Summary and conclusion

Hormonal changes in non-endocrine disease

A) Thyroid function

Low concentrations of tri-iodothyronine (T3) are found in a variety of clinical states, including surgery, myocardial infarction, and starvation. Plasma T3 is largely derived from the peripheral conversion of thyroxin (T4), a process that is suppressed in ill patients.' Low T3 states are also characterized by a reciprocal increase in the metabolically inactive reverse T3, which is primarily due to decreased metabolism of reverse T3 rather than to increased production.

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. Several separate mechanisms probably lead to low T4 concentrations.

Thyroid stimulating hormone responses to thyrotrophic releasing hormone are usually normal but are blunted in chronic renal failure.' Nevertheless, giving iodide to ill patients, which reduces thyroid hormone concentrations, does not result in the normal increase in secretion of thyroid stimulating hormone.

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 thyroxin binding globulin. Thyroid stimulating hormone concentrations may be raised, possibly because of an associated autoimmune thyroiditis.

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 Dopamine and glucocortcoids are drugs widely used in critically ill patients. As both suppress the release of thyroid stimulating hormone and reduce thyroid hormone concentrations that may aggravate low T4 and low T3 states as well as lead to difficulties in diagnosis when given to hyperthyroid or hypothyroid patients.

B) Hormones and energy supply

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.

Catecholamine release may not be wholly beneficial: electrocardiographic changes sometimes observed after an intracranial catastrophe, particularly subarachnoid hemorrhage, may reflect myocardial necrosis induced by massive sympathetic outflow. They have important effects on the pancreas, stimulating glucagon release and inhibiting insulin secretion. Glucagon concentrations are therefore raised in illness, usually in proportion to its severity. Insulin concentrations are inappropriately low for the degree of rise in the blood glucose concentrations.

This alteration in the balance between insulin and glucagon secretion despite hyperglycemia 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, 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. All these endocrine changes explain the hyperglycemia which commonly accompanies illness. To make the important distinction between hyperglycemia due to illness and that due to diabetes mellitus an estimation of the glycosylated hemoglobin 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 catecholamine's 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.

C) Adrenocortical function

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. Other hormones, such as vasopressin

(anti diuretic hormone) and catecholamine, may act synergistically with corticotrophin releasing factor on the anterior pituitary. Aldosterone secretion is primarily controlled by the rennin angiotensin system but adrenocorticotrophic hormone and hyperkalaemia may also have stimulatory effects. Aldosterone concentrations increase because of the activation of the rennin-angiotensin system after surgery and Burns .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. 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.

Hence possibly, when chronically stimulated, the adrenal gland can auto regulate and secrete cortisol preferentially in life threatening conditions. The finding of low aldosterone concentrations in persistently hypertensive ill patients who have raised cortisol and rennin concentrations is compatible with this concept.

D) Gonadal function

In liver disease, Impotence and infertility are common, as is oligospermia or azoospermia. 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. In chronic liver disease the high concentrations of circulating estrogens' probably contribute to the characteristic gynaecomastia, palmer erythema, and spider naevi. Concentrations of testosterone are low or normal but because of high concentrations of sex hormone binding globulin those of free (unbound) testosterone are low.

Luteinizing 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. 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.

Patients with lepromatous leprosy often have testicular atrophy owing to direct invasion of the testes by acid fast bacilli. Hypogonadism due to primary testicular failure is a characteristic feature of myotonica dystrophic a. Reduced testosterone secretion has also been recognized in many other conditions-for example, after surgery, myocardial infarction," burns, and respiratory failure.' 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.

Low gonadotrophin concentrations usually respond normally to the injection of gonadotrophin releasing hormone, which favors a hypothalamic rather than a pituitary

defect. 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 Leyden cells. Though spermatogenesis is less easy to investigate in ill patients, it is thought to be depressed in febrile illness and lymph reticular malignancy and to be abnormal in uremia Patients dying from severe burns which have not directly affected the gonads have abnormal testicular germinal epithelium on histological examination. Women amenorrhea and infertility are common in uremia but, unlike men, women with Hodgkin's disease retain fertility.

Severely burnt women fail to ovulate for some months after injury, while in postmenopausal women a hypothalamic-pituitary defect is suggested by a fall in gonadotrophin concentrations during illness. The raised cortisol concentrations in severe illness: these may affect the gonads directly as well as suppress the hypothalamic-pituitary axis. Alternatively, endogenous opioid peptides may have a role, since they reduce gonadotrophin secretion in normal man. These peptides are secreted concomitantly with adrenocorticotrophic hormone and are therefore likely to be increased in ill patients.

E) Calcium metabolism

Low total serum calcium concentrations are common in severely ill patients. Both total and ionized calcium concentrations may be reduced in several conditions,

including burns, sepsis,' and acute pancreatitis.' 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. Hypophosphataemia is common in severe illness, occurring in hypothermia, burns, septicemia, alcoholism, diabetic ketoacidosis, and others.

Hypomagnesaemia also occurs commonly in the critically ill patient. 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 diarrhea, 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 hypocalcaemia ill patients, and therefore suppression of parathyroid hormone secretion has been suggested as the main cause of hypocalcaemia. Paradoxically, a rise in both parathyroid hormone and calcitonin has been found in hypocalcaemic patients with burns Nevertheless, problems with the assay of parathyroid hormone render changes within the normal range difficult to interpret. Indeed, much of the data on ionized calcium in severely ill patients may be misleading because of the low albumin concentration so often found in ill patients.