ENDOCRINE DISORDERS IN ANAESTHESIA

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Disorders of the pituitary, pancreas, parathyroid, thyroid and adrenal glands may adversely influence the response of a patient to anaesthesia or surgery and so are of particular concern to the anaesthetist. In this connexion diseases of the ovaries or testes are of no importance and will not be discussed further.

Patients with endocrine disease may appear to the anaesthetist in one of two quite distinct roles. The first is the patient with some known endocrine disorder that is to be treated surgically. This seldom presents a problem because in most instances the physician and surgeon will have done everything possible to reduce the risks of operation. The second is the patient who presents with a non-endocrine disease requiring surgical intervention, but who in addition is suffering from an unrecognized glandular disturbance. From the anaesthetist's point of view this second type of patient is the most important if disaster is to be avoided, and often it is the astute anaesthetist who first suspects the additional non-surgical condition during his pre-operative assessment of the patient as a whole.

UNRECOGNIZED ENDOCRINOPATHY
In patients with undetected endocrine disease symptoms are often wholly absent or minimal. Once the condition has been suspected and appropriate direct questions asked, the patient may admit to having noticed some abnormality, but usually the onset of the glandular deficiency is so insidious that the patient is unaware that anything is amiss, and his relatives fail to notice the striking changes that are occurring in his appearance and behaviour. Particularly is this the case in hypothyroidism, whether due to primary thyroid disease or secondary to pituitary insufficiency. In this type of patient routine history taking or the asking of direct questions often fails to raise any suspicion of endocrine disease. True if a sufficiently large number of symptoms are asked about, hints of some endocrine disorder may arise, but the number of questions that would have to be asked to uncover the many possible syndromes makes this impracticable.

There are, however, four questions which should always be asked of any patient about to undergo an operation. Weight-loss is common to many non-endocrine surgical conditions, but if unexplainable on this basis or disproportionate to the major disease, may indicate diabetes mellitus, hyperthyroidism or adrenal insufficiency. Polyuria or polydypsia, which may be equated by the patient with insomnia, may indicate diabetes mellitus, diabetes insipidus or hyperparathyroidism. Rarely menstrual disorders may indicate some major endocrine disorder; amenorrhoea being a symptom of pituitary failure, hyperthyroidism or adrenal insufficiency, and menorrhagia of hypothyroidism.

The fourth question or series of questions, which must never be omitted, is to discover if the patient has ever had systemic treatment with corticosteroid drugs. As regrettably few still have little idea of the nature of any tablets received in the past, it may be necessary to enquire if the patient has suffered from any of the diseases commonly treated with cortisone or its analogues—asthma, hay fever, rheumatoid arthritis or urticaria. The importance of this, to be discussed more fully later, lies in the adrenal suppression induced by steroid therapy—a suppression which may last for two years after treatment has finished.

Physical examination is often helpful in uncovering unsuspected endocrine disease, and only a few seconds are required to detect the diagnostic features. To the eye that sees, hypothyroidism is immediately obvious, yet this is one of the most commonly missed diagnoses, even in its grossest form, and recently two such patients were submitted to operation in a teaching hospital—fortunately without disaster. The pinkness of the cheeks against the yellow pallor of the rest of the
face and the cold dryness of the skin on the limbs are characteristic features of hypothyroidism whether due to primary thyroid disease or secondary to pituitary insufficiency. Facial, axillary and pubic hair is often sparse and may be wholly absent in long-standing pituitary deficiency in which gonadal hypofunction is added to the hypothyroidism. The rubicund moon facies of Cushing's syndrome is also characteristic but may be confused with non-endocrine obesity; in the former condition there is a curious disparity between the fatness of the trunk and upper part of the limbs and the slender delicate structure of the wrists, ankles, hands and feet; whereas in the latter the obesity is uniformly distributed. Acromegaly is unlikely to be overlooked. The pigmentation of Addison's disease may be attributed to racial origin but has an uneven distribution being most marked on areas subjected to pressure—the knees, elbows, waist where belt or skirt band press, and shoulders and thorax where brassiere straps chafe. Pigmentation is usually marked in the inside of the mouth, on the gums below the incisor teeth and in old scars. A low blood pressure is not common except during an adrenal crisis. The neck should always be inspected and palpated: even moderate enlargement of the thyroid as in a simple colloid goitre may add to the difficulties of intubation. Glycosuria is best detected with Clinistix which is speedy, sensitive and specific for glucose—being uninfluenced by any other reducing substance. The presence of acetone in the urine indicates either severe diabetes mellitus or malnutrition—both of a degree which should be corrected before operation.

In general the greater the degree of endocrine dysfunction, the more obvious are the physical signs and the greater the operative risk. In adrenal suppression secondary to steroid therapy physical signs are wholly absent, and the one most often found in diabetes insipidus or hyperparathyroidism is mild dehydration.

**RECOGNIZED ENDOCRINOPATHY**

Once an endocrine abnormality has been diagnosed or is suspected, the management of the patient will depend on the urgency of the surgical condition. Whenever possible the diagnosis of the endocrinopathy should be confirmed by appropriate investigation, and corrective treatment instituted. In many conditions, however, response to treatment is slow, surgical intervention cannot be delayed and the pre-operative state of the patient is less than ideal. Nonetheless the risk is immeasurably reduced by the anaesthetist's awareness of the endocrine abnormality and his readiness to counter any difficulties that may arise during or after the operation.

**Thyroid disease.**

The presence of a goitre or any irregularity in the thyroid substance should immediately give rise to the question: "Is this patient thyrotoxic?" Minor degrees do not materially add to the risk of surgery on other parts of the body, but patients who are more severely affected may have auricular fibrillation, right-sided heart failure or liver damage, which may to some extent offset the increased rate of metabolism of sedatives and hypnotics usually found in hyperthyroidism. Unfortunately there is no treatment that will reduce the activity of the thyroid within a matter of hours. Reserpine in large doses (5 mg intramuscularly thrice daily) will allay the tachycardia, restlessness, tremor and other overt manifestations usually attributed to the peripheral action of excess thyroxine. Potassium iodide, 5 drops of a saturated solution thrice daily, will inhibit the release of thyroxine from the gland but an appreciable effect is not achieved until after 4–5 days, and the maximum response occurs after 10–21 days. Chlorpromazine, hypothermia and intravenous hydrocortisone (200–300 mg) comprise the treatment of choice for a thyroid crisis following thyroidectomy in an inadequately prepared patient with known hyperthyroidism, or in a patient with a nodular goitre erroneously thought to be non-toxic.

Hypothyroidism seriously delays the metabolism of drugs and renders the patient unduly sensitive to them. The operative risk is further increased because of secondary changes in the pituitary and adrenal glands which impair the normal responses to stress. In general the greater the degree of hypothyroidism and the longer its duration, the greater is the operative risk. There are, however, curious individual differences in response.

Two men of the same age and, judging from subsequent basal metabolic rate estimations, suf-
ferring from an equal degree of hypothyroidism, were operated upon before recognition of their endocrine disease. One had a herniorrhaphy and responded normally to his pre-operative medication and anaesthesia. The other showed undue sensitivity to the pre-operative medication and developed severe hypotension during transfemoral aortography which necessitated abandoning the investigation.

Myxoedema retards the responsiveness of the adrenal glands to ACTH and there is similar evidence that the pituitary in the myxoedematous subject is less responsive to whatever stimuli increase its activity. Thus the development of severe hypotension in these patients is thought to be due to adrenal insufficiency; they should be treated with intravenous hydrocortisone hemisuccinate or prednisone-21-phosphate.

If time permits an attempt may be made to correct the hypothyroidism before operation. Tri-iodothyronine acts in a few hours but must be used cautiously in a patient over the age of 50 and particularly in any patient who has a history of angina pectoris or evidence of atherosclerosis. Under-treatment is safer than over-treatment, and the dosage of tri-iodothyronine should not exceed 10–20 μg, 12-hourly.

Adrenocortical disease.

Adrenocortical insufficiency may develop post-operatively after adrenalectomy for Cushing's syndrome (or for the control of carcinomatous metastases), in patients with Addison's disease, and in those having corticosteroid treatment or who have stopped such treatment weeks or months before surgery. This last group contains the largest proportion of patients who are exposed to the greatest risk: pre-operatively they have no abnormal physical signs and the possibility of adrenal suppression being present as a consequence of previous corticosteroid therapy can only be uncovered by direct questioning. Too many patients are unaware of the nature of therapy received in the past and the physician who prescribes corticosteroids has a moral obligation to explain to the patient the physiological consequences and to provide him with a written note of warning and instruction.

All synthetic analogues of cortisol and hydrocortisone cause pituitary inhibition and secondary adrenal suppression. The degree of suppression is more related to the duration of corticosteroid treatment than to dosage, and there are wide, and as yet unexplained individual variations. Any patient currently having steroid therapy is particularly at risk, but the risk persists for weeks or months after stopping treatment even when the dosage is gradually reduced. Irreversible shock has been described after minor surgical procedures in patients who have stopped steroid therapy for as long as 24 months, but have sufficient adrenocortical function to allow a life free of symptoms under more ordinary circumstances.

Attempts to prevent adrenal suppression by giving adrenocorticotrophin concurrently with steroid therapy have not been wholly successful in maintaining the normal responsiveness of the pituitary-adrenal axis to stress. Injections of corticotrophin induce histological changes in the pituitary similar to those found after prolonged administration of corticosteroids, and collapse has occurred during surgery in patients who have had prolonged treatment with ACTH alone. Thus in the practical management of corticosteroid treated patients, administration of ACTH cannot be relied upon to prevent operative complications, and time seldom allows the application of somewhat complicated tests to assess pituitary-adrenal responsiveness. The wisest course is to give prophylactic treatment to any patient currently having steroid treatment or who has had prolonged treatment during the previous two years. These two types of patient constitute an absolute indication for special pre- and postoperative care. Patients whose treatment ended more than two years previously may face an additional operative risk, but usually special pre-operative preparation is unnecessary provided appropriate measures are available and are implemented immediately if collapse occurs.

Corticosteroids are rapidly absorbed from a normally functioning gastro-intestinal tract. An appreciable rise in the plasma steroid concentration occurs within half an hour of administering the tablets; it reaches a maximum in 1 1/2 hours although the metabolic consequences of the increased steroid level may not be manifest for another 3–4 hours. In contrast to many substances corticosteroids are not well absorbed after intramuscular injection; for speed of action this route of administration is much inferior to oral or
intravenous therapy, and plays little part in the emergency treatment of adrenal insufficiency. In prophylaxis, however, intramuscular cortisone provides a useful depot from which absorption will continue for many hours. For intravenous use hydrocortisone hemisuccinate or prednisone-21-phosphate, which are both water soluble, are used in the knowledge that a major operation in a normal individual will call forth the secretion of about 400 mg hydrocortisone in 24 hours from healthy adrenal glands (equivalent to about 100 mg prednisone).

For patients receiving steroid treatment and those who have had corticosteroids during the preceding two years, the amount of additional steroid required depends on the severity of the operation and the degree of adrenal suppression. Both factors are difficult to assess and as too little supplementation may lead to disaster, larger rather than lesser amounts should be used. The same principles should guide the preparation of a known or suspected Addisonian patient. It is now appreciated that patients with partial adrenal insufficiency may lead a normal life for many years and yet succumb suddenly and unexpectedly to some quite trivial operation. The disease is so slowly progressive that the patient may fail to report any symptoms, or only admit to increased fatigue or minor abdominal discomfort and looseness of the bowels on direct questioning. Often pigmentation of minor degree is the sole abnormal finding. Excretion of hydrocortisone and its metabolites in the urine as determined by the currently available routine laboratory methods may not be abnormal and adrenal insufficiency may only be revealed by finding diminished responsiveness to stimulation with ACTH. Whenever the suspicion is raised it is wiser to provide prophylactic coverage.

Forty-eight, twenty-four and again six hours before operation the patient is given 100–200 mg cortisone acetate intramuscularly. If currently taking steroids, the patient continues with his usual dose in addition. At the completion of the operation another 100–150 mg cortisone is given by injection. Subsequent management will depend on whether the patient is vomiting or not. If possible cortisone is given orally in a dose of 50 mg three or four times on the first postoperative days. Thereafter the dosage is reduced gradually over the next week and stopped after 10–14 days in those not having current steroid therapy, or reduced to the pre-operative maintenance dose in those who are. If the patient is vomiting, intramuscular cortisone is used—100–150 mg on the first and second post-operative days and 75–100 mg on the third. Thereafter oral treatment should be used but at all times hydrocortisone hemisuccinate (or prednisone-21-phosphate) must be readily available for intravenous administration if the blood pressure falls or unexplained pyrexia develops.

The same pre-operative treatment should be used for patients with Cushing's syndrome undergoing adrenalectomy. If the cause of the condition is an adenoma or carcinoma, atrophy of the contralateral adrenal will have occurred, and removal of the tumour will be followed by adrenocortical insufficiency. If the cause is bilateral adrenal hyperplasia, total adrenalectomy will certainly lead to adrenal deficiency, and subtotal adrenalectomy will often have the same effect until the adrenal remnant begins to function again.

For patients who have stopped steroid treatment more than two years previously, it is usually safe to omit prophylactic measures provided the treatment (outlined later) is immediately available if collapse develops during or after operation. The same steps should be taken if collapse occurs in patients already having supportive steroid therapy. If the fall in blood pressure is detected early and appropriate action is taken at once, the patient will respond promptly. It is often asked whether this form of treatment should be applied when hypotension occurs unexpectedly and unexplainably during an operation on a patient supposed to have normal adrenal function. There is no doubt that if the hypotension is due to adrenocortical insufficiency it will respond to intravenous steroid therapy given promptly, but that this form of treatment is without apparent benefit in collapse due to other causes. Since there may be no means of determining the aetiology of the hypotension it seems prudent to give steroids intravenously and observe the therapeutic response. More often than not some non-endocrine cause will later become apparent but no harm will follow the administration of intravenous hydrocortisone.

As soon as collapse occurs, 100 mg hydrocortisone (as the sodium succinate salt), or 20 mg of
prednisone or prednisolone (as the 21-phosphate) is injected intravenously. An intravenous infusion of glucose-saline is set up and 500 ml containing a further 100 mg hydrocortisone given over the next twelve hours. During the first 24 hours 400 mg hydrocortisone may have to be infused in 1–1½ l. of fluid. On some occasions 2–4 mg noradrenaline have been added to the infusion bottle; it is doubtful whether this is necessary when adequate amounts of hydrocortisone are used. Furthermore, because of the undesirable local vasoconstrictor effects of noradrenaline, "Aramine" is preferable if the blood pressure does not rise in response to corticosteroid treatment.

**Phaeochromocytoma.**

The anaesthetist plays an important part in the surgical treatment of phaeochromocytoma. Preoperatively the hypertension can be controlled by oral administration of phenoxybenzamine, and the resulting persistent sympathetic blockade will allow considerable improvement in the patient's cardiovascular system. The dosage required usually varies between 20 and 200 mg daily and is adjusted to produce the desired reduction in blood pressure. During the operation, handling of the tumour may induce extreme elevation of the blood pressure and fatal cardiac arrhythmias. Anaesthetic agents, such as cyclopropane, which may produce cardiac arrhythmias should be avoided, and sudden rises in blood pressure checked with intravenous phentolamine in doses of 0.1 mg/kilo body weight. A precipitous fall in blood pressure after removal of the tumour should be countered by the intravenous infusion of noradrenaline, which is best administered through a polythene catheter introduced into the superior vena cava (to avoid local ischaemic effects in the arm).

**Diabetes insipidus and hyperparathyroidism.**

The pre-operative preparation of patients with diabetes insipidus, or hyperparathyroidism, is directed towards correcting dehydration, and maintaining the fluid balance postoperatively at a time when the patient cannot drink but the urinary loss of water continues unabated. Pitressin tannate in oil, 2–5 units subcutaneously, will stem the diuresis in diabetes insipidus, but in hyperparathyroidism intravenous infusion of isotonic glucose solution may be required to make good the fluid losses.

**Diabetes mellitus.**

Diabetes is perhaps the endocrine disease most often encountered by the anaesthetist and the one which poses the most difficult problems. The situation is straightforward if the patient is known to have diabetes which is under good control—his treatment is left unchanged until the day of operation and provided there are no renal complications, the operative risks are not substantially different from those of a non-diabetic patient. Other patients, although known to have diabetes, may become inadequately controlled as a result of the surgical condition requiring treatment, or because they have deliberately but wrongly reduced the dosage of insulin when anorexia or vomiting diminished their food intake. Others are not discovered to have an abnormality of carbohydrate metabolism until their urine is tested on admission to hospital. It is essential in these patients with glycosuria to assess the severity of the diabetes. First it is necessary to confirm that the reducing substance detected with Benedict's solution, or Clinistest tablets, is truly glucose, and this is done with a specific glucose-oxidase method such as Clinistix. Although the severity of the diabetes is to some extent reflected by the degree of glycosuria, ketonuria is the most important simple guide. This must be tested for with Acetest tablets, or ferric chloride solution, but the latter may give a positive result if the patient has been taking salicylates or p-aminosalicylic acid. The presence of ketonuria calls for immediate emergency treatment and the operation must be delayed at all costs for at least 6–12 hours. More accurate assessment must be obtained in patients who are uncontrolled or in whom the disease was previously unrecognized, by determining the blood sugar level and the degree of acidosis as shown by the CO₂ combining power. A blood sugar level of 250–300 mg per cent in the absence of ketonuria calls for some adjustment of the insulin dosage in a patient known to have diabetes, and the institution of insulin therapy in a young person who gives a history of thirst, polyuria and weight loss; in a middle-aged or older overweight person, who on direct questioning denies any diabetic symptoms, no special preoperative measures are necessary. When the blood sugar level exceeds 300 mg per cent and there is concomitant acidosis as shown by ketonuria...
and a lowering of the CO₂ combining power, insulin therapy and correction of dehydration are essential pre-operative steps.

Pre-operative preparation. The treatment outlined here is designed for those patients who require insulin therapy but are not in diabetic coma or precoma. The objectives are to eradicate any ketosis; control the blood sugar level and avoid hypoglycaemic reactions. Most patients will have marked glycosuria and some ketonuria but the CO₂ combining power will not be reduced below 20 m.equiv/l. Food is given 6-hourly in four equal amounts providing 100 g. carbohydrate, 100 g. protein and about 50 g. fat per day. Whether this food should be solid or liquid will depend on the patient's surgical condition. Insulin is given six-hourly before each meal. Soluble insulin is used because its duration of action is comparatively brief. If the patient had been taking insulin, the first dose should be one-third the total previous daily dose irrespective of the type of insulin used before. If the patient has never required insulin in the past, the initial dose should be 12–16 units. Thereafter the amount of insulin given is determined by the amount of sugar excreted in the previous six hours. If the urine is red or orange, 20 units are injected; if green or yellow, 10 units.

Day of operation. It is important to avoid hypoglycaemia on the day of operation because unconsciousness may erroneously be attributed to the anaesthesia. Provided ketosis is avoided it does not matter if the blood sugar level is undesirably high and it is safer to have glycosuria rather than no sugar at all in the urine. The principle is to feed the patient every six hours and give insulin before each feed.

Usually parenteral feeding will be necessary on the day of operation because the stomach should be empty when anaesthesia is induced and the patient may vomit postoperatively. A simple and satisfactory regimen is to give 500–750 ml of 5 per cent glucose during each 6-hour period. This can be given by mouth or intravenously according to the patient's condition, and during every third period the glucose should be dissolved in physiological saline rather than water. Soluble insulin is used throughout and administered subcutaneously. If the patient has been satisfactorily stabilized pre-operatively the first period should be preceded by an amount of insulin which is one-quarter of his previous total daily requirements. Thereafter the amount of insulin must be judged from the amount of glucose excreted in the urine.