work or family life.[7] These patients include the jet lagged businessman, the shift worker, and the bereaved.

Benzodiazepines are generally useful in those with transient insomnia. Because the patient is not anxious and wants to keep alert the next day the doctor should choose a drug with minimal residual effects: temazepam or lormetazepam are preferable when the problem is to stay asleep (often the problem in shift workers), and triazolam when the subject cannot fall asleep—for example, in a hotel with traffic noise. Because of biological variation, however, more than one drug may need to be tried. Patients in hospital awaiting investigations or operations may welcome longer acting drugs that provide some sedation the next day, but these must be withdrawn before discharge.

Short term insomnia is not an automatic indication for a hypnotic. All too easily what starts as short term use for an emotional problem may slide into long term use, with rebound or even a withdrawal syndrome when the drug is stopped. If a drug is used the dosage should be moderate and the patient should be encouraged to take it intermittently. Difficulty in getting to sleep is the usual complaint but varies from night to night; the patient should be urged to try without drugs and to take them only if unable to sleep after an hour or so. Drugs should not be needed after two weeks or so. If the patient is anxious a modest dose of a longer acting hypnotic or diazepam may be used with minimal risk of rebound; otherwise, a shorter acting compound in modest dose will minimise residual effects.

Chronic insomnia is the most difficult type to manage, and careful assessment and general supportive measures are essential. Caffeine and alcohol may need to be restricted in the evening, and moderate exercise earlier in the day often helps. Psychiatric syndromes should be excluded, but antidepressants may be tried if other possible depressive symptoms such as poor appetite are present. Hypnotics should be resorted to only intermittently as these patients may end up using them long term and experiencing rebound and withdrawal symptoms if they try to stop.[8] Again, use as needed is best as chronic insomniacs often vary greatly from night to night in the severity of their insomnia.

The dosage of the hypnotic must be kept low: both residual and rebound effects increase sharply with increased dosage. The duration of prescription must also be kept short, and in my view pleas to make benzodiazepines more freely available underestimate the hazards.[9]

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Regular Review

Hormonal changes in non-endocrine disease

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Illness produces a wide variety of metabolic effects. As the endocrine system is intimately concerned in regulating metabolism, not surprisingly extensive hormonal changes also result from illness. Some have clear advantages to the patient—notably, the surge in catabolic hormones after illness allowing mobilisation of energy stores which may be necessary for survival. Others have less obvious advantages for survival.

Failure to recognise hormonal changes that accompany illness may lead to a mistaken diagnosis of primary endocrine disease and inappropriate treatment. Thus it is important to recognise those abnormalities which may be expected to occur to prevent mistaken diagnosis of a primary endocrine problem. This review outlines those changes in each major endocrine system which may be encountered in ill patients.

Thyroid function

Alterations in thyroid function have been extensively studied and recently reviewed.[1 2] Thyroid function tests are commonly performed, and certain ill patients—notably, those with hypothermia or chronic renal failure—appear clinically hypothyroid. Thus abnormalities of thyroid function in ill patients may lead to clinical confusion, and the ability to interpret thyroid function tests correctly is important.

Low concentrations of triiodothyronine (T3) are found in a variety of clinical states, including surgery,[3] myocardial infarction,[4] and starvation.[5] Plasma T3 is largely derived from the peripheral conversion of thyroxine (T4), a process that is suppressed in ill patients.[6] Low T3 states are also

characterised by a reciprocal increase in the metabolically inactive reverse T3,[7] which is primarily due to decreased metabolism of reverse T3 rather than to increased production.[8] In vitro evidence suggests that the conversion of T4 to T3 and of reverse T3 to its diiodothyronine derivative may be regulated by the same 5'-deiodinase.[9] Any inhibition of this enzyme system may therefore account for most of the changes in the low T3 state.

In more severely ill patients both T4 and T3 concentrations are low. Interestingly, T4 concentrations correlate inversely with the severity of illness, patients with the lowest concentrations having the poorest prognosis.[10] Several separate mechanisms probably lead to low T4 concentrations. Thyroid hormones are tightly bound to protein, primarily to thyroxine binding globulin but also to thyroxine binding prealbumin and albumin. In most examples of non-thyroidal illness a decreased affinity of T4 for its binding proteins is seen despite normal or only moderately low concentrations of thyroxine binding globulin.[11 12] An inhibitor of T4 binding is found in the serum of such patients[11] and also in extrathyroidal tissues, whence it may be released into the circulation during illness.[13]

Measurement of the metabolically active, non-protein bound hormones, free T4 and free T3, is difficult when binding inhibition is present, commonly used free T4 indices and some kit methods for measuring free T4 giving unreliable results.[14] The more dependable but laborious equilibrium dialysis method gives free T4 concentrations that are normal or high and free T3 concentrations which are normal or low.[12 14]

Thyroid stimulating hormone concentrations are within the normal range unless primary hypothyroidism is also present. Thyroid stimulating hormone responses to thyrotrophin releasing hormone are usually normal but are blunted in chronic renal failure.[15] Nevertheless, giving iodide to ill patients, which reduces thyroid hormone concentrations, does not result in the normal increase in secretion of thyroid stimulating hormone.[16] Further evidence for the role of hypothalamic-pituitary suppression as a factor in low T4 states was provided by Wehman and colleagues, who showed a reduction in thyroid stimulating hormone concentrations after marrow transplantation for haematological malignancy[17]; thyroid stimulating hormone secretion increased with subsequent recovery.

Further diagnostic difficulties may occur in other clinical conditions. Acute and chronic hepatitis provide exceptions to the rule as T4 and T3 concentrations are usually normal or high because damage to the liver cells releases increased amounts of thyroxine binding globulin.[18 19] Thyroid stimulating hormone concentrations may be raised, possibly because of an associated autoimmune thyroiditis.[19] Further difficulties in interpretation may occur in hyperthyroid patients who have become acutely ill: thyroid hormone concentrations may fall to within the normal range, only to rise once more with recovery.[20] In mildly hypothyroid patients with concurrent illness, on the other hand, thyroid stimulating hormone concentrations may fall so that values lie within the normal range.[21] Dopamine[22] and glucocorticoid[23] are drugs widely used in critically ill patients. As both suppress the release of thyroid stimulating hormone and reduce thyroid hormone concentrations they may aggravate low T4 and low T3 states as well as lead to difficulties in diagnosis when given to hyperthyroid or hypothyroid patients.

Most ill patients with low T4 and T3 values are considered to be euthyroid as other indices of thyroid function, such as systolic time intervals and ankle jerk relaxation times, are normal.[14 15] Moreover, the low T3 state may be a homoeostatic mechanism leading to reduced catabolism; certainly no studies have shown a beneficial effect of thyroid hormone replacement.

Hormones and energy supply

During illness energy requirements alter and there is an increased demand for supply of energy substrate. Whereas insulin is the sole anabolic hormone concerned in the storage of lipid and carbohydrate, there are several opposing or "counter-regulatory" hormones—in particular, the catecholamines, glucagon, cortisol, and growth hormone, all of which promote catabolism and the supply of substrate.

Activation of the sympathetic nervous system in ill patients leads to the release of catecholamines. Sometimes this is short lived, but it is often prolonged in very ill patients, who may display a rapid fall before death.[24] Catecholamine release may not be wholly beneficial: electrocardiographic changes sometimes observed after an intracranial catastrophe, particularly subarachnoid haemorrhage, may reflect myocardial necrosis induced by massive sympathetic outflow.[25] Catecholamines promote the breakdown of glycogen and the formation of glucose by the liver as well as stimulating lipolysis with the subsequent release of free fatty acids and glycerol. They also have important effects on the pancreas, stimulating glucagon release and inhibiting insulin secretion.[26] Glucagon concentrations are therefore raised in illness, usually in proportion to its severity.[27] Insulin concentrations are inappropriately low for the degree of rise in the blood glucose concentrations.[27] This alteration in the balance between insulin and glucagon secretion despite hyperglycaemia allows the glucagon mediated events in the liver to persist—in particular, glycogenolysis and gluconeogenesis.

Activation of the hypothalamic-pituitary-adrenocortical axis stimulates release of cortisol, a steroid with many effects on intermediary metabolism, most of which lead to increased catabolism and supply of substrate for gluconeogenesis. The plasma concentration of growth hormone also increases after injury despite concentrations of plasma glucose which would inhibit its secretion in the normal person.[28] Concentrations usually fall rapidly to normal, although in severely burnt patients raised values may be sustained for weeks.[29]

All these endocrine changes explain the hyperglycaemia which commonly accompanies illness. In most patients the results of oral glucose tolerance tests are normal after recovery. To make the important distinction between hyperglycaemia due to illness and that due to diabetes mellitus an estimation of the glycosylated haemoglobin will help by giving an indication of the plasma glucose concentrations in the weeks before the acute event. Again, raised plasma concentrations of growth hormone or catecholamines during an acute illness should not be considered as signifying an endocrine disorder, and when there is clinical suspicion of an endocrine abnormality tests should be performed after recovery.

Adrenocortical function

The adrenal cortex secretes three different types of steroid: glucocorticoids, mineralocorticoids, and androgens. The major glucocorticoid, cortisol, is essential for the survival of the stressed patient. The major mineralocorticoid,

aldosterone, is an important regulator of fluid and electrolyte balance. The function of adrenal androgens, which are the most abundant circulating adrenal steroids, is uncertain.

Raised cortisol concentrations are found in ill patients, activation of the hypothalamic-pituitary axis stimulating increased secretion; the extent and duration of the rise depend on the severity of the insult.[30] Factors other than hypothalamic secretion of corticotrophin releasing factor may act on the pituitary to release adrenocorticotrophic hormones since its concentration is often greater than that seen after intravenously injected corticotrophin releasing factor. Other hormones, such as vasopressin (antidiuretic hormone) and catecholamines, may act synergistically with corticotrophin releasing factor on the anterior pituitary.[31]

Aldosterone secretion is primarily controlled by the renin-angiotensin system but adrenocorticotrophic hormone and hyperkalaemia may also have stimulatory effects. Aldosterone concentrations increase because of the activation of the renin-angiotensin system after surgery[32] and burns.[33] This rise probably protects the ill patient by counteracting the volume depletion which so often results from trauma or acute illness.

The secretion of adrenal androgens is also under the control of adrenocorticotrophic hormone, although there may be a specific adrenal androgen stimulating hormone.[34] These androgens have not been widely studied in ill patients, but recent work has suggested that patients severely ill for over a week with raised cortisol concentrations also have reduced concentrations of adrenal androgens.[35] Hence possibly, when chronically stimulated, the adrenal gland can autoregulate and secrete cortisol preferentially in life threatening conditions. The finding of low aldosterone concentrations in persistently hypotensive ill patients who have raised cortisol and renin concentrations is compatible with this concept.[36]

Gonadal function

Both aspects of gonadal function—the formation of gametes and the production of sex hormones—are abnormal in a variety of illnesses. Thus testicular function is well known to be abnormal in chronic renal failure and in liver disease. In the former impotence and infertility are common, as is oligospermia or azoospermia.[37] Testosterone concentrations are low with gonadotrophin concentrations that are normal or raised—but not as high as occurs if the hypothalamic-pituitary feedback systems are working normally.[37] In chronic liver disease the high concentrations of circulating oestrogens probably contribute to the characteristic gynaecomastia, palmar erythema, and spider naevi.[38] Concentrations of testosterone are low or normal but because of high concentrations of sex hormone binding globulin those of free (unbound) testosterone are low.[38,39] Luteinising hormone concentrations are variable but normal values in some patients with low testosterone concentrations suggest that a hypothalamic-pituitary abnormality may be present as well as a primary testicular defect.[39]

Hypogonadism is a feature of several clinical conditions—for example, haemochromatosis, in which it is probably caused by the deposition of iron in the hypothalamus or pituitary, or both.[40] Patients with lepromatous leprosy often have testicular atrophy owing to direct invasion of the testes by acid fast bacilli.[41] Hypogonadism due to primary testicular failure is a characteristic feature of myotonica dystrophica.[42] Reduced testosterone secretion has also been recognised in many other conditions—for example, after surgery,[43] myocardial infarction,[44] burns,[45] and respiratory failure.[46] The mechanisms leading to low testosterone concentrations are not clear and may not be the same with each disease. Gonadotrophin concentrations are lower than would be expected for the degree of testosterone reduction, suggesting a hypothalamic-pituitary defect.[47] Low gonadotrophin concentrations usually respond normally to the injection of gonadotrophin releasing hormone, which favours a hypothalamic rather than a pituitary defect.[45-47] Nevertheless, a primary testicular disturbance may be a factor in some instances (as in severely burnt patients) given that the injection of human chorionic gonadotrophin fails to release testosterone from the Leydig cells.[45]

Though spermatogenesis is less easy to investigate in ill patients, it is thought to be depressed in febrile illness and lymphoreticular malignancy[48] and to be abnormal in uraemia.[37] Patients dying from severe burns which have not directly affected the gonads have abnormal testicular germinal epithelium on histological examination.[49]

In women amenorrhoea and infertility are common in uraemia[50] but, unlike men, women with Hodgkin's disease retain fertility.[51] Severely burnt women fail to ovulate for some months after injury,[52] while in postmenopausal women a hypothalamic-pituitary defect is suggested by a fall in gonadotrophin concentrations during illness.[53]

Possible mediators of these gonadal abnormalities are the raised cortisol concentrations in severe illness: these may affect the gonads directly[54] as well as suppress the hypothalamic-pituitary axis.[55] Alternatively, endogenous opioid peptides may have a role, since they reduce gonadotrophin secretion in normal man.[56] These peptides are secreted concomitantly with adrenocorticotrophic hormone[57] and are therefore likely to be increased in ill patients.

Calcium metabolism

Low total serum calcium concentrations are common in severely ill patients. Chernow found that almost two thirds of patients in intensive care units had low total serum calcium values but only 13% had low ionised calcium concentrations.[58] Both total and ionised calcium concentrations may be reduced in several conditions, including burns,[59] sepsis,[60] and acute pancreatitis.[61] Such changes are usually short lived, although in severely burnt patients hypocalcaemia persisted for several weeks in the presence of normal or low urinary excretion of calcium.[59,62]

Hypophosphataemia is common in severe illness, occurring in hypothermia, burns, septicaemia, alcoholism, diabetic ketoacidosis, and others.[63] Many cases are related to treatment with intravenous dextrose, which stimulates the entry of phosphate into the cells. Hypomagnasaemia also occurs commonly in the critically ill patient.[64] Most cases are due to decreased intake, as in chronic alcoholism, starvation, prolonged parenteral nutrition, and malabsorption, but another cause is an increased loss, as in patients with chronic diarrhoea, or bowel or biliary fistula, or who are receiving diuretics.

The hormones primarily concerned in regulating these ions are parathyroid hormone, vitamin D, and to a lesser extent calcitonin. Hypocalcaemia, which is the main physiological stimulus to parathyroid hormone secretion, does not seem to lead to the expected rise in parathyroid hormone in hypocalcaemic ill patients, and therefore suppression of parathyroid hormone secretion has been suggested as the

main cause of hypocalcaemia.[60 61] Paradoxically, a rise in both parathyroid hormone and calcitonin has been found in hypocalcaemic patients with burns.[62] Nevertheless, problems with the assay of parathyroid hormone render changes within the normal range difficult to interpret. Indeed, much of the data on ionised calcium in severely ill patients may be misleading because of the low albumin concentration so often found in ill patients.[65] The mechanism of these ionic changes is not clear and may not be solely attributable to endocrine changes.

Conclusions

The importance of these extensive endocrine changes in ill patients is not always clear but they may be an adaptation in the patient's best interest. Endocrine investigations in ill patients should always be ordered and interpreted with considerable care, as any abnormalities may resolve as the patient's general condition improves.

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