells in this section are necrotic. The cytoplasm of the cells has shrunk from the basement membrane.

FIG. 3.—Adrenocortical carcinoma in Case 2. The cells are arranged in solid trabeculae which are divided by thin vascular spaces. Many cells have a vesicular nucleus with prominent nucleolus. There is no marked pleomorphism and few mitotic figures. The cytoplasm of these cells is eosinophilic and the cells are vacuolated. A number of dark staining necrotic cells are seen. The mixture of vesicular and pyknotic nuclei is shown. The hyaline vacuolated cytoplasm is prominent in the cells.

Moreover, the ratio of the latter to the former, 55.0, agrees well with that found in normal 39.7, individuals with ranges of $\frac{8 - 22 \text{ mg./24 hours}}{5 - 15 \text{ mg./24 hours}}$ thereby strengthening the conclusion that hydroxylation at position 21 was normal.

In 1955, however, a further enzymatic defect was described in which there is failure of 11 β -hydroxylation, resulting in the urinary excretion of large amounts of tetrahydro compound S (Eberlein and Bongiovanni, 1955, 1956). This produced virilism together with hypertension due to excessive DOC production and was associated

with a lower excretion of pregnanetriol than was found in the common variety. Such a defect would help to explain the hypertension previously reported in our case (190/110), and would account for the increased 17-hydroxycorticoid excretion in the absence of Cushingoid signs since compound S is very feebly glycogenic. The relatively elevated figure obtained for the 11-deoxy 17-ketogenic steroids would also be compatible with a partial blockage in 11 β -hydroxylation. Thus apart from the low pregnanetriol excretion which is against an 11 β -hydroxylation defect of any marked degree, the findings could be explained on the basis of incomplete blockage of 11 β -hydroxylation.

No attempt was made to demonstrate the presence of the rare form of congenital adrenal hyperplasia more recently described, in which there is a 3 β -hydroxysteroid dehydrogenase enzyme deficiency (Bongiovanni, 1961).

The failure of either DOCA or intravenous aldosterone to raise the patient's blood pressure during the present admission is an interesting finding and one for which two explanations are possible. The first is that, concomitant with the long continued excess of 11-deoxycorticosterone, the adrenal gland was also manufacturing a hormone antagonistic in action to DOC. This antagonist might even be a metabolite of DOC. A similar situation pertains in Cushing's syndrome where the administration of DOCA produces a paradoxical rise in the urinary sodium (Soffer, Lesniek, Sorkin, Sobotka and Jacobs, 1944, Soffer, Jabriolove and Jacobs 1949). Unfortunately urinary electrolytes were not estimated at the time of the DOCA or aldosterone therapy. The other, and probably more likely explanation is that for hypertension or even orthotension to obtain, it may be necessary to have a threshold amount of cortisol present, without which the blood pressure is unresponsive to even massive doses of aldosterone. This hypothesis would place cortisol in the key role for the subsequent action by aldosterone in sensitising blood vessels to noradrenaline (Ross, 1961).

In the present case, it is suggested that the development of the urinary infection increased the demands for cortisol beyond the rate at which the adrenal glands, with their possibly defective 11 β -hydroxylation, could effect production, thereby precipitating circulatory collapse. This role of cortisol as a permissive agent is analogous to that found in craniopharyngioma involving destruction of both anterior and posterior pituitary function where the diabetes insipidus may remain latent until the anterior pituitary failure is treated with glucocorticoids (Williams, 1962a).

Case 2. Basically the same tests were used as in case 1, the principal difference being that

an 8-hour ACTH infusion was administered. Certain workers have claimed that differentiation between an adrenal adenoma and an adrenal carcinoma can usually be achieved by measuring the response to ACTH, only the former tumour showing a response (Williams, 1962b, Brooks 1962). On the other hand, it has been stated that neither tumour may respond to ACTH (Soffer and others, 1961), whilst in direct contrast to this stands the report of response to ACTH by an adrenal carcinoma (Ibbertson and O'Brien, 1962). The unpredictability of findings in adrenal tumours both with regard to hormonal and chemotherapeutic agents has been mentioned by Gallagher (1957). Probably all that can be said is that a lack of response in ACTH is strongly suggestive of adrenal tumour, which may be either an adenoma or a carcinoma. So, too, the finding in the present study of a normal excretion of dehydroepiandrosterone has previously been observed in adrenocortical carcinoma (Van der Wiele, Christy, Lieberman and Jailer, 1958).

As in the first case, a possible failure of 11 β -hydroxylation, supported by the increased 11-deoxy 17 ketogenic steroids/ 11-oxy 17-ketogenic steroids ratio, would explain the high 17-hydroxycorticoid figures without the features of Cushing's syndrome. The wide discrepancy between the 17-hydroxysteroids as estimated by the two methods (Kornel 49.7 mg., Moxham and Navarro 149.8 mg.) suggests, however, that there was either a failure of 21-hydroxylation or else excessive reduction at carbon atom 20 to CHOH , or perhaps a combination of both features. There are two findings in support of these assumptions. First, compound S, which results from failure of 11 β -hydroxylation, is metabolised and excreted largely in the C-20 reduced form (Gold, Dimimondo and Forsham, 1960). Second, the report (Lipsett and Wilson, 1962), in several cases of adrenocortical carcinoma, of the presence of a similar gross disparity between Silber-Porter chromogens and total 17-hydroxysteroids, due to the excretion of 17, 20, 21-triols.

It is of interest to note that while case 2, showing hydroxylation defects affecting carbon atoms 11 and possibly 21, was one of adrenocortical carcinoma, similar mixed defects have been reported in cases of congenital adrenal hyperplasia (Birke, Diczfalusy, Plantin, Robbe and Westman, 1958; Gandy, Reutmann and Iggo, 1960). This similarity of abnormal steroid patterns is not so surprising, however, since both conditions are associated with enzyme deficiencies in the pathways of steroid biosynthesis rather than with the development of new enzyme systems.

It is worthwhile considering moreover, that whilst only two probable enzyme deficiencies have

been demonstrated in the case of the adrenal tumour, several others could possibly be implicated if special studies were made. In this connection it is plausible to speculate that, fundamentally a loss of biosynthetic ability could be explained as being secondary to a parallel loss of chromosomal ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), since this would lead in turn to a lack of specific microsomal RNA, and thereby, of associated protein (enzyme) formation. Recent densitometric determinations of nuclear nucleic acid concentrations in adrenocortical carcinomata have yielded results which accord, initially at least, with this hypothesis (Symington, 1964).

Finally, the use of betamethasone instead of dexamethasone in the suppression tests was justified by numerous studies showing that both compounds have roughly comparable activities with regard to adrenocortical suppression (Coke, 1961; Glyn and Fox, 1961; Wilkinson, 1961). Furthermore, it has been argued (Williams, 1962c) that steroid therapy in adrenocortical hyperplasia must vary, depending on the nature and extent of the enzymatic defect involved. In the type with impaired 21-hydroxylation and sodium-losing syndrome coexistent with virilisation, cortisone for ACTH suppression must be combined with 9 α -fluorocortical to substitute for deficient mineralocorticoid secretion. On the other hand, in the type with defective 11 β -hydroxylation and hypertension due to excessive secretion of 11-

deoxysteroids, as suggested in our case 1, the only therapeutic measure required is a glucocorticoid with low sodium-retaining properties. For this reason the selection was made of betamethasone, to produce suppression of ACTH secretion and hence of adrenocortical hyperactivity.

Summary

Two cases of adrenocortical hyperactivity are described.

Both were discovered following admission for investigation of abdominal pain. The biochemical diagnosis of one as possible congenital adrenal hyperplasia and the other as adrenocortical carcinoma is dealt with in detail.

The paradoxical finding of elevated 17-hydroxysteroids without manifestations of Cushing's syndrome is considered, with special reference to the various enzymatic defects present in congenital adrenal hyperplasia and adrenocortical carcinoma.

The treatment is discussed of the former patient using betamethasone.

Thanks are due to Dr. I. A. Anderson for his guidance in the biochemical investigations; to Mr. J. P. Galloway and Mr. R. J. Webster, consultant surgeons, under whose care the patients were treated; and to Dr. J. E. Craik who reported the pathology of the tumour. Acknowledgment is made to Professor T. Symington and Dr. J. K. Grant for permission to publish results of their morphological and enzymatic studies on the adrenocortical carcinoma.

REFERENCES

- APPLEBY, J. I., GIBSON, G., NORBYERSKI, J. K., and STUBBS, R. O. (1955): Indirect Analysis of Corticosteroids. The Determination of 17-hydroxycorticosteroids, *Biochem. J.*, **60**, 453.
- BELL, M., and VARLEY, H. (1960): The Estimation of Pregnenetriol and 17-hydroxypregnanolone in Urine in Congenital Adrenal Hyperplasia, *Clin. Chim. Acta.*, **5**, 396.
- BIRKE, G., DICZFALUSY, E., PLANTIN, L. O., ROBBE, H., and WESTMAN, A. (1958): Familial Congenital Hyperplasia of the Adrenal Cortex, *Acta endocr. (Kbh.)*, **29**, 55.
- BONGIOVANNI, A. M. (1961): Unusual Steroid Pattern in Congenital Adrenal Hyperplasia: Deficiency of 3 β -hydroxy Dehydrogenase, *J. clin. Endocr.*, **21**, 860.
- BROOKS, R. V. (1962): Disorders of Biosynthesis in Man. In 'The Adrenal Cortex', *Brit. med. Bull.*, **18**, No. 2, 149.
- COKE, H. (1961): A Preliminary Trial of Betamethasone, *Rheumatism*, **17**, 70.
- EBERLEIN, W. R., and BONGIOVANNI, A. M. (1955): Congenital Adrenal Hyperplasia with Hypertension: Unusual Steroid Pattern in Blood and Urine, *J. clin. Endocr.*, **15**, 1531.
- EBERLEIN, W. R., and BONGIOVANNI, A. M. (1956): Plasma and Urinary Corticosteroids in the Hypertensive Form of Congenital Adrenal Hyperplasia, *J. biol. Chem.*, **223**, 85.
- GALLAGHER, T. F. (1957): On Alterations in Adrenal Function, especially with Adrenocortical Carcinoma, *Cancer Res.*, **17**, 520.
- GANDY, H. M., KEUTMANN, E. H., and IZZO, A. J. (1960): Characterization of Urinary Steroids in Adrenal Hyperplasia: Isolation of Metabolites of Cortisol, Compound S, and Desoxycorticosterone from a Normotensive Patient with Adrenogenital Syndrome, *J. clin. Invest.*, **39**, 364.
- GLYN, J. H., and FOX, D. B. (1961): Preliminary Clinical Assessment of Betamethasone, *Brit. med. J.*, **i**, 876.
- GOLD, E. M., DIRAIMONDO, V. C., and FORSHAM, P. H. (1960): Quantitation of Pituitary Corticotropin Reserve in Man by Use of an Adrenocortical 11-beta Hydroxylase Inhibition (SU-4885), *Metabolism*, **9**, 3.
- HASLAM, R. M., and KLYNE, W. (1952): Micro-method for Determination of Urinary α -ketosteroids and β -ketosteroids. By Digitonin Fractionation and Colorimetric Estimation, *Lancet*, **i**, 285.
- HILL, E. E. (1960): Chromatography of the 17-ketogenic Steroids in the Diagnosis and Control of Adrenal Hyperplasia, *Acta endocr. (Kbh.)*, **33**, 230.

- IBBERTSON, H. K., and O'BRIEN, K. P. (1962): Adrenal Autografts in Treatment of Cushing's Disease, *Brit. med. J.*, **ii**, 703.
- JAILER, J. W. (1953): Virilism, *Bull. N.Y. Acad. Med.*, **29**, 377.
- KLOPPER, A., MICHIE, E. A., and BROWN, J. B. (1955): A Method for the Determination of Urinary Pregnenolone, *J. Endocr.*, **12**, 209.
- KORNEL, L. (1959): An Improved, Rapid Method for Free and Conjugated 17-hydroxycorticosteroids in Urine, *Metabolism*, **8**, 432.
- LAMP-HINTZEN, D. A. V. M., and HUIS IN'T VELD, L. G. (1955): Atypical Porter-Silber Reaction after the Administration of Sulfamerazine, *J. clin. Endocr.*, **15**, 1152.
- LIPSETT, M. B., and WILSON, H. (1962): Adrenocortical Cancer: Steroid Biosynthesis and Metabolism Evaluated by Urinary Metabolites, *J. clin. Endocr.*, **22**, 906.
- MARKS, L. J., and LEFTIN, J. H. (1954): A Note of Caution on the Lack of Specificity of the Porter-Silber Reaction for 17, 21-dihydroxy-20-ketosteroids, *J. clin. Endocr.*, **14**, 1263.
- MOXHAM, A., and NABARRO, J. D. N. (1956): Urinary Glucocorticoid Excretion, *J. clin. Path.*, **9**, 351.
- PATTERSON, J. (1947): Diagnosis of Adrenal Tumours, *Lancet*, **ii**, 580.
- PORTER, C. C., and SILBER, R. H. (1950): A Quantitative Color Reaction for Cortisone and Related 17, 21-dihydroxy-20-ketosteroids, *J. biol. Chem.*, **185**, 201.
- ROSS, E. J. (1961): The Adrenal Medulla, the Adrenal Cortex, Sodium and Blood Pressure, *Proc. roy. Soc. Med.*, **54**, 1005.
- SILBER, R. H., and PORTER, C. C. (1954): The Determination of 17, 21-dihydroxy-20-ketosteroids in Urine and Plasma, *J. biol. Chem.*, **210**, 923.
- SOFFER, L. J., DORFMAN, R. I., and GABRILOVE, J. L. (1961): The Human Adrenal Gland, p. 417, London: Henry Kimpton.
- SOFFER, L. J., LESNICK, G., SORKIN, S. Z., SOBOTKA, H., and JACOBS, M. D. (1944): The Utilization of Intravenously Injected Salt in Normals and in Patients with Cushing's Syndrome before and after Administration of Desoxycorticosterone Acetate, *J. clin. Invest.*, **23**, 51.
- SOFFER, L. J., GABRILOVE, J. L., and JACOBS, M. (1949): Further Studies with the Salt Tolerance Test in Normal Individuals and in Patients with Adrenal Cortical Hyperfunction, *J. clin. Invest.*, **28**, 1091.
- SYMINGTON, T.: Personal Communication.
- VAN DE WIELE, R., CHRISTY, N. P., LIEBERMAN, S., and JAILER, J. W. (1958): Cushing's Syndrome. IV. Urinary 17-ketosteroids in Patients with Adrenocortical Tumours (24405), *Proc. Soc. exp. Biol. (N.Y.)*, **99**, 520.
- WILKINS, L. (1962): Congenital Virilizing Adrenal Hyperplasia, *Arch. Dis. Child.*, **37**, 231.
- WILKINS, L., GARDNER, L. I., CRIGLER, J. F., Jr., SILVERMAN, S. H., and MIGEON, C. J. (1952): Further Studies on the Treatment of Congenital Adrenal Hyperplasia with Cortisone. (1) Comparison of Oral and Intramuscular Administration of Cortisone with a Note on the Suppressive Action of Compounds F and B on the Adrenal, *J. clin. Endocr.*, **12**, 257.
- WILKINSON, D. S. (1961): Betamethasone, *Brit. med. J.*, **i**, 1319.
- WILLIAMS, R. H. (1962a): Textbook of Endocrinology, Third Edition, p. 89. Philadelphia and London: W. B. Saunders Company.
- WILLIAMS, R. H. (1962b): *ibid*, p. 367.
- WILLIAMS, R. H. (1962c): *ibid*, p. 364.

MENINGISM AND PITUITARY COMA

J. M. S. PEARCE, M.B., M.R.C.P.*

Registrar in Neurology

J. I. BALLA, M.B., M.R.C.P.(Ed.)

Registrar in Neurology

From the Regional Neurological Centre, Newcastle-upon-Tyne.

IRIS SWANSON, M.B., B.S.

Senior House Officer

J. B. FOSTER, M.B., M.R.C.P.

Consultant Neurologist

Non-iatrogenic hypopituitarism usually results from one of two pathological processes, post-partum pituitary necrosis (Sheehan & Summers, 1949) or pressure upon the secretory cells of the gland by tumour tissue. The former condition presents with features of adrenal, thyroid and gonadal hypofunction; the latter is manifest by a combination of these signs of hypopituitarism accompanied by visual failure due to chiasmal compression. Less commonly the first indication of pituitary failure is the clinical state described as pituitary coma. Disturbance of consciousness in hypopituitarism may be due to hypoglycaemia, hypotensive fainting attacks, acute adrenal crisis, myxoedema coma, and water intoxication. The

onset of impaired consciousness is commonly precipitated by operation (particularly those involving the skull), by infection, or the inadvertent administration of narcotics, insulin or intravenous fluids. These features are frequently superimposed upon those of chronic pituitary failure, that is dry skin, loss of axillary and pubic hair, vulval atrophy, pallor and puffiness of the face. However, these signs may be minimal in degree and therefore easily overlooked. Various reviews of the subject have been written by Sheehan and Summers (1949, 1952), Farquharson (1950), Allott and Simmons (1951), Ingraham, Matson and McLaurin (1952), Perkins and Rynearson (1952), Caughey and Garrod (1954), and Caughey (1958).

*Present address: Senior Registrar, Dept. of Neurology, The General Infirmary, Leeds 1.