underwent dilatation and curettage at home, though this figure was reduced to 3.4% from 1951 to 1961. Nine out of our 25 calls were for complications of abortion and only one was shocked. We have neither the intention nor the facilities for carrying out a curettage at the patient's home.

We also found that the flying squad is very rarely called because of difficulties in labour or delivery, and these calls are unlikely to increase as all potentially complicated cases are booked for hospital confinement. We found no cause for administering an anaesthetic in the home and only two cases where an unmatched blood transfusion was necessary.

Most of our patients were admitted to hospital for further management and in every case we considered that the patient would have done as well if not better had she been brought straight to hospital by ambulance rather than waiting for the arrival of the obstetric flying squad. This conclusion pertains only to an urban area, where the distance to the hospital is likely to be short.

Unlike the experience of earlier surveys we were depressed by the many unjustified calls. These usually occur because the ambulance crew on the spot cannot differentiate between minor and major bleeding problems in pregnancy, and they have been trained to call the flying squad in all cases of doubt. Previously the flying squad has relied to a large extent on the "awareness and confidence of the general practitioner, obstetrician, and midwife,"¹ with the result that the vast majority of the calls

have been justifiable. In our area, where few general practitioners practise midwifery, the patient in difficulty at home will usually call the ambulance service first, so that the initiating call for the flying squad comes from a comparatively inexperienced service.

In common with the American Forces' experience in the Vietnam war we believe that acute emergencies are best dealt with by immediate transfer to an effective hospital and that in the urban area, where the hospital is never far from the patient's home, this cause is best served by taking the patient to the hospital rather than carrying out first aid in the home. In this respect we are no different from our surgical and medical colleagues.

In the exceptional case requiring emergency resuscitation at home we think that the task could be achieved by one person, possibly covering several specialties, and functioning either from the casualty department or from the local general practitioner unit.

References

- ¹ Liang, D Y S, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1963, **70**, 83.
- ² Stabler, F, *British Medical Journal*, 1947, **2**, 878.
- ³ Lloyd, H, *Proceedings of the Royal Society of Medicine*, 1949, **42**, 1.
- ⁴ Shotton, D M, *Proceedings of the Royal Society of Medicine*, 1949, **42**, 4.
- ⁵ Dewhurst, C J, *Lancet*, 1952, **2**, 746.
- ⁶ Fraser, A C, and Tatford, E P W, *Lancet*, 1961, **2**, 126.

Today's Treatment

Endocrine and metabolic diseases

Adrenal diseases

G M BESSER, W J JEFFCOATE

British Medical Journal, 1976, **1**, 448-451

Each adrenal gland is composed of two embryologically, anatomically, and functionally distinct parts—the medulla and cortex. Diseases of the adrenal medulla are confined to the development of tumours, which may be benign or malignant and which may or may not secrete catecholamines (table). There

Diseases of the adrenal medulla

Tumour	Cell type	Age	Note
Sympathoblastoma	Sympathogone	Infancy	Highly malignant
Neuroblastoma	Sympathoblast	Childhood	Highly malignant, may secrete catecholamines
Ganglioneuroma	Ganglion cells	Young adults	Benign or malignant
Phaeochromocytoma	Chromaffin cells	Adults	Benign or malignant, secrete catecholamines

Department of Endocrinology, St Bartholomew's Hospital, London EC1A 7BE

G M BESSER, MD, FRCP, professor

W J JEFFCOATE, MB, MRCP, research registrar

is no recognised clinical syndrome involving underactivity of the adrenal medulla. Diseases of the adrenal cortex on the other hand may be characterised by either over- or under-production of its hormones: glucocorticoids, mineralocorticoids, or sex steroids. When a hormone (or hormones) is produced in excess, it may derive from an adenoma, carcinoma, or generalised hyperplasia of the glands. When hormone production is inadequate, it may be the result of congenital defects, organic disease of the gland, or impaired adrenocorticotrophic hormone (ACTH) or renin production.

Diseases of the adrenal medulla

POORLY DIFFERENTIATED TUMOURS

The sympathoblastoma of infancy is highly malignant and treatment is almost uniformly unsuccessful. Neuroblastomas tend to occur in older children. They also are highly malignant although a combination of surgery and radiotherapy is rewarded by apparent cure in 10%. Neuroblastomas may secrete catecholamines. Ganglioneuromas are rare tumours which occur in young adults. They may be benign or malignant.

PHAECHROMOCYTOMAS

About 10% of phaeochromocytomas are bilateral and about 10% are not in the adrenal at all: they may be anywhere in the distribution of sympathetic neural tissue. When extra-adrenal they are most commonly found in the sympathetic chain, the bladder wall, or para-aortic bodies of Zuckerkandl; 10% are malignant.

Because of the excessive secretion of catecholamines from these tumours hypertensive crises and arrhythmias may occur. These attacks may, however, be entirely or largely blocked by treatment with alpha- and beta-adrenoceptor blocking drugs. Oral propranolol (40-80 mg eight hourly) and oral phenoxybenzamine (10-20 mg eight hourly) are recommended for those patients in whom removal of the tumour is either impossible or deferred. Care should be exercised in using these drugs together since hypotension may follow. They should preferably be first introduced while the patient is in hospital. If a patient has the rare form of phaeochromocytoma which is characterised by hypotensive attacks propranolol should be given alone.

Hypertensive crises and arrhythmias may occur also during investigative procedures such as arteriography, during abdominal surgery of any kind, and during labour. Preparation with alpha- and beta-blocking agents for these and for removal of the adrenal tumour itself must therefore always be performed. Daily infusions of phenoxybenzamine should be given for three days—in a dose of 1 mg/kg body weight in 250 ml of 5% dextrose infused over 1 hour. Propranolol is given by mouth, 40 mg eight hourly, over the same period—the first dose being given after the first infusion of phenoxybenzamine.¹

Profound hypotensive collapse may follow removal of a phaeochromocytoma. Patients with these tumours have a low plasma volume as a result of tonic vasoconstriction, and removal of the tumour is followed by widespread vasodilatation and the blood pressure falls. The preoperative preparation with phenoxybenzamine and propranolol allows expansion of the blood volume before surgery and prevents collapse. Nevertheless, adequate volumes of blood must be available for transfusion if necessary.

Diseases of the adrenal cortex

CUSHING'S SYNDROME

The causes of Cushing's syndrome fall into two main groups: (a) ACTH-dependent, due to excessive secretion of ACTH from the pituitary (Cushing's disease), from non-endocrine hormone secreting tumours (the ectopic ACTH syndrome), or due to treatment with exogenous ACTH; and (b) non-ACTH-dependent—benign or malignant adrenocortical tumours, or treatment with exogenous corticosteroids.

Pituitary-dependent bilateral adrenal hyperplasia (Cushing's disease)

The logical treatment of Cushing's disease is to remove the source of ACTH production from the pituitary. Unfortunately, this logical approach is not always possible. External irradiation of the pituitary gland produces cure in 25% and improvement in only a further 20%. The pituitary may be attacked by external irradiation using protons, implantation of radioactive yttrium or gold seeds, cryosurgery, and microdissection of the pituitary by the transphenoidal route; each has its advocates but no technique is in widespread use. Pituitary microdissection may well prove to be the treatment of choice in the future for good results have been claimed; it is sometimes possible to recognise and remove a small adenoma with only minimal disturbance to the rest of the gland. At the moment the technical expertise required for this operation is not widely available and experience is limited.

The main problem of conventional external irradiation is the delay of up to four years which may occur before it is fully effective. Often the patient with Cushing's disease is severely ill and this delay is unacceptable. This is why the combination of pituitary irradiation and bilateral adrenalectomy remains the treatment of choice in most centres. If a patient has an adrenalectomy but no irradiation he runs the risk of developing hyperpigmentation and enlargement of the pituitary fossa (Nelson's syndrome). This may be prevented by conventional external pituitary irradiation (4500 rads over four to five weeks) given within two months of adrenalectomy. After adrenalectomy patients must receive replacement treatment as for Addison's disease (see below).

We now use metyrapone for the long-term control of Cushing's disease. Its use is associated with a rapid clinical improvement which is maintained for long periods (one patient has been followed for four years). When used in combination with pituitary irradiation it provides a reversible "medical adrenalectomy" which controls the disease until the radiotherapy is effective. This regimen, however, has not been used for long enough for us to be sure of its overall long-term efficacy. Metyrapone lowers the production of cortisol in the adrenocortical cells by blocking enzymes controlling its synthesis. The dose chosen has to be individually tailored to each patient; it varies from 250 mg twice daily to 1 g six hourly. An average plasma fluorogenic corticosteroid level of 331-386 nmol/l (12-14 µg/100 ml) throughout the day is the aim since this will be associated with a normal 24-hour cortisol production rate.

Rarely, metyrapone will not control cortisol production fully and then aminoglutethimide may be added in a dose of 250 or 500 mg eight-hourly. It is, however, much more toxic than metyrapone. Because of the danger of adrenocortical insufficiency this "medical adrenalectomy" should be confined to those centres with facilities for frequent and rapid measurement of plasma cortisol. Undoubtedly, however, surgery may be avoided in many patients as a result of this treatment.

Adrenocortical adenoma

Treatment of adrenocortical adenoma is by excision. As with phaeochromocytoma, the tumours are bilateral in about 10% of cases and unless the side they are on can be precisely determined it is usual to recommend exploration of both glands. This is a big operation usually performed through an anterior approach and is associated with considerable morbidity. The risks are high because the untreated patient may be hypertensive and diabetic, has a bruising tendency, and has poor wound healing. Chronic potassium depletion may be present. Attempts may be made to localise the tumour before surgery. Plain abdominal x-ray examination or intravenous pyelography may help if the tumour is large.

Selective adrenal vein catheterisation may be used, but the most promising technique is the recently developed one of adrenal scanning with radioactively labelled iodocholesterol. With information from these investigations the surgeon may opt for the quicker, safer operation—exploring only one side through a loin incision.

As in Cushing's disease we also use metyrapone when preparing patients with adrenal tumours for operation. If a patient receives this drug for three months before surgery many features of this disease, including hypertension, diabetes, heart failure, plethora, and obesity will improve; the operation is easier and morbidity is considerably reduced.

Adrenocortical carcinoma

Similar principles relate to managing adrenal carcinoma. While leisurely preoperative preparation is obviously inappropriate, preparation with metyrapone need not be omitted altogether. Another drug which may be used is mitotane (o-p'-

DDD), which was originally discovered as a contaminant of DDT and which destroys both normal and malignant adrenocortical cells. Its use provides palliative control of the carcinoma and metastases for long periods. Eventually, however, the tumour escapes from its control. The doses used are often large (between 10 and 20 g in divided doses) and it may cause considerable gastrointestinal side effects.

Ectopic ACTH syndrome

The management of ectopic ACTH syndrome is similar to that of Cushing's disease. If the source of ACTH can be removed, it should be done. Alternatively, the primary lesion may respond to irradiation or chemotherapy. The greatly raised cortisol levels in blood may be controlled using metyrapone as in Cushing's disease. Often these patients are very sensitive to this drug and close monitoring of plasma corticosteroid levels throughout the day is necessary until the effective dose is reached. Some cover their patients with prednisolone (5 mg three times daily) or dexamethasone (0.5 mg three times daily) until the therapeutically adequate dose of metyrapone is reached but doing this may worsen the Cushingoid state. In these often very ill patients average daily plasma corticosteroid levels of about 552 nmol/l (20 µg/100 ml) should be the aim of treatment. Spironolactone should not be used to treat the hypokalaemia since it interferes with the usual fluorescent assay of plasma cortisol. Triamterene (50 to 100 mg three times daily) is better. Oral potassium supplements are also necessary at least initially.

Iatrogenic Cushing's syndrome

Withdrawal of the corticosteroids should be performed with care since it is well known that their use suppresses the hypothalamic-pituitary-adrenal axis. Any prolonged suppression which occurs is at the level of the hypothalamus or pituitary, and not the adrenal since adrenal atrophy quickly recovers. Hence a patient who has been withdrawn from steroids and is shown to have a normal cortisol response to ACTH need not necessarily have a normal cortisol response to stress.

HYPERALDOSTERONISM

Primary hyperaldosteronism (Conn's syndrome) may result from either adenoma or hyperplasia of the zona glomerulosa. It may be that when there is hyperplasia the hyperaldosteronism is not primary but secondary to some unrecognised adrenal-stimulating factor.

Adenomas occur more commonly on the left side, but they may be bilateral. As in other types of adrenal tumour it is conventional to explore both sides through an anterior approach although use of the localising techniques described above may allow the surgeon to explore only one side. Malignancy of these tumours is rare.

Spironolactone competitively blocks the effect of circulating aldosterone. In this condition the doses need to be high (100-400 mg daily) but it is not necessary to divide the dose. It may be used to control the disease before surgery; preoperative preparation is recommended since the patients are usually severely potassium depleted and hypertensive. Indeed, spironolactone controls the condition so effectively that it may be used for long-term control if for any reason surgery is contraindicated. In most cases oral potassium supplements should be used in addition to spironolactone, at least until the patient has been stabilised.

After removal of an aldosterone-secreting adenoma there may be temporary rebound hyperkalaemia resulting from suppressing the remaining normal zona glomerulosa. Fludrocortisone

may then be required temporarily in doses of 0.05 mg on alternate to 0.1 mg daily.

Renin-secreting tumours of the kidney, haemangiopericytomas, are a rare cause of secondary hyperaldosteronism. The patients present with hypertension, hypokalaemia, and bilateral hyperplasia of the zona glomerulosa with hyperaldosteronism. The condition may be cured by removing the tumour.

VIRILISING AND FEMINISING TUMOURS

Both virilising and feminising tumour are uncommon, particularly the latter. After the diagnosis is made treatment is by excision.

ADRENOCORTICAL INSUFFICIENCY

There may be deficient secretion of glucocorticoids, of mineralocorticoids, or of both. The causes of adrenal insufficiency are: (a) primary: autoimmune, tuberculosis, carcinomatosis, amyloidosis and other infiltrations, haemochromatosis, post-adrenalectomy; and (b) secondary: ACTH deficiency and renin deficiency. When there is organic disease of the adrenals or after adrenalectomy there is deficient secretion of both cortisol and aldosterone and both must be replaced. ACTH deficiency, on the other hand, does not lead to a fall in aldosterone secretion and only cortisol replacement is required. Congenital enzyme defects occur in the group of diseases known as congenital adrenal hyperplasia. These are dealt with below. Isolated mineralocorticoid deficiency is diagnosed only rarely, but its true incidence is unknown. It is probably always the result of diminished renin secretion.

The traditional replacement treatment for cortisol deficiency in the past has been cortisone acetate (such as 25 mg in the morning and 12.5 mg in the evening), but this drug is now being abandoned in most centres since it is irregularly absorbed from the bowel and because it has to be converted to hydrocortisone in the body before becoming active. Hydrocortisone should be used instead in doses of about 20 mg on waking and 10 mg in the evening but the dose should be tailored to each individual patient. This may be done by measuring the levels of cortisol in the plasma throughout the day—the peak after the morning oral dose should be 690-966 nmol/l (25-35 µg/100 ml); before the evening dose the levels should be 165-276 nmol/l (6-10 µg/100 ml) and after the evening dose peak levels should not exceed 690 nmol/l (25 µg/100 ml). Prednisolone (5 mg and 2.5 mg) and dexamethasone (0.5 mg and 0.25 mg) may be used instead of hydrocortisone, but their levels cannot be easily measured in the plasma.

When patients are receiving long-term replacement treatment with prednisolone, hydrocortisone, or dexamethasone, the morning dose should be taken as soon as the patient awakes. The evening dose should be taken at about 6 pm. If it is taken later the patient may be troubled by wakefulness or nocturia. Every patient should wear a bracelet or necklet with the diagnosis and reference number engraved upon it.* If he suffers any injury or illness other than a slight head cold he should double the dose of his tablets. If he has a more severe illness or one in which he is unable to take his tablets for any other reason the doctor should be called and he should be given intramuscular hydrocortisone (50 to 100 mg every six to eight hours). We give our patients a supply of parenteral hydrocortisone to keep in the house in case of emergency.

Mineralocorticoid deficiency is usually replaced with fludrocortisone. The drug is given daily or on alternate days in doses of 0.05 or 0.1 mg. Overdose is uncommon and is attended by clinical evidence of fluid overload. It is not necessary to increase the dose of fludrocortisone during intercurrent illness.

*Obtainable from Medic-Alert Foundation, 9 Hanover Street, London W1R 9HF.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia results from the congenital deficiency of one or more enzymes required for the normal formation of adrenal corticosteroids. The commonest deficiency is that of the 21-hydroxylase enzyme. As a result of the corticosteroid deficiency, ACTH secretion increases, the gland becomes hyperplastic, and the precursors of hydrocortisone accumulate and are converted to androgenic steroids. Girls are therefore virilised at birth; boys have precocious sexual development in infancy. Both boys and girls are tall and strong as young children, but their epiphyses fuse early (if untreated) and they are stunted as adults. Treatment is simple and consists of providing corticosteroids which they lack. Less often these patients are also "salt-losers" at birth—that is, they cannot conserve sodium efficiently. They need added salt and fludrocortisone in addition to glucocorticoid. The circadian rhythm of ACTH secretion has its nadir at the normal time of retiring and its peak in the early morning. In congenital adrenal hyperplasia the object of treatment is to suppress endogenous ACTH

as fully as possible and it has been found that this is best achieved by giving the larger part of the corticosteroid dose at the nadir. This is why these patients should be given two thirds of the total daily dose of prednisolone or dexamethasone last thing at night and the remainder on waking. On this regimen urinary 17-oxosteroids should be less than 10 $\mu\text{mol}/24\text{ h}$ (3 mg/24 h), urine pregnanetriol less than 2 mg/day, plasma cortisol less than 110 nmol/l (4 $\mu\text{g}/100\text{ ml}$), and plasma ACTH suppressed. The total dose in children depends on body weight and in adolescents and adults is 7.5 mg per day of prednisolone.

The condition of congenital adrenal hyperplasia is nowadays usually recognised at birth. If lifelong replacement is started immediately in these babies their subsequent development will be almost entirely normal, the only exception being that some girls may require minor plastic surgery to their external genitalia.

Reference

- ¹ Ross, E J, *et al*, *British Medical Journal*, 1967, 1, 191.

There seem to be no cogent reasons for avoiding injecting varicose veins in women taking the pill, and the only logic for this would seem to be that if such a woman suffered a thrombotic episode then any legal action would be indefensible. What should the doctor advise?

Pregnancy, surgical operation, and the contraceptive pill are all potentially thrombogenic. Injection of varicose veins is intended to produce thrombi, though it is expected that the extent of these will be controlled and remain local. It is hoped that none of these things will cause lasting damage or be lethal. In all cases it seems sensible to minimise risk, which is why one tries not to add one thrombogenic risk to another, unless there are really cogent reasons or the added risk is unavoidable. Prohibiting injection of varicose veins while a woman is on the pill would, on these several grounds, seem wisest. The alternative is simple. Take the woman off the pill for six to eight weeks, and get her to use some other form of contraception; inject her varicose veins; and, when the thrombophlebitis has settled down, return her to oral contraception.

Is there any evidence that instructing patients to take indomethacin and phenylbutazone "in short courses" (say one week "on" with 3-7 day rest) lessens the incidence of causation or aggravation of gastrointestinal ulceration and duodenal ulcer—or aplastic anaemia?

A relationship has been suggested between plasma levels and toxic effects of phenylbutazone¹ and there is some support for short-term courses.² A clear recommendation, however, cannot be made because the mechanisms in causing or aggravating peptic ulcer and aplastic anaemia are complex.³ For example, gastrointestinal ulceration may be produced when either drug is given parenterally and genetic influences affect the metabolism of phenylbutazone. In practice, both drugs should be avoided in patients with a history suggestive of peptic ulcer. The development of aplastic anaemia cannot be predicted.

- ¹ Cunningham, J L, *et al*, *British Medical Journal*, 1974, 3, 313.
- ² Woodbury, D M, in *Pharmacological Basis of Therapeutics*, ed L S Goodman and A Gilman, p 337. London, Macmillan Company, 1970.
- ³ Prescott, L F, in *Side Effect of Drugs*, ed L Meyler and A Herxheimer, p 165. Amsterdam, Excerpta Medica, 1972.

A 48-year-old man who has had a normal sex life and two healthy children is now unable to ejaculate after sexual intercourse though erection is normal at the start of the act. Are there any measures which can help him?

First we need to know whether this patient can ejaculate in his dreams, with another partner, or by masturbation. Next one must ask whether he has been taking any medication, especially for hypertension¹; has had any abdominal operation especially on the aorta, sympathetic ganglia, or any other retroperitoneal dissection²; has any evidence of diabetes,³ amyloidosis,⁴ or systemic vascular disease with loss of the femoral pulses and symptoms of ischaemia of the legs. If these can

be eliminated, and if the difficulty is that the patient's erection subsides after penetration and ejaculation is not achieved, the cause is virtually certain to lie in the psyche, and until this has been looked into treatment should be withheld.

- ¹ Bulpitt, C J, and Dollery, C T, *British Medical Journal*, 1973, 3, 485.
- ² Whitelaw, G P, and Smithwick, R H, *New England Journal of Medicine*, 1951, 245, 121.
- ³ Norris, H J, and Yunis, E, *Archives of Pathology*, 1964, 77, 126.
- ⁴ Andersson, R, and Hofer, P-A, *Acta Medica Scandinavica*, 1974, 195, 49.

How long after prostatectomy may a man normally expect a return to his previous level of sexual activity?

Not all men do return to their previous level of sexual activity after prostatectomy; the reasons are not clear. In some this decline may be related to the method used in removing the adenoma, the transurethral technique being less likely to interfere with sexual function than open methods.¹ In others the reasons for sexual activity failing to return are obscure but are probably related to more than one factor including the patient's general health and that of his wife.² When the general health is good and the patient's sexual activity has been well maintained before operation, one may expect it to return almost unaffected; there will often be reflux of semen owing to the need to remove the neck of the bladder with the adenoma. When the patient may safely resume intercourse depends: one of my patients complained that coitus was a little painful five days after transurethral resection, but usually it seems wiser to allow the tissues to heal, and to advise the patient to resume this at around the time he returns to other active exercises and pastimes—that is, about five to six weeks.

- ¹ Finkle, A L, and Prian, D V, *Journal of the American Medical Association*, 1966, 196, 139.
- ² Caine, M, *British Journal of Urology*, 1954, 26, 205.
- ³ Finkle, A L, *et al*, *Journal of the American Medical Association*, 1959, 170, 1391.

Should women taking oral contraceptives have cervical smears taken more often than women using other methods of contraception?

Probably not. Kastner and Holzer¹ analysed 2237 smears from women using oral contraceptives and compared them with 2000 smears where such contraceptives had not been taken. They found no difference between the two groups. Suspicious and positive findings occurred in 1%. The length of time for which the contraceptives had been used made no difference to the cytological appearances. Ayre *et al*² followed abnormal cytological findings while their patients continued on steroid hormones. In 27 with dysplasia, 17 showed no change and nine regressed, four of them to normal. The view seems to be gaining ground that it is increased sexual activity, possibly with trichomonal infection, which causes cytological changes, rather than the effects of oral contraceptives on the cervical epithelium.

- ¹ Kastner, H, and Holzer, E, *Wiener klinische Wochenschrift*, 1973, 85, 175.
- ² Ayre, J E, *et al*, *Obstetrics and Gynecology*, 1969, 34, 545.