postgraduate surgery lectures

John McFarland

Postgraduate Surgery Lectures

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Foreword

The Royal College of Surgeons of England has been very lucky in its Surgical Tutors. That the College should energetically involve itself in the postgraduate training of surgeons throughout the country is clearly right (after all it is the Royal College of Surgeons of England, not London!) but the means to implement such an objective could not have been found without the enthusiastic support of the younger consultants who, well established in their various areas and with demands upon their time steadily increasing, nevertheless made time in order to organize and take part in courses of lectures and educational schemes particularly aimed at the surgical registrar about to take his Final F.R.C.S. Examination.

Mr John McFarland is well known not only as a surgeon but also as a teacher and organizer of great ability and the postgraduate surgical training in the Liverpool area where he works has long been known to be outstandingly good. The course of surgical lectures arranged has become so well attended that it has become clear that it is useful to a much wider circle of surgeons than merely those about to sit the Final F.R.C.S. Examination. The idea that these splendid lectures should not merely be delivered on a single occasion but also preserved in a book as a series of linked monographs has much to commend it. The subject matter is so presented and the standard is such that far from appealing only to surgeons at the start of their career, all surgeons, whatever their status and seniority, will find much to learn from them. Mr John McFarland is to be congratulated upon producing a most enjoyable, readable and, above all, helpful and informative book.

RODNEY SMITH

Preface

For several years distinguished surgeons have been invited to visit Liverpool and contribute to a postgraduate lecture series. Financial support for this came originally from the Royal College of Surgeons and more recently from the Liverpool Joint Committee for Postgraduate Medical Education, The lectures have been given at the Liverpool Medical Institution and the records that I have kept show that an average of sixty people have been present on each occasion.

Attendance has not been limited to young surgeons studying for the F.R.C.S. examination, the group for which the programme was initially designed, for there has invariably been a good proportion of senior registrars and consultant surgeons, and, on one occasion or another, the audience has included members of every branch of the profession, not excepting the basic sciences. It was this evidence of the wide and continuing appeal of the lectures, coupled with the distinction of the list of speakers for the 1971-72 season, which led me to consider publication of the major part of this lecture series.

Editorial direction has been minimal but I have suggested to each author that, as far as possible, the immediacy of the verbal presentation should be preserved. Furthermore, although references are inevitable, I have asked that these should not be presented as a feature but should be included only when essential to the text.

A tape recorder was used to capture the question and answer session which followed each lecture and was always a popular part of the evening. This afforded each author the opportunity of following his text with an account of the discussion, In the event, only Mr Bruce Torrance actually did this but others have found it helpful to incorporate some of this material in their contributions.

My gratitude is due to all the speakers who have co-operated in this venture, firstly, by visiting Liverpool and giving us an account of a subject on which each is an international authority, and, secondly, for agreeing to write this in a form suitable for this book.

It is a pleasure, also, to acknowledge my indebtedness to

Mr Rodney Smith, M.S., F.R.C.S. for writing the foreword, and to Mr Raymond Helsby, Regional Adviser to the Royal College of Surgeons, who initiated this lecture series.

My secretary, Miss Gwen Williams, has given unstinting support from the moment of inviting the first speaker to the completion of the book.

JOHN MCFARLAND

Contents

1 Cushing's Syndrome and Phaeochromocytoma

Terence Kennedy

CUSHING'S SYNDROME

In 1932 Harvey Cushing described a syndrome which we recognize by its distinctive clinical and biochemical characteristics. Obesity, largely limited to the trunk, is often associated with striae, especially around the hips and shoulders, and with a fatty pad, or "buffalo hump" over the lower cervical and upper dorsal spine; the face is red and rounded—the well-known moon-face—and in women it is often hirsute. In contrast to the trunk the limbs appear quite thin, due not only to absence of fat, but also to muscle atrophy; muscle weakness is an important feature of the syndrome. Potassium depletion is associated with sodium retention and alkalosis. There is hypertension of moderate or severe degree, diastolic levels of 110 or even 120 mm of mercury being quite common; this hypertension may lead to cardiac failure or cerebral haemorrhage. Subcutaneous ecchymoses are common as a result of excessive capillary fragility, and there may be polycythaemia and leucocytosis. Decalcification of the skeleton leads to moderate or severe degrees of osteoporosis, which may cause bone pain or pathological fractures, especially of ribs or vertebral bodies. Blood glucose levels are often raised and there may be glycosuria; frank diabetes is found in about 10 per cent of patients. With the altered carbohydrate metabolism and excess of cortisol, it is not surprising to find an increased tendency to infections and a decreased resistance to them. The disease occurs more commonly in women, in the ratio of three to one. In the active, reproductive period there may be amenorrhoea and sterility. In males the syndrome may be associated with impotence. In severe cases mental disorders, usually of depressive type, are quite common. It will be appreciated that all these clinical features can be produced

by prolonged high therapeutic dosage of glucocorticoids, such as cortisone acetate, or prednisone.

In spontaneous Cushing's syndrome there is an increase of the naturally occurring steroid, cortisol and, most characteristically, a loss of the normal circadian or nyctohemeral rhythm, the cortisol secretion rate remaining constant throughout the 24-hour period, whereas normally it is low around midnight and high around 7 or 8 a.m.

The normal adrenal cortex, which weighs from 3 to 5 g is under the control of the anterior pituitary (*Figure 1.1*). Corticotrophin

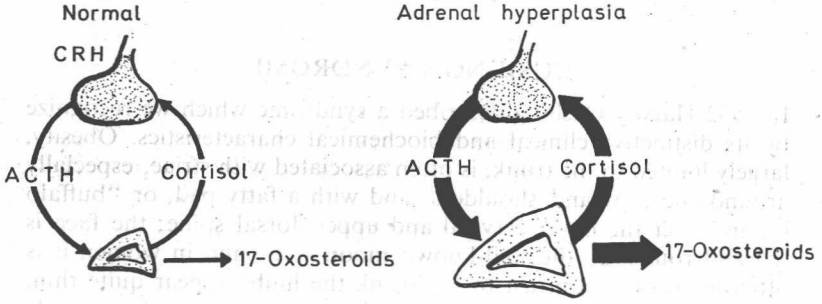

Figure 1.1. The pituitary-adrenal axis in health and in adrenal cortical hyperplasia

releasing hormone (CRH) derived from the hypothalamus, causes the release of adrenocorticotrophic hormones (ACTH) from the pituitary and this, in turn, stimulates the release of cortisol from the adrenal cortex. Circulating cortisol has an inhibitory effect on the release of ACTH and it is this feed-back mechanism that normally prevents excessive steroid production. In Cushing's syndrome there is an excess secretion of cortisol due, in most patients, to adrenal cortical hyperplasia caused by excess ACTH, which may be due to a basophil adenoma of the pituitary, though no pituitary tumour can be demonstrated in the great majority of patients, when the clinical diagnosis is first made. ACTH excess may be due to hyperfunction of the hypothalamus. In about 15 per cent of cases Cushing's syndrome is due to tumour of the adrenal cortex, which may be benign or malignant, and in either case is independent of ACTH, that is to say, is is autonomous (*Figure 1.2*). Here the steroid levels are usually considerably higher, but this fact alone is not reliable in differentiating these cases. Radiological examination may help when the

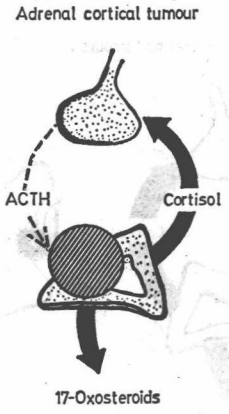

Figure 1.2. Autonomous Cushing's syndrome due to adrenal cortical tumour

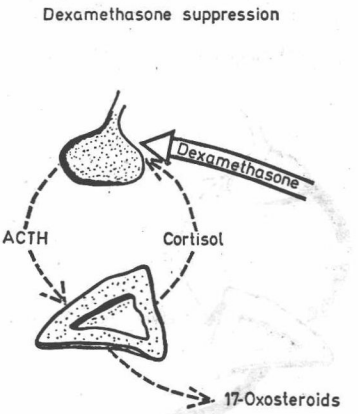

Figure 1.3. Suppression of cortisol secretion and oxosteroid excretion by dexamethasone

tumour is large, but is of little value with an adenoma weighing only 4 or 5 g. When deciding on treatment it is most important to decide whether the syndrome is autonomous or not. Adrenocorticotrophic hormone assays are extremely complex, and are thus available in only one or two centres, but fortunately we have other reliable tests. The powerful synthetic steroid, dexamethasone, may replace cortisol and inhibit ACTH secretion to such an extent that there is a marked fall in plasma cortisol levels and oxogenic steroid excretion in the urine (*Figure 1.3*). This suppression will not be found in cases with adrenal tumour because ACTH is already suppressed by the high circulating cortisol levels.

The synthesis of cortisol can be interrupted by the drug metyrapone, which removes the feed-back inhibition of ACTH thus leading to an increased excretion of urinary oxosteroids (*Figure 1.4*).

A rare, but increasingly recognized condition is the ectopic ACTH syndrome (*Figure 1.5*) in which very large amounts of corticotrophin may be secreted by tumours, usually malignant, arising in extra adrenal sites; the most common ectopic ACTH producing tumour is oat-cell carcinoma of the bronchus. In this situation there is no feed-back inhibition mechanism, cortisol levels are very high and the

metabolic effects may be very severe. Cushing's syndrome in these cases is usually rapidly progressive, with an early fatal issue.

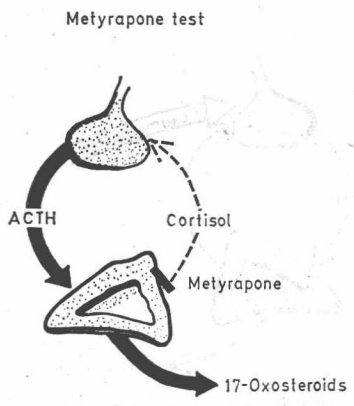

Figure 1.4. The effect of metyrapone on adrenal function

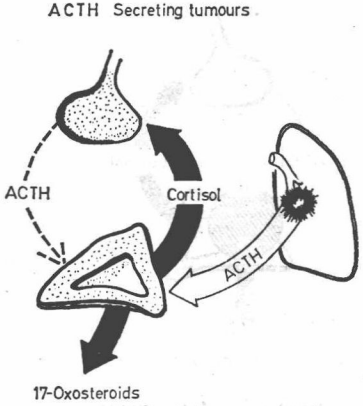

Figure 1.5. The ectopic ACTH syndrome

Treatment and Results

Early control of Cushing's syndrome is vital as about half of all untreated cases will die within five years, usually from cardiovascular causes or infections. Where the syndrome is shown to be due to adrenal cortical hyperplasia it is most important to look for a pituitary adenoma. If such a tumour is found it is logical to remove it as a first step, leaving the adrenals intact. We have, however, sometimes preferred to do a bilateral adrenalectomy as a first step, thus guaranteeing immediate control of the syndrome. In four cases out of five there is no evidence of pituitary tumour when the patient first presents for treatment.

The concept of control of cortical hyperplasia by inhibiting ACTH production is attractive, and this has been achieved in a high proportion of cases by other workers, using sophisticated radiation techniques, but it has been shown that orthodox external irradiation produces satisfactory remission in only about one-third of all cases. Better results can be achieved with implantation of the pituitary fossa with ^{90}Yttrium, but this has a high complication rate and a success rate of about 50 per cent.

The most reliable method of treatment is bilateral adrenalectomy, which carries a low mortality and causes remission of the syndrome

in all cases. The blood pressure generally returns to normal, but severe cardiovascular complications may not be influenced, and are an important cause of death in the first two years after adrenalectomy.

Most surgeons remove the whole of both adrenal glands, so that the patient will require cortisone acetate or hydrocortisone replacement indefinitely, with increased dosage at times of stress such as operation or infection. Through the operative period large doses of hydrocortisone are required, as these patients may be very sensitive to cortisol withdrawal and severe hypoadrenal crises may occur. The dosage is gradually decreased over a period of two to three weeks, and we have found that a daily maintenance dose of 37½ mg of cortisone acetate, or equivalent hydrocortisone is appropriate in most individuals.

A rather more sophisticated way of handling the problem is to leave a part of one adrenal, in the hope that the patient will ultimately be able to manage with no replacement therapy—a concept rather like that of subtotal thyroidectomy for thyrotoxicosis. One aims to leave about 1 g of one gland, usually the left, retaining its blood supply if possible. Only about half of these patients will eventually be weaned from cortisone replacement therapy, and this should not be attempted until at least three or four months after operation. The viability of the remnant can be tested by ACTH stimulation. A drawback of this method is that the remnant may hypertrophy under the influence of continued ACTH stimulation, leading to recurrence of the syndrome. I have had to remove the remnant twice now, but in each case this has produced a good remission. In favour of this policy is the possibility that the patient's autogenous cortisol may inhibit the pituitary and perhaps delay or prevent the development of adenoma.

Operative Approach

The anatomy of the arterial supply and venous drainage of the adrenals is somewhat variable. On the left side one or more small arteries usually arise directly from the aorta, the venous drainage is principally into the left renal vein, but also into the inferior phrenic vein. On the right side adrenal arteries usually arise from the right renal artery and the aorta; there is usually a short, stout vein not more than 1 cm in length entering the vena cava. Occasionally the main venous drainage on the right side is directly into the right hepatic vein and this may lead to considerable operative difficulty. The right gland is intimately related to the vena cava and dissection of a

large gland may be very difficult, whereas mobilization of the left adrenal is normally quite straightforward.

Through a long transverse epigastric incision, with mobilization of the spleen and greater curve of the stomach, the left adrenal may be removed; dissection above and lateral to the duodenum exposes the right gland. Unfortunately, this exposure may be difficult in obese individuals, as Cushing's patients nearly always are. A further disadvantage in our hands has been an unexpectedly high incidence of subphrenic abscess, perhaps predisposed to by the high cortisol levels.

Either adrenal can be approached from the back by an extrapleural approach through the bed of the eleventh or twelfth rib. Both glands can be removed at one sitting if the patient is in a face down position, but we have found this difficult and prefer the lateral position. If the patient is considered to be a bad operative risk we have waited two or three weeks before exploring the second side, but with increasing experience we now normally prefer to turn the patient on to the other side and proceed at once to the second adrenalectomy. In the immediate post-operative period very careful monitoring of the blood pressure and electrolytes is mandatory, in order that incipient hypoadrenal crisis may be detected.

Results of Adrenalectomy for Hyperplasia

Remission of the syndrome occurs in every case of bilateral total adrenalectomy. Within a few weeks the skin begins to peel, the striae cease to be a livid purple colour and gradually fade, and the florid moon-face reverts to a normal appearance. Provided that permanent vascular and renal damage has not occurred, the blood pressure returns to normal, carbohydrate intolerance improves, hypokalaemia resolves and the skeleton slowly recalcifies, though deformities such as collapsed vertebrae persist. Mental disorders clear up completely with the remission. There is also a dramatic improvement of sexual function; potency returns in the impotent males and menstruation is restored in the hitherto infertile women with amenorrhoea—several of our patients have had normal pregnancies after adrenalectomy.

All this sounds perhaps a little too good to be true, and it is. Careful follow-up reveals that some patients ultimately develop adenomata or invasive tumours of the pituitary. It may be that some of these tumours were already present at the time of the adrenalectomy, but were too small to be diagnosed, or it may be that they have developed as a result of the removal of the feed-back pituitary

inhibition from autogenous cortisol. Warning of the advent of a pituitary adenoma may be given by the finding of excessive pigmentation, especially marked in operation scars, which is associated with high levels of β-melanophore stimulating hormone (MSH) secreted in association with ACTH. This pigmentation antedates the headaches and defects of visual fields which ultimately arise with the pituitary tumours. When ACTH assay is more readily available it will, no doubt, be used routinely in the follow-up period.

A striking example of some of these problems is shown by a man now aged 42, who had subtotal adrenalectomy in 1953 with an excellent remission. In 1964 he developed a recurrence, but after removal of an 8 g remnant he again had a complete remission. He remained well for six years, but was then lost to follow-up. When he reappeared recently he was very deeply pigmented, had headaches and bitemporal hemianopia. A large basophil pituitary adenoma was removed. At the time of his first operation he received conventional radiotherapy to the pituitary, a dose of 2,000 rads. We now regard this dosage as inadequate, and are considering irradiating the pituitary in higher dosage in every case at the time of primary treatment.

ADRENAL CORTICAL TUMOURS

Adenomata may be multiple and are sometimes associated with the pluriglandular syndrome, but in Cushing's syndrome they are more often solitary. When adenoma is suspected it is perhaps wiser to explore by the anterior route to facilitate palpation of the opposite gland in case the tumour should prove to be bilateral. Carcinoma of the adrenal cortex may be associated with Cushing's syndrome and there may be a variable amount of associated virilism. Removal of the tumour will produce remission, and even though the tumour usually recurs, metastases do not always contain functioning tissue so the syndrome does not necessarily relapse. With recurrent adrenal carcinoma the tumour may be controlled by the drug, *o*, *p*'DDD, which is closely related to the insecticide DDT and is specifically toxic for the adrenal cortex. This drug was discovered when tested as an insecticide for dogs' fleas; the dogs licked themselves and all died with adrenal cortical necrosis—a remarkable example of serendipity. Aminoglutethimide is a drug which blocks the synthesis of cortisol and aldosterone, but it does not destroy adrenal cells and is thus less useful in treating recurrent carcinoma.

THE ADRENAL MEDULLA

The cells of the adrenal medulla, phaeochromocytes, are derived embryologically from the neural crest, and are thus closely related to the cells of the sympathetic ganglia and other extra-adrenal chromaffin tissue. These chromaffin cells have the ability to synthesize the catecholamines, noradrenaline and adrenaline. A much simplified scheme of the synthesis and degradation of the catecholamines is shown in *Figure 1.6*. Catechol-*o*-methyl transferase, which

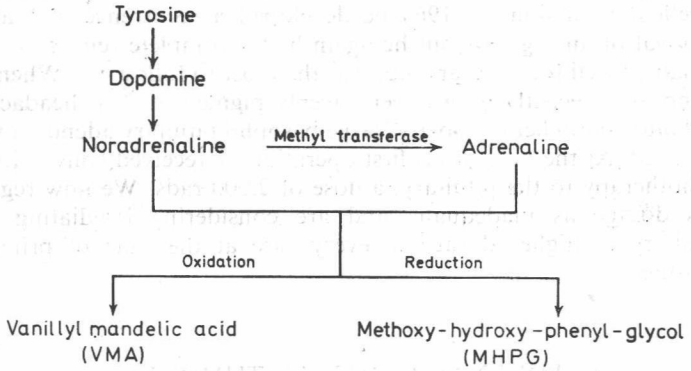

Figure 1.6. A simplified diagram of catecholamine metabolism

is involved in the conversion of noradrenaline to adrenaline, is not found in extra adrenal tissue, so that tumours in which there is an excess of adrenaline are never ectopic.

PHAEOCHROMOCYTOMA

These rare tumours are said to occur at the rate of 1/1·5 million population per annum, are said to be multiple or bilateral in 10 per cent, ectopic in 10 per cent and malignant in about 10 per cent of cases. Having encountered 15 cases in a population of 1·5 million during the past three years, five of them being multiple, I believe that the condition is probably a lot more common than has been supposed. In addition to the adrenal medulla, tumours may be found in sympathetic ganglion tissue, in the abdomen or thorax, in the organ of Zuckerkandl close to the aortic bifurcation, and even in the wall of the urinary bladder. Through the excess of pressoramines which they secrete, they have a profound effect on the blood pressure,

producing sustained hypertension in about half of all cases; in the other half hypertension is episodic and may easily be overlooked. Most tumours secrete noradrenaline predominantly, but the small number which are mainly adrenaline secretors, though producing less severe hypertension, may prove more dangerous to treat.

With operation or stress there may be massive secretion of catecholamines leading to dangerous hypertensive crises in patients where perhaps the presence of a tumour has not even been suspected. Women given anaesthetics during pregnancy and childbirth are particularly vulnerable when they harbour an unsuspected phaeochromocytoma.

Symptoms

Hypertension found on routine examination in the absence of any other symptoms is unusual. The most important symptom, present at some time in at least 80 per cent of all cases, is headache. It tends to be episodic, intense and with a curious bursting character. Sweating is associated with attacks and may be profuse; it is absolutely characteristic and present in nearly every case (Table 1.1). Nausea

TABLE 1.1
The Most Important Symptoms Found in 12 Cases of Phaeochromocytoma

Sweating	10
Headache	8
Nausea and vomiting	4
Abdominal pain	3
Palpitation	3
Dyspnoea	3
Weakness and fatigue	4
Nervousness and anxiety	3
Personality change	4

and vomiting are common and may be associated with abdominal pain, sometimes simulating peptic ulcer. A duodenal ulcer can occur, which is somewhat surprising, as catecholamines depress the secretion of acid by the parietal cells. Surprisingly we have found that fasting levels of gastrin are raised in these patients, though we do not yet know the significance of this observation.

Palpitations are often complained of, and may be associated with pallor and a feeling of weakness. Some patients may complain of dyspnoea during an attack. We have been impressed by the frequency of nervousness, anxiety and personality change. This may be so marked that the patient is regarded as neurotic, the unfortunate experience of several of our patients. Many patients have the signs