Core Topics in Endocrinology in Anaesthesia and Critical Care
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The clinical interface between endocrinologists/diabetologists and anaesthetists/intensive care physicians and the joint management of their patients is more than a marriage of convenience. Endocrinologists are all too aware that patients with underlying endocrine disease bring additional anaesthetic risks and concerns. Examples include patients with acromegaly and hypopituitarism, thyrotoxicosis and phaeochromocytoma. Perhaps one of the most common concerns necessitating cross-referral in hospitals is the patient with established diabetes mellitus. The optimal management of such a patient in terms of metabolic control and insulin therapy across anaesthesia and in an intensive care setting is of paramount importance.

But the area has moved on much further: research advances over the last 5 years have highlighted how careful metabolic control of patients on intensive care units can significantly improve outcome. This is particularly true in the management of hyperglycaemia and hyponatremia and may also now include the concept of relative adrenal insufficiency. For the endocrinologist/diabetologist, therefore, it is essential that this knowledge now becomes embedded in their evidence-based clinical practice. For the anaesthetist and the intensive care physician, a greater appreciation of the endocrine basis for abnormal biochemical results in patients within intensive care units is equally important if improvements in patient morbidity and mortality are to be realised.

In this timely publication, Professors Hall and Hunter and Dr Cooper have solicited and edited 18 topical chapters from experts in the field that will address all of these issues. Section 1 details the perioperative care of patients with endocrine disease; Section 2 – the care of patients with diabetes; and Section 3 – endocrine disorders that arise in the critically ill patient. To have this information under one cover is an admirable achievement and one that will be of immense value to medical practitioners involved in managing sick patients.

Paul M Stewart MD FRCP FMedSci
Professor of Medicine
Endocrine disorders are a disparate group of diseases of complex pathophysiology. Some of these disorders, such as diabetes mellitus, are increasingly common in the developed world. Diabetic patients can present at any age to anaesthetists of all grades and in every subspecialty. In this specialist anaesthetic text, there is a detailed discussion of all aspects of an anaesthetist's involvement with diabetes, be it in paediatric, obstetric or intensive care practice, or when these patients undergo routine surgery. For greater understanding, an outline of the pathophysiology of diabetes mellitus is provided.

Thyroid dysfunction is another common endocrine disorder of which all anaesthetists have significant experience. It is essential for anaesthetists to understand the many different diseases that affect this gland, be they malignant or autoimmune, how such diseases are managed medically and how they affect anaesthetic practice.

Other endocrine disorders are far less common than diabetes mellitus and thyroid disease. The challenges for any anaesthetist with the rarer disorders of the adrenal, pituitary and parathyroid glands, or with endocrine disorders of the gut, are very different from managing a diabetic patient. No practitioner will have great experience of anaesthetising such patients. Thus it is apposite to have contributions from well recognised experts in these areas brought together into one text.

Only recently have endocrine disorders in critically ill patients been given detailed consideration. This book considers not only the topical subjects of glucose control in the critically ill and the critically ill diabetic patient, but also the very rare disorders of the thyroid gland that present to intensivists. Fluid and electrolyte imbalance, the effects of critical illness on adrenal physiology and the role of glucocorticoid replacement are considered. Understanding of such disorders is incomplete, but in this text we update all anaesthetists involved in acute medicine in these complex areas.

To increase the understanding of the pathophysiology and medical management of such patients, it has been most advantageous to have a distinguished endocrinologist as a co-editor. We hope that Mark Cooper's significant contributions will enhance anaesthetists' understanding of the multidisciplinary approach that is required in the management of the complex endocrine patient perioperatively.
Introduction
The human neuroendocrine system has two components – hormonal secretion that is controlled by the hypothalamo-pituitary axis and the extra-hypothalamic neurohormones, such as somatostatin, atrial natriuretic peptide and the peptide hormones of the gastrointestinal tract. This chapter principally concentrates on the clinically significant disorders of the hypothalamo-pituitary axis, which through their anatomical and physiological complexity can present the anaesthetist with a wide variety of challenging perioperative problems. The most common lesions of this axis are benign adenomas of the anterior lobe of the pituitary gland. While principal attention focuses on the resulting endocrine hypersecretion that may be associated with such disorders, due regard should also be given to the potential ‘mass effect’ that such lesions may be exerting on neighbouring brain tissue as well as any consequences of the treatment that a patient may have received for their condition.

Clinical anatomy and physiology of the hypothalamo-pituitary-neuroendocrine axis
The hypothalamus is responsible for the maintenance of homeostasis and the integration of nervous and endocrine control mechanisms. It regulates many of the body’s autonomic functions, such as temperature, thirst and hunger, blood pressure and volume, sleep and sexual function, and is intimately related, both anatomically and functionally, to the pituitary gland [1]. Anatomically it is regarded as a component of the diencephalon, the most rostral part of the brainstem, and lies within the walls and floor of the third ventricle of the brain. It is a complex collection of nervous and endocrine tissue, and contains a number of nuclei that have either a direct (neuronal) or indirect (vascular) communication with the pituitary gland.

The pituitary gland is similarly a composite of endocrine and nervous tissue that is located at the base of the brain and connected to the hypothalamus by the pituitary stalk. It weighs less than 1 g under normal circumstances, and lies within the sella turcica, a bony fossa of the skull base. The roof of the pituitary fossa is created by an incomplete fold of dura, the diaphragma sella, through which passes the pituitary stalk. The fossa is limited posteriorly by the clivus and both anteriorly and inferiorly by the bony air sinuses of the sphenoid bone. Important anatomical relationships of the pituitary gland are shown in Figure 1.1 [2]. Laterally on either side lie the cavernous sinuses, various cranial nerves and beyond them the temporal lobes. Superiorly are found the pituitary stalk, the diaphragma sella and the optic nerves/chiasm, and beyond them the hypothalamus and third ventricle.

The gland itself is organised embryologically, anatomically and functionally into two parts (Figure 1.2). The anterior lobe (adenohypophysis) is derived embryologically from Rathke’s pouch, an upgrowth from the roof of the pharynx, and consists of cords of endocrine secretory tissue organised around an extensive network of sinusoids which arise from a local vascular network that extends from the hypothalamus to the anterior lobe along the pituitary stalk.

Classically, cell types of the anterior lobe have been categorised histologically according to the presence and staining characteristics of intracellular granules, this being a reflection of a more fundamental functional characteristic of endocrine tissue that has differentiated into one of five secretory cell types (Table 1.1). The secretory functions of the anterior lobe are under indirect (vascular) hypothalamic control, mediated by releasing...
hormones which are synthesised within the supra-optic nuclei of the hypothalamus and then delivered to the adenohypophysis via the portal vascular network described above. In contrast, the posterior lobe (neurohypophysis) is true nervous tissue, a caudal extension of nerve fibres that project from cell bodies within the paraventricular and supra-optic nuclei to the posterior lobe via the pituitary stalk. The hormones antidiuretic hormone (ADH, alternatively known as arginine vasopressin or simply vasopressin) and oxytocin are synthesised in these cell bodies prior to neuronal transport to nerve endings within the posterior lobe, their release remaining under direct nervous hypothalamic control.

The synthesis and secretion of the hormonal products of the adenohypophysis is subject to complex, multilevel regulation, as summarised in Figure 1.3. With the exception of the lactotroph, the dominant hypothalamic influence is a stimulatory one, which is in turn regulated by negative feedback control exerted at both the pituitary and hypothalamic level. The classic example of such a self-regulating negative feedback system is the hypothalamo-pituitary-thyroid axis. In contrast, prolactin secretion is under largely inhibitory control that is mediated by dopamine. The synthesis and release of growth hormone (GH) is stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin. Despite such individual variations, the overall ‘set point’ for the various hypothalamo-pituitary endocrine systems is influenced by a variety of neuro-environmental inputs from higher brain centres (Figure 1.3) that include stress, exercise, sexual activity, environmental temperature, altered day/night patterns and steroid hormone levels.
## Table 1.1 Hormone products of the pituitary gland.

<table>
<thead>
<tr>
<th>Hormone (adenohypophysis)</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth hormone (GH)</strong></td>
<td>The 191-amino-acid product of the somatotroph cells that amount to as much as 50% of the total secretory capacity of the anterior lobe. Widespread anabolic properties, including promotion of bone and muscle development. Promotes use of lipid as an energy source by stimulating lipolysis. Impairs glucose utilisation and induces insulin resistance, 'pancreatic burnout' and frank diabetes mellitus. Effects largely mediated by the somatomedins, such as insulin-like growth factor (IGF), which are synthesised in the liver in response to GH. The hypothalamic peptides somatotropin and somatostatin respectively stimulate and inhibit the secretion of GH. Secretion is increased by starvation (particularly chronic protein deficiency), hypoglycaemia, glucagon, exercise, stress trauma and sleep. Excess of GH leads to acromegaly (or gigantism if developing prior to epiphysial fusion), while an absence of it or its peripheral receptors causes pituitary dwarfism.</td>
</tr>
<tr>
<td><strong>Prolactin (PRL)</strong></td>
<td>Protein product of the lactotroph, the extent of which increases markedly during pregnancy and lactation. Promotes lactation and plays a minor role in breast development. Synthesis and release of prolactin is largely under hypothalamic inhibitory control mediated by dopamine. Secretion is increased by suckling, stress, exercise and sexual intercourse.</td>
</tr>
<tr>
<td><strong>Thyroid stimulating hormone (TSH)</strong></td>
<td>Glycoprotein product of thyrotroph cells. Stimulates all known secretory activities of the thyroid glandular tissue, including the proteolysis of thyroglobulin, and iodide uptake. Release is stimulated by thyroid releasing hormone (TRH), a tripeptide synthesised by neurons found throughout the hypothalamus. Negative feedback control is very sensitive, and operates principally at the level of the pituitary rather than the hypothalamus. TRH secretion is increased principally by prolonged exposure to cold environments, and also rises in response to anxiety or excitement. The absence of TRH reduces but does not abolish TSH secretion.</td>
</tr>
<tr>
<td><strong>Adrenocorticotropic hormone (ACTH)</strong></td>
<td>Secreted by corticotroph cells that comprise approximately 15% of anterior lobe secretory tissue. Synthesised as a large precursor molecule, proopiomelanocortin, which also has within its 240 amino-acid sequence γ-melanocyte stimulating hormone (γ-MSH), β-lipotropin and β-endorphin. ACTH itself is a 39-amino-acid polypeptide, which stimulates the synthesis of glucocorticoids and androgens from the zona fasciculata and reticularis of the adrenal cortex. Tissue degradation of ACTH releases α-MSH. Secretion of ACTH is stimulated by corticotrophin releasing hormone (CRH), a 41-amino-acid polypeptide synthesised by neurons arising mainly from the paraventricular nucleus of the hypothalamus. Cortisol exerts negative feedback control on the synthesis and release of ACTH at the level of both the hypothalamus and the pituitary. CRH production is increased in response to all kinds of stress, including trauma, surgery, pain, infection, extremes of temperature and many debilitating diseases. There is very little ACTH production in the absence of CRH.</td>
</tr>
<tr>
<td><strong>Gonadotrophins (follicular stimulating hormone, FSH, and luteinising hormone, LH)</strong></td>
<td>Glycoprotein products of the gonadotroph cells. In the male, LH stimulates the secretion of testosterone while FSH is responsible for stimulating spermatogenesis. In the female, FSH and LH are intimately involved in the production of oestrogen and progesterone, and the regulation of the menstrual and ovulatory cycles. Release is controlled by gonadotrophin releasing hormone (GnRH), a 10-amino-acid polypeptide, which is synthesised in neurons concentrated in the arcuate nucleus of the hypothalamus. Negative feedback control is largely at the hypothalamic level, and exerted by testosterone in the male, and oestrogen and progesterone in the female. GnRH release is also modulated by higher centres, most notably the limbic system.</td>
</tr>
</tbody>
</table>

## Posterior lobe (neurohypophysis)

| Antidiuretic hormone (ADH) | Nonapeptide, also known as arginine vasopressin or simply vasopressin, that acts upon vasopressin 1 receptors in peripheral vascular smooth muscle and vasopressin 2 receptors in the kidney. Its principal physiological action is to promote renal reabsorption of water from distal convoluted tubule and collecting duct; also induces vasoconstriction in hypovolaemia. Duration of effect 1–2 hours. |
| Oxytocin | Nonapeptide, chemically very similar to ADH. Promotes contraction of the myometrium during labour of myoepithelial cells in the breast during lactation. |
Clinical features of pituitary disease

The majority of clinically significant pituitary conditions are the result of tumour or tumour-like conditions that arise from either within the gland itself or in surrounding parasellar tissues. Although the differential diagnosis of a mass within or around the pituitary fossa is extensive and a reflection of the diverse histology of this area of the skull base, the majority are adenomas of the anterior lobe that develop from one or other of the differentiated secretory cell types of the adenohypophysis. Although they commonly display a variable degree of local invasiveness they very rarely metastasise, and so cannot be considered to be malignant by the usual definition.

Only a proportion of pituitary tumours declare themselves clinically – indeed incidental pituitary lesions are found in up to 25% of autopsies [3]. In general terms, pituitary adenomas can present in one of three ways: by virtue of the hypersecretion of the hormonal product(s) of the gland, by growing to a size sufficient to exert a mass effect on neighbouring structures, or through a combination of the two. Adenomas that secrete adrenocorticotrophic hormone (ACTH) or thyroid stimulating hormone (TSH) have profound physiological effects and usually present as small tumours (microadenomas) that can be difficult to locate both radiologically and surgically. The functional consequences of prolactin-secreting tumours in females of childbearing age may similarly present early in their natural history, although this will be less likely in males or postmenopausal females. In contrast, a quarter of adenomas are endocrinologically inert [4]. Such tumours only become clinically significant when they have grown to a size sufficient to elicit a mass effect, and are known as macroadenomas. Tumours of the somatotroph that secrete GH usually present with features of both a mass effect and hormonal hypersecretion: this is because of the insidious pathophysiological consequences of an excess of GH and the extended time interval between onset and clinical diagnosis [5].

The principal clinical features of a sellar mass lesion are headache, visual disturbance and endocrine hyposecretion. Headache results from either stretching of the diaphragma sella, erosion of the bony sella turcica, or, in acromegaly, re-architecturing of the membranous bones of the skull. Very occasionally, headache may be indicative of raised intracranial pressure secondary to obstruction of the third ventricle or foramen of Munro, and it is essential therefore that clinical assessment is supplemented by appropriate imaging to exclude the possibility of obstructive hydrocephalus. The classical visual disturbance of a pituitary mass lesion is a bitemporal haemianopia.
that results from compression of the optic chiasm by a tumour arising from the pituitary fossa, although this may be further complicated by ophthalmoplegia if the tumour extends laterally. Some degree of hypopituitarism is frequently seen in patients with macroad- enomas, and is a result of either direct destruction of secretory tissue by the expanding tumour mass, or by so-called 'stalk compression' in which obstruction of the pituitary stalk by tumour deprives the anterior lobe of the hypothalamic hormones that normally regulate secretion. The hypopituitarism of stalk compression is therefore usually accompanied by modest hyperprolactinaemia, since, as noted above, the lactotrophic cells are under predominantly inhibitory control.

**Endocrine hyposecretion syndromes**

The endocrine hyposecretion syndromes associated with pituitary disease of relevance to perioperative care include adrenocortical insufficiency, hypothyroidism and diabetes insipidus. Sellar or parasellar lesions rarely present with failure of posterior lobe function [6], although it is a relatively frequent complication of surgical resection. Regardless, it is important to confirm the adequacy of adrenocortical, thyroid and posterior lobe function preoperatively, and to plan perioperative hormone replacement accordingly.

Although frequently asymptomatic, adrenocortical insufficiency can be a life-threatening condition, particularly in patients with acute concurrent illness. Clinical features include nausea and vomiting, anorexia and weight loss, orthostatic hypotension, general malaise, hyponatraemia and hypoglycaemia. The renin-angiotensin-aldosterone axis is preserved, so that in comparison to Addison’s disease, fluid and electrolyte abnormalities are less severe. Persistently low levels of plasma cortisol are suggestive of adrenal insufficiency, although dynamic tests of pituitary function, that examine the ability of the hypothalamo-pituitary-adrenal axis to increase cortisol secretion in response to a biochemical stress (e.g., hypoglycaemia or glucagon) are a more sensitive measure of the reserve of this component of the stress response. Diagnosis of adrenocortical insufficiency requires a high index of suspicion, particularly when faced with a patient who is unexpectedly hypoten- sive, hyponatraemic and hypoglycaemic. In the acute setting, patients require hydrocortisone 100 mg i.v. statim, followed by 25–50 mg 6 hourly together with saline resuscitation, and possibly glucose.

Similarly, pituitary-related hypothyroidism is usually less severe than primary thyroid failure. Clinical features include reduced metabolic rate, lethargy, voice change, cold intolerance, constipation, bradycardia and heart failure, dry cold skin and myxoedema, memory loss and confusion. Anaesthesia and surgery in patients with untreated hypothyroidism carries a high mortality. Patients show exquisite sensitivity to and reduced metabolism of all classes of anaesthetic drugs, and doses should be reduced accordingly and wherever possible titrated against effect. Emergence from anaesthesia may be very prolonged, necessitating postoperative respiratory support. The normal ventilatory responses to hypercapnia and hypoxia are obtunded and perioperative hypothermia is common. Furthermore, clinical response to thyroid replacement therapy may take 10 days or more and, although more rapid correction can be achieved with liothyronine (triiodothyronine, T3), there is a significant risk of precipitating myocardial ischaemia and heart failure.

Central diabetes insipidus (DI) is the principal consequence of failure of the posterior pituitary lobe, and is the result of failure of secretion of ADH. The cardinal features of DI are excessive thirst and the excretion of large volumes of dilute urine, sometimes in excess of 1000 ml per hour. It is easily treated with desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), a synthetic analogue of ADH that has a longer half life and which lacks the vasoconstricting properties of the endogenous hormone. Although desmopressin is usually administered orally or intranasally, postoperatively it can be given as a subcutaneous or intra-muscular injection. Withholding DDAVP in the postoperative period will result in excessive diuresis, hypovolaemia and electrolyte disorders, and clinicians should be particularly aware of the potential to confuse oligo-anuria with urinary retention. Failure to secrete oxytocin only becomes clinically evident during and after childbirth. Although spontaneous labour and vaginal delivery may be possible [7], some have reported a high incidence of failed labour [8], and it is prudent to consider this group of patients as high-risk parturients. Difficulties with breastfeeding may also be encountered, both because of failure of the ‘let down’ reflex that is mediated by oxytocin and also because of anterior lobe failure and inadequate prolactin secretion.

**Hormone hypersecretion syndromes**

Whilst prolactinomas are the commonest functional pituitary adenoma, the pathophysiological consequences of hyperprolactinaemia make no specific demands on perioperative care. Thyroid stimulating
hormone-secreting tumours are very uncommon, so that in practice it is Cushing's disease and acromegaly that are of greatest significance, although the clinician should also be aware that pituitary tumours occasionally coexist with neoplasias of extra-hypothalamic endocrine tissue (Chapter 6).

**Cushing's syndrome/disease**

The term Cushing's disease is reserved for an excess of glucocorticoid that is the result of hypersecretion of ACTH from a pituitary corticotroph adenoma, the more generic term Cushing's syndrome being applied to a non-specific state of chronic glucocorticoid excess regardless of cause. Cushing's disease is more common in women, and carries a 50% 5-year mortality if left untreated. Corticotroph adenomas usually present as microadenomas, and inferior petrosal venous blood sampling may be required in order to distinguish between pituitary and ectopic sources of excess ACTH. Although surgical removal is considered to be the definitive treatment for Cushing's disease, many of the adverse physiological features of the condition, listed in Table 1.2, can be promptly checked and indeed reversed with agents such as ketoconazole, metyrapone and trilostane that interfere with the synthesis of cortisol in the adrenal cortex. Such therapies may also be of value in the acute setting.

**Table 1.2** Clinical features of Cushing's syndrome.

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical features</th>
</tr>
</thead>
</table>
| General       | Central obesity with limb wasting ('orange on a stick')  
Dorsocervical fat pad ('buffalo hump')  
Supraclavicular fat pads  
Moon and plethoric facies  
Exophthalmos                                                                                   |
| Dermatological| Skin atrophy, with loss of subcutaneous fat and increased fragility, striae  
Liddle's sign (skin peels off with removal of adhesive tape)  
Easy bruising  
Poor wound healing and increased risk of dehiscence  
Hyperpigmentation (when condition is a result of excess ACTH)  
Oily facial skin with acne and hirsuitism                                                   |
| Cardiovascular| Refractory systemic hypertension with left ventricular hypertrophy and diastolic failure  
Na +/– water retention and dependent oedema  
Congestive cardiac failure  
Cardiomyopathy and myocardial irritability  
Increased incidence of venous thromboembolism                                           |
| Respiratory   | Obstructive sleep apnoea  
Respiratory function may be impaired by obesity, kyphoscoliosis, cortisol-induced myopathy and hypokalaemia                                          |
| Musculoskeletal| Proximal muscle wasting (aggravated by hypokalaemia); may be unable to rise from the squatting position, and in severe cases are unable to climb stairs  
Accelerated osteoporosis, vertebral compression fractures, leading to kyphoscoliosis  
Aseptic necrosis of femoral head  
Pathological rib fractures                                                                   |
| Gastrointestinal| Peptic ulceration  
Gastro-oesophageal reflux                                                                                                                      |
| Metabolic     | Hyperinsulinaemia, glucose intolerance and insulin-dependent diabetes mellitus  
Hypercalcuria secondary to increased bone resorption  
Polyuria and polydypsia  
Hypokalaemia and hypochloraemic alkalosis in severe cases                                       |
| Neurological  | Psychiatric disorders                                                                                                                                  |
| Genito-urinary| Infertility, amenorrhoea, reduced libido, impotence  
Asymptomatic bacterial colonisation of urinary tract                                           |
| Immunological| Standard inflammatory response to infection may be masked  
Increased susceptibility to infection in severe cases                                         |
| Haematological| Polycythaemia, granulocytosis and lymphopenia                                                                                                         |