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THE PITUITARY AND ADRENAL CORTEX IN GENERAL MEDICINE*

BY

J. D. N. NABARRO, M.D., F.R.C.P.

Assistant Physician, Middlesex Hospital, London

The Anterior Pituitary Gland

The hormones of the anterior pituitary gland include corticotrophin, thyrotrophin, gonadotrophin, prolactin, and growth hormone. They are polypeptides, and in some cases the amino-acid composition and sequence have been ascertained. Growth hormone shows a considerable degree of species specificity (Knobil and Greep, 1956) associated with differences in amino-acid sequence (Li and Papkoff, 1956). The anterior pituitary hormones are not easy to purify, and their estimation in body fluids and tissues is still in a very primitive stage.

Corticotrophin regulates the production of hydrocortisone and sex hormones by the adrenal cortex, and in its absence the adrenal stops secreting hydrocortisone although aldosterone production continues. Animal experiments have suggested that there may be two pituitary hormones acting on adrenal cortex—one affecting

adrenal weight and the other concerned with metabolic activity (Liddle *et al.*, 1954). In addition to its effect on the adrenal cortex, corticotrophin has a direct effect on metabolism of fatty tissue with liberation of unesterified fatty acids (White and Engel, 1958); this effect is not seen with injections of corticotrophin and measurement of plasma unesterified fatty acids (Raben and Hollenberg, 1959). Corticotrophin also has a skin-pigmenting effect, independent of but similar to melanocyte-stimulating hormone (*British Medical Journal*, 1957). Bioassay methods for corticotrophin measurement are available, and increased plasma levels have been detected in Addison's disease and occasional cases of Cushing's syndrome secondary to a corticotrophin-producing pituitary adenoma or carcinoma (Clayton, 1958; Lipscomb and Nelson, 1959).

In the case of thyrotrophin, clinical evidence suggests that there is an exophthalmos-producing substance independent of the thyroid-stimulating hormone. This has been demonstrated experimentally in animals (Dobyns and Steelman, 1953). Although thyrotrophin plays an important part in the regulation of thyroid activity the gland can accumulate iodine and secrete thyroxine in the absence of the pituitary and presumably of any thyrotrophin. This has only been demonstrated in patients with thyrotoxicosis or thyroid adenomata (Becker, 1959; Gurling *et al.*, 1959).

Studies with growth hormone have been limited on account of its species specificity and because there is no simple method for its estimation in body fluids. It has been shown that as much growth hormone can be extracted from the pituitaries of adult humans as from those of growing children (Gershberg, 1957), but its role in adult metabolism and physiology has not yet been defined. Metabolic studies have been performed, using human and monkey growth hormone, and have shown nitrogen and calcium retention more marked in patients with deficiency of growth hormone than in normal subjects (Beck *et al.*, 1957). Increased urinary calcium excretion has been noted in several studies (Ikkos *et al.*, 1959; M.R.C. Clinical Endocrinology Committee, 1959). Growth hormone has an *in vivo* effect on fat-metabolism with elevation of the plasma unesterified fatty acids (Raben and Hollenberg, 1958). The possible role of growth hormone in complicated juvenile diabetes and in certain types of cancer is discussed later.

A fat-mobilizing substance has been found in plasma and in urine. Chalmers *et al.* (1958) have isolated it from urine, and found that it is increased on fasting and disappears after hypophysectomy. Whether it is identical with one of the known pituitary hormones has not yet been determined. It is a polypeptide, but does not have the same properties as corticotrophin or growth hormone (Chalmers, 1960, personal communication). Originally isolated in studies on obesity, its relationship to this and other human diseases is at present only a matter of speculation.

Total hypophysectomy by the transfrontal, trans-septal-sphenoid (Heck *et al.*, 1957), and trans-antrosphenoidal (Hamberger *et al.*, 1959) routes has been undertaken for a number of conditions, including juvenile diabetes with complications, disseminated cancer, especially of the breast or prostate, and malignant exophthalmos. The operation is a considerable undertaking in any of these conditions, and other methods of reducing pituitary function have been investigated. External irradiation by conventional and supervoltage techniques has been disappointing and may be hazardous, though

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external irradiation by high-energy proton-beams may be effective (Tobias *et al.*, 1958). Internal irradiation with γ -ray sources—radioactive gold and radon—is dangerous because the surrounding brain tissue and nerves may be affected. β -ray emitters are safer because of the reduced penetration of the rays. The most satisfactory isotope at present is yttrium-90, and the technique developed in Glasgow of screwing the pellets into the floor of the sella turcica is the best method of pituitary destruction so far developed (Forrest *et al.*, 1959).

An alternative method of reducing pituitary function was suggested by a report of Professor Dorothy Russell on the effect of stalk section (Russell, 1956). The Neurosurgical Unit at the Middlesex Hospital (the late Miss Diana Beck, Mr. Valentine Logue, Mr. F. L. Davies) carried out a small series of pituitary-stalk sections two to three years ago. The endocrine changes resulting from this operation have been followed, and have confirmed some of the reported results of animal experiments on the control of pituitary function. (Preliminary accounts of these cases have been given by Davies and Buxton, 1957; Buxton *et al.*, 1958.)

Pituitary-Stalk Section

This operation was performed on 15 patients between September, 1956, and March, 1957. Thirteen had carcinoma of the breast and one each of carcinoma of the prostate and adrenal. Three patients died within ten days of the operation. In 11 of the remaining 12, pituitary function was reduced and in six there was a remission of the malignant disease. Initially the operation was performed without steroid cover; the patients were drowsy after operation but responded to intravenous hydrocortisone. The urinary steroid excretions fell to a very low level (Fig. 6). There was an early striking

FIG. 6.—Urinary steroid excretion following pituitary-stalk section in woman aged 58.

fall of radioactive iodine uptake, but in all cases some thyroid function began to return at about 10 weeks. This could have been due to autonomous activity on the part of the thyroid gland or production of thyrotrophin by a pituitary not connected with the hypothalamus. The

fact that the iodine uptake by the thyroid gland was suppressed by triiodothyronine (Fig. 7) suggests continued thyrotrophin production. Endocrine-function studies on patients surviving more than three months are shown in Table V. From gradual steroid withdrawal tests it appeared that adrenal function was at a very low level in three cases. The test in Case 12 was an acute steroid withdrawal; Dr. D. N. Baron reported the presence of 6.7 γ -free hydrocortisone per 100 ml. of plasma after three days off replacement therapy.

The patient at this time had undoubted clinical evidence of acute adrenal insufficiency.

The urinary excretion of follicle-stimulating hormone was followed in cases in which it was raised before stalk section. Drs. R. D. Bulbrook and F. C. Greenwood

FIG. 7.—24-Hour radioactive iodine uptake by the thyroid gland after pituitary-stalk section in woman aged 51 (Case 18). Uptake suppressed by triiodothyronine.

TABLE V.—Endocrine-function Tests in Patients Surviving Three Months after Pituitary-stalk Section

Case	Time (Months Post-op.)	Adrenal Function	Thyroid ¹³¹ I Uptake (24 Hrs.)	Urinary Oestrogens (μ g. 24 Hrs.)	Urinary F.S.H.
15	3	0	—	0	0
13	4	0	20%	—	—
10	6	—	14%	2.4	0
20	8	—	28%	—	—
16	12	0	30%	1.3	0
18	20	—	26%	6.3*	0
12	22	+	8%	0	0

* Zero for 12 months after operation.

estimated the urinary oestrogens. In Case 18 they disappeared from the urine after operation but reappeared 12 months later, and there was evidence of renewed activity of the neoplasm. It is not possible to say whether there had been regeneration of the hypothalamic-pituitary vascular channels, because hypophysectomy was undertaken. The pituitary fossa appeared empty and curettings showed on microscopy dense hyaline fibrous tissue with occasional cells of pituitary type.

Pathological specimens of the pituitary were obtained in most of these cases. Those from patients dying 12 months or more after the operation showed very little pituitary tissue.

Reports on the results of pituitary-stalk section have now been published from a number of centres. In patients with disseminated breast cancer it has generally been found that remissions are shorter than after total hypophysectomy (Baron *et al.*, 1958; Dugger *et al.*, 1958). In juvenile diabetics with retinitis the results have been disappointing, although reduction of insulin requirement has been noted (Javid *et al.*, 1958; Lundbaek *et al.*, 1960). Animal experiments have suggested that pituitary secretion of corticotrophin and gonadotrophin stops after stalk section (Fortier *et al.*, 1957), although thyrotrophin secretion may continue (Brown-Grant *et al.*, 1957). Van Wyk *et al.* (1960) have claimed that corticotrophin may still be secreted in response to stress but not to a reduction of the circulating level of hydrocortisone. Jessiman (1959) has suggested on clinical

grounds that growth-hormone secretion is reduced by stalk section, whereas that of prolactin continues (Ehni and Eckles, 1959).

Pituitary Surgery for Severe Exophthalmos

Treatment of severe exophthalmos is unsatisfactory. Various measures have been advocated, including triiodothyronine suppression, steroid therapy, orbital irradiation, and orbital decompression. Pituitary surgery tried has included total hypophysectomy (Albeaux-Fernet *et al.*, 1955; Becker, 1959), stalk section alone and with electrocautery of the pituitary (McCullagh *et al.*, 1958), and implantation of radioactive yttrium into the pituitary (Dogliotti and Ruffo, 1958; Molinatti *et al.*, 1959). The results of any form of treatment are difficult to assess because the course of the condition is punctuated with apparently spontaneous exacerbations and remissions. Stalk section alone seems to be less successful than total hypophysectomy, yttrium implantation, or electrocautery with stalk section. We have no experience of pituitary surgery in this condition, but it does seem logical to consider a pituitary approach in any case in which the condition appears to be endangering the patient's sight.

Total Hypophysectomy in Diabetic Retinitis

Young people developing diabetes can usually be kept symptom-free and in good health with insulin. However, with the passage of time it has become obvious that insulin therapy is not the complete answer to this problem and that later complications may develop, including coronary artery disease, diabetic retinitis, and renal damage. It has been suggested that these complications occur earlier if the diabetic control, judged by blood-sugar levels, is indifferent or poor (Keiding *et al.*, 1952; Johnsson, 1960). Others have claimed that the control of the diabetes has little or nothing to do with the development of these complications (Dolger, 1947; Downie and Martin, 1959). Whatever their cause, there is no doubt that these complications do occur in young people after fifteen or more years of diabetes and that they are extremely distressing. In some cases coronary artery disease or renal disease predominates and results in early death of the patient. If the retinitis progresses more rapidly than the other conditions we are faced with a young patient rapidly going blind. Unfortunately, once the retinitis is marked it usually progresses regardless of measures adopted for improvement of diabetic control.

Poulsen (1953) reported the case of a patient with long-standing diabetes complicated by retinitis who suffered from post-partum necrosis of the pituitary gland. As hypopituitarism developed the insulin requirement fell and the retinitis regressed. Subsequent to this observation Olivecrona and Luft started doing total hypophysectomies in patients with progressive retinitis and other diabetic complications. In an account of the first 20 cases they reported that seven of these patients had died, that hypertension and renal function had improved in the remainder, and that seven showed improvement of vision (Luft *et al.*, 1955). Kinsell (1957) described a series of nine patients; only three were still alive at the time of his report, and although their vision had improved he considered the operation to be the last resort. In another series of 10 cases, six showed great improvement of vision, but two of these patients and two of the other four died subsequently of hypoglycaemia (Javid *et al.*, 1958). A further 10 cases have

recently been reported from Finland. Only one of these patients died; improvement of vision is claimed in four (Hernberg *et al.*, 1959).

We came to the conclusion that the outlook for a young diabetic faced with blindness is bad enough to justify consideration of this heroic procedure, and we have offered hypophysectomy to a number of carefully selected patients. They have all been of the "juvenile" type with adequate renal function, inulin clearance being greater than 100 ml./minute. The operation has been performed on five patients, the first died eight days post-operatively, and one case is too recent for comment, the results of the other three are shown in Table VI.

TABLE VI.—*Hypophysectomy for Diabetic Retinitis*

Case	Before Operation		Date of Operation	After Operation	
	Insulin	Vision		Insulin	Vision
II	70 u.	6/9 : 6/60	March, 1957	12 u.	6/9 : 6/12
III	90 "	0 : 6/60	Oct., 1957	68 "	0 : 6/18
IV	76 "	0 : C.F.	July, 1958	36 "	0 : 6/9
IV	Blood urea, mg./100 ml.			Before 43	After 29
	Plasma albumin, g./100 ml.			3.7	4.1
	Urine protein, g./24 hrs.			1.1	0.4

The present insulin requirement suggests that hypophysectomy is incomplete in Case III and possibly in Case IV. Fundus paintings of Case II are shown in Fig. 8.

FIG. 8.—Total hypophysectomy for diabetic retinitis. Case II (Table VI). Fundus paintings—Institute of Ophthalmology. (a) Left eye before operation. (b) Left eye two years after operation.

The operation is a formidable undertaking both for the neurosurgeon and for the physician. It seems that to be of lasting value the hypophysectomy must be complete. Long-standing diabetics are bad risks for intracranial operations and prolonged post-operative unconsciousness and fits are common. The diabetes in the immediate post-operative period is unstable and difficult to control. The development of diabetes insipidus adds to the problems because the osmotic diuresis of glycosuria is greatly exaggerated.

Why hypophysectomy has this effect on the complications of diabetes is not yet clear. The patients receive physiological amounts of adrenal steroid and thyroid hormone after operation; one therefore suspects that removal of growth hormone is the operative factor. It has been shown that giving human growth hormone to these patients after operation results in hyperglycaemia and ketosis (Greenberg *et al.*, 1958; Fankhauser *et al.*, 1959; Luft *et al.*, 1959). Vallance-Owen *et al.* (1958) demonstrated on one of our patients that the insulin antagonist present in the plasma albumin of normal people and diabetics disappears after hypophysectomy, but its identity and relation to the complications cannot yet be defined.

Endocrine Surgery in Metastatic Cancer

Total hypophysectomy has been used for the treatment of disseminated cancer of the breast and prostate. Originally it was thought that by removing sources of corticotrophin and gonadotrophin it would have the same effect as oophorectomy and adrenalectomy in lowering the level of circulating oestrogens and benefiting patients with oestrogen-stimulated tumours. Two observations suggest that hypophysectomy does more than this. A proportion of patients who have undergone oophorectomy and adrenalectomy obtain a further remission if hypophysectomy is performed when the

condition relapses. We have had two patients in whom objective improvement has been shown in this situation (Fig. 9). The second is that although oestrogen administration will cause an exacerbation of oestrogen-dependent tumours in intact patients or after oophorectomy it fails to do so after hypophysectomy, suggesting that oestrogens are able to stimulate the tumour only in the presence of an as yet unidentified pituitary factor (Pearson and Ray, 1959). Some studies have been made with human growth hormone, but the results so far have been inconclusive (Pearson and Ray, 1959).

Luft has reported on the results in a series of 59 cases with evidence of remission in 57% of 47 evaluated (Luft *et al.*, 1958). Pearson and Ray (1959) reported remissions in 54% of a series of over 100 cases. It is reasonable to compare the results of adrenalectomy with those from hypophysectomy in general terms, rather than to consider exclusively the effect on the neoplasm. The replacement therapy after adrenalectomy is undoubtedly simpler than after hypophysectomy, but the complete lack of aldosterone after adrenalectomy may lead to the sodium-depletion type of Addisonian crisis. The hypophysectomized patient is not exposed to this hazard, though she has to take thyroid hormone and, in some cases, at least temporarily, pitressin. Schon (1958) has been unable to demonstrate any intellectual or psychological changes after hypophysectomy. It has been our impression that there may be an unexpected euphoria in some cases which, although perhaps beneficial in patients with advanced cancer, has on occasion caused some anxiety. We are doubtful whether it is justified to undertake surgical hypophysectomy in patients with advanced cancer, though it may produce remissions slightly more often than adrenalectomy (Atkins *et al.*, 1957). The current methods of yttrium-90 implantation seem to have advantages over surgical hypophysectomy and bilateral adrenalectomy.

Steroid Therapy

The addition of physiological amounts of cortisone has greatly improved the replacement therapy available for patients with Addison's disease or hypopituitarism. Larger or pharmacological amounts of steroids have been used in the treatment of diseases unrelated to the adrenal gland. Steroids of the cortisone group inhibit the inflammatory reaction of connective-tissue cells, but in many instances the inflammatory reaction is part of the body's defence mechanism and is to be encouraged rather than inhibited. It has, however, become apparent that there are diseases which are really due to the body's reaction being quite disproportionate to the noxious stimulus. The manifestations of the disease are, in fact, those of an exaggerated or inappropriate inflammatory response, and if steroid therapy can inhibit this inappropriate response the manifestations of the patient's disease will be suppressed. The underlying condition is not cured, though it may ultimately burn itself out.

The anti-inflammatory action of steroids is used for this purpose in allergic conditions and diseases like rheumatoid arthritis, rheumatic carditis, disseminated lupus erythematosus, and polyarteritis nodosa. Large doses of steroid will also inhibit antibody production and help in the management of auto-immune conditions like some of the haemolytic anaemias and thrombocytopenic purpuras. Steroid therapy may also be used to suppress the patient's adrenal glands; the doses required, however, are nearer the physiological levels. This may be

FIG. 9.—Carcinoma of breast with multiple bony metastases. Oophorectomy and adrenalectomy in April, 1956. Hypophysectomy in March, 1957. X-ray films of femur taken in December, 1956 (A), and July, 1958 (B).

needed in cases of adrenal dysfunction where abnormal androgenic steroids are being made, or in cases of disseminated breast cancer to inhibit adrenal secretion of oestrogens, the so-called medical adrenalectomy.

When large doses of steroids are given for their pharmacological action, the result will be to produce an iatrogenic Cushing's syndrome. There is a tendency to forget that Cushing's syndrome is a serious illness with a grave prognosis—so serious, in fact, that one has no hesitation in advising total adrenalectomy for its treatment. Admittedly, treatment with high doses of steroid may in some situations be life-saving, or produce a temporary remission in an incurable disease. There has been a tendency to overlook the dangers of treatment with cortisone and the newer synthetic steroid hormones and to use them in cases where the treatment may prove more dangerous or disabling than the original disease. It seems likely that many of the complications of steroid therapy are intimately associated with their therapeutic action, but attempts have been made by modifying the steroid molecule to reduce some of the side-effects.

Synthetic Steroid Derivatives

The modified steroids that are now available are shown in Fig. 10. The substitution of a fluorine atom in the 9 α position of hydrocortisone leads to a remarkable sodium-retaining action and makes fludrocortisone a

FLUDROCORTISONE 9 α fluoro.
PREDNISOLONE 1=2.
6-METHYL PREDNISOLONE 1=2: 6-methyl.
TRIAMCINOLONE 1=2: 9 α fluoro: 16 α hydroxy.
DEXAMETHASONE 1=2: 9 α fluoro: 16 α methyl.
FIG. 10.—Modifications of hydrocortisone.

sone and prednisolone, derived from cortisone and hydrocortisone respectively. Therapeutic activity is enhanced five times on a weight basis without any increase of sodium retention (Demartini *et al.*, 1955). With these compounds, steroid therapy can be given at least in moderate doses without any fear of sodium retention, oedema, or hypertension. If very large doses of prednisone or prednisolone are used—more than 50 mg. a day (equivalent to 250 mg. of cortisone)—sodium retention may still occur.

The first modification of prednisolone was 6-methyl prednisolone, which has less sodium-retaining action and slightly greater therapeutic action. It has been claimed to be less likely to produce some of the other side-effects of prednisolone, but it is a little early to be definite about this (McMahon and Gordon, 1958). Triamcinolone has a hydroxy group substituted in the 16-position and a fluorine atom at the 9 α position of prednisolone. The sodium-retaining action is completely inhibited in this way, and therapeutic potency is about that of prednisolone (DiRaimondo and Forsham, 1958). Triamcinolone has some side-effects not seen with other

steroids—tendency to produce headache, facial flushing, and rather marked anorexia (Hartung, 1958; Kendall and Hart, 1959). The latter may be an advantage because the patient is less likely to gain weight excessively.

The latest modified steroid is dexamethasone. It has enormously enhanced therapeutic potency and very little sodium-retaining action. Why the therapeutic potency is enhanced in this way is not known, but it seems that the degree of enhancement varies from patient to patient. In preliminary studies it was found that on the same moderate dose, 4 mg. a day (equivalent to 150 mg. of cortisone), negative nitrogen balances over a three-weeks period varied from 50 to 150 g. (Slater *et al.*, 1959a). The nitrogen loss can be serious and muscular weakness may occur. The calcium balance became negative because of increased loss in the faeces. In one patient with hypercalcaemia and impaired renal function the plasma calcium rose with dexamethasone, whereas it fell later with prednisone. It had been hoped as a result of animal experiments that dexamethasone would be less likely to cause or aggravate diabetes than other steroids (Arth *et al.*, 1958), but in one patient that we studied no difference could be demonstrated.

Figures for the therapeutic potencies and salt-retaining activities of the various modified steroids are shown in Table VII.

TABLE VII.—Therapeutic and Sodium-retaining Potencies of Modified Adrenal Steroids

	Therapeutic Potency	Na-retaining Potency
Cortisone	1	1
Hydrocortisone	1.2	1
Prednisone, prednisolone	5	0.8
6-methyl prednisolone	6	0
16 α -hydroxy, 9 α -fluoro, prednisolone (triamcinolone)	6	0
16 α -methyl, 9 α -fluoro, prednisolone (dexamethasone)	37	0
9 α -fluorohydrocortisone (fludrocortisone)	15–20	> 100

Dangers of Steroid Therapy

At the present time it seems necessary to emphasize the dangers of steroid therapy rather than to discuss the indications for its use. The following comments are based on 322 patients treated with cortisone, hydrocortisone, and their newer analogues. Of these, 140 received

TABLE VIII.—Long-term Steroid Therapy. Duration

6–12 months	39 cases
1–2 years	30 "
2–3 "	14 "
3–4 "	9 "
4–5 "	6 "
> 5 "	6 "

TABLE IX.—Long-term Steroid Therapy. Average Dose in Terms of Cortisone mg./day

Steroid Used	50–100	100–200	200–400	> 400	Total
Cortisone	13	6	5	0	24
Prednisone	27	30	10	3	70
Triamcinolone	2	3	0	0	5
Dexamethasone	1	4	0	0	5

TABLE X.—Long-term Steroid Therapy. Complications

Infections (pneumonia 8, joints 2, renal 2, abdomen 3, abscesses 2, encephalitis 1, mycotic aneurysm 1)	19
Osteoporosis—severe	7
Muscle weakness	7
Diabetes { caused	10
aggravated	5
Duodenal ulcer	7
"Cushing's facies"	19
Mental disturbance	1

47 patients did not develop any complications.

physiological doses for Addison's disease, panhypopituitarism, or after adrenalectomy or hypophysectomy, and 78 were given larger doses for less than six months. These are excluded from the following analysis. Of the remaining 104 patients who were treated for more than six months, 30 had collagen diseases and 27 malignant lymphomata and leukaemias. The duration of treatment, the order of dose used, and the complications are shown in Tables VIII, IX, and X.

The most serious side-effects of steroid therapy are associated with infections. Four deaths were directly attributable to treatment and all were the result of infection. The manifestations tend to be suppressed and the patients may be afebrile and feeling well, despite the presence of large abscesses or spreading infection (Beck *et al.*, 1950; Allanby, 1957). Striking examples of this are seen in patients with rheumatoid arthritis developing pyoarthroses (Mills *et al.*, 1957). One patient in this series with disseminated lupus erythematosus and joint-involvement complained of increasing stiffness in the shoulders. Her general condition remained satisfactory, but the joints gradually became swollen and aspiration yielded about 400 ml. of pneumococcal pus from each side. A patient with rheumatoid arthritis developed staphylococcal septicaemia and osteomyelitis of the cervical spine which was detected following the development of neurological symptoms. This patient died, and the other deaths from infection were due to pulmonary aspergillosis in a patient on prolonged steroid therapy for pemphigus; recurrent lung infections aggravated by collapsed thoracic vertebrae due to steroid osteoporosis; and, in one case, to encephalitis occurring during steroid therapy.

Osteoporosis caused symptoms in seven patients; only one of them was suffering from rheumatoid arthritis. Three have had collapsed vertebrae, and in two of these there were troublesome lung infections. One patient, a boy aged 13, developed osteoporosis and renal calculi. Anabolic steroids have been used in an attempt to combat the tendency to osteoporosis (Reifenstein, 1958), but it is not possible to produce objective evidence of their efficacy. Muscle weakness is a well-recognized symptom of Cushing's syndrome, and it is not surprising that it may complicate steroid therapy. Marked weakness occurred in seven patients; in five it followed prednisone treatment and in two dexamethasone. The two who developed weakness on dexamethasone were the patients with the most strongly negative nitrogen balances. It has been suggested that a specific type of myopathy may be produced by triamcinolone (Williams, 1959), but it may well be that the reduction of appetite produced by this steroid accentuates the negative nitrogen balance.

Steroid diabetes developed in 10 cases; this figure is unexpectedly high because some patients were seen in the diabetic clinic after the development of this complication. The diabetes has seldom been severe, though a few patients have had to be given insulin, usually after the development of an infection. Seven patients had trouble with peptic ulceration; these include two in whom an unsuspected periduodenal abscess was found at necropsy and two who bled from their ulcers. Changing to enteric-coated tablets of prednisolone was beneficial in two patients with pain due to duodenal ulceration.

Difficulties may arise as the result of adrenal suppression during prolonged steroid therapy (Salassa *et al.*,

1953). In any severe physical stress, illness, or operation, a considerable increase of plasma hydrocortisone level is needed for maintenance of blood-pressure; this is produced through an increase of pituitary corticotrophin secretion and subsequent increase of adrenal hydrocortisone output. It was originally thought that the defect in patients treated with steroids lay primarily in the adrenal (Larzelere *et al.*, 1957), but it now seems that in some cases the pituitary is at fault and is slow to produce corticotrophin (Holub *et al.*, 1959). Not only is this defective response seen during the course of steroid therapy, but it has been observed for at least two years afterwards (Hayes, 1956). We have had trouble with three patients on this account. One case is of particular interest because it sheds some light on the mechanism.

The adrenal response to corticotrophin is easily tested, but until recently there has been no way of testing the pituitary capacity to produce corticotrophin. One stimulus to increased corticotrophin output is a fall in the circulating level of hydrocortisone. Using the new amphenone analogue 2-methyl-1,2 bis-(3-pyridyl)-1-propanone (SU 4885), it is possible to inhibit the 11-

FIG. 11.—Synthesis of hydrocortisone. SU 4885 is an inhibitor of 11-hydroxylase and blocks the last step in hydrocortisone (cortisol) synthesis.

FIG. 12.—Effect of oral administration of an 11-hydroxylase inhibitor (SU 4885) on urinary steroid excretion in four patients with normal pituitary reserve of corticotrophin.

hydroxylation step in the synthesis of hydrocortisone (Fig. 11). The circulating level of hydrocortisone falls, and normally the corticotrophin output rises and the adrenal responds by secreting more 11-deoxyhydrocortisone (compound S) and 17-ketosteroids (Jenkins *et al.*, 1959; Liddle *et al.*, 1959). Hydrocortisone, compound S, and their metabolites are all measured by the standard methods used for estimating 17-hydroxycorticosteroids, and typical responses to SU 4885 in subjects with a normal pituitary reserve of corticotrophin are shown in Fig. 12.

A patient has recently been studied who was having a neck exploration and who had had a short course of steroid therapy five months before (triamcinolone

FIG. 13.—Effect of corticotrophin and SU 4885 on urinary steroid excretion in a woman aged 51 with impaired corticotrophin reserve after steroid therapy.

16 mg./day for six weeks). No steroid cover was given, and twelve hours after the operation there was a period of hypotension responding to intravenous hydrocortisone. Subsequently she showed a completely normal response to corticotrophin but delay in increasing the corticotrophin output (Fig. 13). Similar studies have been

reported by Holub *et al.* (1959), Gold *et al.* (1960), and Nelson and Meakin (1960). It appears that in assessing the degree of adrenal suppression after steroid therapy before, for example, a surgical operation, in addition to giving corticotrophin to test the adrenal response, a test of pituitary reserve using SU 4885 should also be undertaken.

There is one final observation on this series of 104 patients treated with steroids in pharmacological doses for more than six months. Five of the patients have, during or shortly after treatment, developed cancer from which they have died. The details of these cases are shown in Table XI. This may well be a chance finding,

TABLE XI.—Cancer Complicating Long-term Steroid Therapy

Age and Sex	Original Disease	Steroid Therapy	Site of Cancer	First Evidence of Cancer	Died
F 46	D.L.E.	June/57–Aug./59	Ovary	Feb./58	Nov./59
M 45	Haemolytic anaemia	Sept./52–June/58	Bronchus	March/58	June/58
F 63	Cranial arteritis	Apr./55–June/56	Duodenum	Oct./57	Dec./58
M 52	Scleroderma	Oct./54–Apr./55	Bronchus	July/57	Feb./58
M 20	Ulcerative colitis	Oct./55–Apr./56	Bile-duct	Nov./58	March/59
		May/53–Oct./55			
		Sept./57–Mar./59			

but there are two reasons for drawing attention to it. First, that in published series of cases on long-term steroid therapy there are a number of cases of cancer noted among the “deaths from unrelated causes” (Bunim *et al.*, 1955; Stevenson, 1960). Secondly, there is evidence that carcinomata develop not infrequently in young patients with Cushing’s syndrome (Crooke, 1946; Thorne, 1952).

C

Summary

The two important hormones of the adrenal cortex are hydrocortisone and aldosterone.

The main actions of hydrocortisone are maintenance of blood-pressure and renal function, and the proper distribution of water and sodium in the body fluids.

In severe physical illnesses and surgical operations the circulating level of hydrocortisone must be increased if its function is to be maintained. In some cases the level required may exceed that which the normal adrenal cortex can achieve. The metabolic changes after surgery are not the result of alterations of steroid level although increased hydrocortisone secretion is necessary for the normal metabolic response.

Methods of urinary aldosterone estimation depending on the pH 1 extractable fraction are not entirely reliable because this represents a variable proportion of aldosterone secretion in any particular patient.

Aldosterone secretion is often increased in patients with oedema. This appears to be a secondary phenomenon. Blocking the action of aldosterone with the spiro-lactone compounds may result in a diuresis, even though the aldosterone secretion rate is normal.

Total adrenalectomy has been performed for a number of non-endocrine conditions, including metastatic carcinoma from breast and prostate, malignant hypertension, intractable oedema, and diabetes with complications. Steroid cover for the operation and post-operative replacement therapy are discussed.

There are many unsolved problems concerning the hormones of the anterior pituitary gland, including the extra-adrenal action of corticotrophin and the role of growth hormone in the adult.

The endocrine effects of pituitary-stalk section are described; it is suggested that thyrotrophin but not corticotrophin or gonadotrophin may be secreted in the absence of any vascular connexions between the hypothalamus and pituitary.

The indications for surgical hypophysectomy include metastatic breast cancer, malignant exophthalmos, and progressing diabetic retinitis. In metastatic cancer it is suggested that radioactive yttrium implantation is more suitable than surgical hypophysectomy. The results of hypophysectomy in five patients with severe diabetic retinitis are described.

The new synthetic steroids include prednisone, prednisolone, methyl prednisolone, triamcinolone, and dexamethasone. The main dangers of long-term steroid therapy include infection, osteoporosis, muscle weakness, diabetes, and peptic ulceration.

Attention is drawn to the development of cancer in five patients out of 104 during or shortly after steroid therapy given for more than six months.

Adrenal insufficiency after steroid therapy may be due to delay of corticotrophin release by the anterior pituitary or delay of adrenal cortical response to corticotrophin. Tests with an 11-hydroxylase inhibitor make it possible to detect patients liable to delay of corticotrophin release.

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THE FATE OF THE CLAUDICATOR

BY

ADOLF SINGER, M.B., F.R.C.S.

AND

CHARLES ROB, M.C., M.Chir., F.R.C.S.

Surgical Unit, St. Mary's Hospital, London

Arterial insufficiency of a limb presents either with pain or with gangrene. The former usually occurs only after exercise—that is intermittent claudication—but may be present at rest. The fate of the gangrenous leg is known; unless the circulation can be improved by direct arterial surgery or a sympathectomy, amputation is the usual outcome. The prognosis for the claudicator, with or without additional rest pain, is not so well documented, but is more favourable.

The natural history of such patients regarding their arterial disease forms the subject of this investigation. It describes the initial assessment and progress of patients who attended with symptoms and signs of atherosclerotic arterial disease in one or both lower limbs. The patient's doctor was then sent a standard letter which requested information on the patient's survival, the state of the affected limbs, manifestations of atherosclerosis in other parts of the body, and, if applicable, the date and cause of death. Where necessary, details of date and cause of death were obtained from the Registrar-General's records.

Clinical Material

A total of 359 patients were taken at random from the vascular index at this hospital. All were first seen before 1958, to allow for a minimum follow-up period of two years. This represented approximately half of all the patients who attend the vascular clinic during this period. The follow-up period was taken to begin with the first hospital attendance at which a definite diagnosis was made. Diagnosis was based on history and signs of impaired circulation. Incipient or actual gangrene was present in 62 patients. To confirm the clinical diagnosis 205 arteriograms were carried out. Patients thought to have Buerger's disease (thrombo-angiitis obliterans) were excluded, the diagnosis being made on the younger age, the episodic course, the occurrence of attacks of superficial thrombophlebitis, the common localization of the arterial lesions in the distal vessels of upper and lower limbs, and sometimes by arteriography.

There was no other selection of cases, all patients conforming to the above-mentioned criteria being included.