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ESSENTIALS Tumours (usually but not invariably malignant), other ‘nonendocrine conditions’ and drugs can be associated with a wide variety of endo- crine syndromes. ‘Ectopic’ hormone secretion, defined as the release of a hormone from a site different from the gland that normally produces it, has classically been recognized in the context of neo- plasia, but it is now apparent that many hormones are synthesized by ‘nonendocrine’ tissue. Although a particular endocrinopathy may be associated with a specific type of tumour in a particular organ, the relationship is not invariable, and many neoplasms elaborate more than one hormonal substance at the same or at different times and thus produce a mixed endocrine picture. Syndromes of ectopic hormone secretion Most syndromes of ectopic hormone secretion are due to peptide hormones. Clinically evident syndromes are much less common than laboratory abnormalities, which are frequently found if exten- sive biochemical and hormonal assays are applied to patients with cancer. Well-described syndromes include the following: Ectopic calciotropic hormones—hypercalcaemia in the absence of detectable bony metastases occurs in about 15% of patients with squamous cell carcinoma (usually bronchial), carcinoma of the kidney, ovary, or breast. Parathyroid hormone-related protein (PTHrP) is responsible for most cases, but sometimes increased pro- duction of 1,25-dihydroxyvitamin D3 (lymphoproliferative tumours) or transforming growth factor α (TGFα) may be involved. Syndrome of inappropriate antidiuresis (SIAD)—is reported in 40% of cases of small cell lung cancer; usually associated with high levels of circulating AVP, but other unidentified antidiuretic substances are sometimes involved. Presentation is with hyponatraemia, with diagnosis requiring exclusion of the very many other causes of this condition. Ectopic ACTH secretion—pro-opiomelanocortin (POMC), the pre- cursor for ACTH and other polypeptides, can be

secreted by a var- iety of nonpituitary tumours (e.g. small cell lung cancer, carcinoids), which are responsible for about 10–20% of patients with Cushing's syndrome. Presentation is variable, but with rapid onset and pro- gression the physical manifestations of Cushing's syndrome may not have time to develop, and selected features may predominate (e.g. weight loss, proximal muscular weakness, oedema, type 2 dia- betes mellitus (T2DM), and hypokalaemic alkalosis). Ectopic secretion of insulin-like growth factors (IGFs)—IGF-2 is most typically (although rarely) secreted by large mesenchymal tumours; presentation is with symptoms of neuroglycopenia.
Endocrine manifestations of nonmalignant nonendocrine diseases Systemic disease of nonendocrine glands may influence endo- crine function due to (1) a specific effect of the disease itself (e.g. hypercalcaemia in sarcoidosis driven by 1,25 dihydroxyvitamin D3 produced by alveolar macrophages); opportunistic infections, lymphoma, or Kaposi's sarcoma involving the adrenal glands in HIV/AIDS; and (2) as a general response to either acute or chronic illness, for example, nonthyroidal illness ('sick euthyroid syndrome'), where reduced peripheral conversion of thyroxine (T4) to tri- iodothyronine (T3) is associated with a normal or reduced thyroid stimulating hormone in association with low T3 (± T4). Drug-induced endocrine manifestations Drugs may (1) induce manifestations of endocrine disease (e.g. amiodarone may cause hyperthyroidism because of its high iodine content or due to a destructive thyroiditis) and (2) influence the re- sults of hormonal assays and lead to mistaken diagnosis (e.g. oes- trogen increases thyroid-binding globulin, hence women on the combined oral contraceptive pill have high total T4 concentrations but are euthyroid). Oral oestrogen also increases cortisol-binding globulin, which can lead to spurious interpretation of results from short Synacthen testing during assessment for hypocortisolaemia.
Introduction Several endocrine syndromes may develop in association with dis- eases that are not primarily disorders of an endocrine gland. In most the cause is a tumour, usually but not invariably malignant, that develops in tissue which is not normally the origin of the particular hormone synthesized. Other nonendocrine condi- tions may also be associated with either hormonal excess or defi- ciency (e.g. sarcoidosis and AIDS). Certain drugs may also modify 13.10 Hormonal manifestations of nonendocrine disease Thomas M. Barber and John A.H. Wass

 hormonal biochemistry and cause hormonal imbalance syndromes. Albright suggested that the hypercalcaemia sometimes associated with malignant disease without osteolytic metastases might be due to the secretion by the tumour of a parathyroid hormone (PTH)- like peptide; we now know that this is true (parathyroid hormone- related protein, PTHrP). Later it was shown that hypersecretion of ACTH, not from the pituitary but from an ectopic site, was the cause of ACTH-dependent Cushing's syndrome in up to one-fifth of pa- tients with this condition. Syndromes of ectopic hormone secretion—general considerations Although ectopic hormone secretion has classically been recog- nized in the context of neoplasia, and defined as the release of a hor- mone from a gland different from that which normally produces the hormone, it is increasingly recognized that many hormones are synthesized by nonendocrine tissue. Thus, the syndromes of neo- plastic ectopic hormone secretion are actually due to the patho- logical oversecretion and/or inappropriate production of hormones within nonendocrine tissue. Increasing recognition of the import- ance of paracrine secretion of hormones such as insulin-like growth factors (IGF-1), their modulation by growth factors and binding proteins (e.g. IGFBP1, 2, and 3), and their role in progression of neo- plasia adds greatly to these complexities. Many different hormones are ectopically secreted by neoplasms arising in diverse organs, notably the bronchus, breast, pancreas, kidney, and ovary as well as in mesenchymal tissue. Although a particular

endocrinopathy may be associated with a specific type of tumour in a particular organ, the relationship is not invariable. An example is the lung, where squamous cell carcinomas may be associated with hypercalcaemia due to production of PTHrP, while small cell lung cancer and bronchial carcinoid tumours are both as- sociated with ectopic ACTH secretion, but with very different clin- ical manifestations. Many neoplasms produce ectopically more than one hormonal substance concurrently or at different times and thus may produce a mixed endocrine picture (e.g. pancreatic endocrine tumours producing ACTH and insulin). The amount of ectopic hormone(s) produced may fluctuate from time to time (e.g. cyclical Cushing's syndrome in ectopic ACTH secretion). The clinical and biochemical changes induced by the ectopic hormone may mimic very closely, and be clinically indistinguishable, from those found in the true endocrinopathy. In other patients, clinical features are less characteristic and dominated more by abnormalities of bio- chemistry or hormone levels. Thus, in many cases of ectopic ACTH production by small cell lung cancer, the deteriorating nature of the underlying illness may be too rapid for the classical features of florid Cushing's syndrome to develop, and hypokalaemic alkalosis with T2DM predominate. Definition The diagnosis of ectopic hormone production depends on many criteria, although it is seldom practicable or possible to confirm them all: 1. There is an association of the tumour with an endocrine syndrome. 2. Even though the endocrine syndrome may not be clinically florid, there is an elevated or inappropriately raised plasma level of the putative hormone. 3. Removal or suppression of the tumour induces a regression of the endocrinopathy and a fall in the hormone level. 4. The clinical picture and hormone levels are uninfluenced by re- moval of the gland that normally secretes the hormone. 5. The putative hormone level is higher in venous blood draining the tumour than in the arterial blood supplying it. 6. Extraction or immunohistochemical staining shows a higher concentration of the hormone in the tumour than in adjacent, noninvolved tissue. 7. Demonstration can be made of tumour cell synthesis of identifi- able hormones in vitro or of mRNA coding for the hormone. Chemical structure Most syndromes of ectopic hormone secretion are due to peptide hormones. It is rare for tumours to secrete steroid hormones because of the complexity of the enzyme cascade required for steroid bio- synthesis. Tumours may, however, be associated with altered steroid metabolism (e.g. increased aromatase activity in hepatocellular car- cinoma leads to feminization and gynaecomastia due to androgen conversion to oestrogens). The precise amino acid sequences of hormones of ectopic origin are being increasingly defined. In general, they appear to resemble closely those of their normally occurring counterparts (except PTH and PTHrP). There is a tendency for a greater proportion of higher molecular weight precursors, prohormones, subunits, and fragments to be associated with an ectopic origin than with true endocrinopathies, but it is not always clear whether this is due to differences in biosynthesis or in intracellular or extracellular pro- cessing. Minor differences in molecular structure are sometimes re- flected in disparities between bioassay and immunoassay. Prevalence Clinically evident syndromes are less common than biochemical or hormonal abnormalities. The prevalence of ectopic production of ACTH, corticotrophin-releasing hormone (CRH), PTHrP, calci- tonin, human chorionic gonadotrophin (hCG), prolactin, or growth hormone (GH), without clinical manifestations, is high when exten- sive biochemical and hormonal assays are applied to patients with cancer. These assays bring closer the prospect of identifying a diag- nostic marker for tumours in general and, in particular, as is already the case with the monitoring of hCG or its subunits, to determine the response of tumours to treatment. Hypercalcaemia in the absence of detectable bony metastases is the most common abnormality resulting from ectopic hormone se- cretion. It occurs in about 15% of patients with squamous cell car- cinoma (usually of the bronchus), carcinoma of the kidney, ovary, or breast. Next most common in neoplastic diseases is the syndrome of

inappropriate antidiuresis, usually associated with a small cell lung cancer and reported in 40% of such cases. Cushing's syndrome due to ectopic ACTH or CRH secretion occurs in about 5% of patients with small cell lung cancer, and in association with other neoplasms. Biochemical accompaniments of Cushing's syndrome in the absence of the clinical features are much more common, occurring in up to 50% of patients with small cell lung cancer.

13.10 Hormonal manifestations of nonendocrine disease 2543 Pathogenesis As techniques for molecular analyses have evolved, it has become clear that every somatic cell is capable of synthesizing every polypep- tide hormone. However, only under pathological circumstances is that capability ever likely to be expressed. A variety of hypotheses for ectopic hormone synthesis and secretion have been proposed. None explains all of the observed facts. Fundamentally, all cells inherit an identical complement of DNA. They are therefore totipotential and have all the coded information required for the synthesis of all proteins and peptides, including protein hormones. The normal in- ability of nonendocrine tissue to synthesize hormones is ascribed to repressors that mask specific segments of the DNA molecule. It seems possible that when a cell becomes malignant this normal repression becomes ineffective, allowing the unmasked DNA to synthesize pro- teins or peptides foreign to the cell concerned. Such a derepression hypothesis does not explain why certain tumours are more prone to secrete specific ectopic hormones. Neuroendocrine cells, character- ized by the presence of peptide hormone granules, are likely to be the origin of some tumours associated with hormone secretion, such as small cell lung cancer and bronchial carcinoids. Another hypothesis suggests that there are a small number of special proliferative cells in normal mature tissues that have fetal characteristics with the ability to produce peptide hormones—a process of dysdifferentiation ra- ther than de-repression. There is currently no unifying mechanism with supportive experimental evidence to explain ectopic hormone production. Further information on the control of gene expression and hormone production, the role of oncogenes, and paracrine growth factors may provide further insight. Treatment Treatment of the clinical or biochemical abnormalities associated with endocrinopathies of nonendocrine origin is best directed at the primary disorder. In neoplastic disease, this may involve sur- gical excision, radiotherapy, or chemotherapy. Sometimes, the tumour secreting the ectopic hormone is extremely difficult to lo- cate even with the use of sophisticated imaging techniques such as MRI, radiolabelled isotope scanning (e.g. indium-111 pentetreotide imaging), or using selective venous catheterization. More specific therapy may be necessary to manage the associated metabolic abnormality until such time as the underlying disorder can be controlled. For example, immediate measures may be re- quired to reduce hypercalcaemia with fluids and bisphosphonates, or steps taken (administration of metyrapone) to diminish cortico- steroid secretion from adrenal glands stimulated by ectopic ACTH secretion. Particular syndromes of ectopic hormone secretion Ectopic secretion of calciotropic hormones Malignancy is the most common cause of hypercalcaemia in hos- pital inpatients and may be due to direct tumour spread to the bones or related to ectopically secreted calcium-releasing factors. Often several different mechanisms are involved in the same patient. After its discovery in 1987, it was shown that PTHrP is responsible for hypercalcaemia in up to 70% of patients with tumour-associated hypercalcaemia. Many of these patients also have bone metastases. PTHrP shares amino acid homology with PTH between positions 2 and 13 of the 84 residues of PTH and acts via the PTH receptor, resulting in an elevation of extracellular calcium concentration. The PTHRP gene is located on the short arm of chromosome 12; that of PTH is on chromosome 11. The PTHRP gene may be activated by transactivation, hypomethylation (renal carcinomas), or the effect of growth factors and cytokines, including IGF-1 and epidermal growth

factor, while glucocorticoids and vitamin D3 suppress PTHrP levels. Unlike PTH-mediated hypercalcaemia, dihydroxycholecalciferol is suppressed in PTHrP-mediated hypercalcaemia. PTHrP is pro- duced by squamous carcinomas as well as renal, bladder, ovary, skin, pancreas, and breast carcinomas, and lymphomas. Other factors can be involved in hypercalcaemia unassoci- ated with osseous metastases. It is not uncommon for 1,25- dihydroxyvitamin D3 to be produced by lymphoproliferative tumours, which are either high grade or widely disseminated. Transforming growth factor-α (TGFα) which stimulates osteo- clastic bone resorption, is also made by squamous carcinoma, and renal and breast carcinomas. Some tumours cosecrete both TGFα and PTHrP. Interleukin-1 (IL-1), which is a very powerful stimu- lator of osteoclastic bone resorption, is also made by squamous carcinomas as well as some haematological malignancies. Tumour necrosis factor (TNF) and lymphotoxin also stimulate osteoclastic bone resorption. These related cytokines cause hypercalcaemia in vivo; lymphotoxin is also produced by cultured myeloma cells in vitro and accounts for the hypercalcaemia seen in this condi- tion. Prostaglandins of the E series may also cause hypercalcaemia. Finally, vascular endothelial growth factor (VEGF) and IL-8 and IL-11 may be implicated in the development of hypercalcaemia of malignancy. It is important to remember that primary hyperparathyroidism itself is common, particularly in older people; two diseases may co-exist. For this reason, primary hyperparathyroidism should always be considered when hypercalcaemia occurs, even if it is in a patient within the setting of malignant disease. It is now possible to differ- entiate between these two conditions by using the PTH two-site radioimmunoassay. Paraneoplastic hypercalcaemia may be either asymptomatic or dominate the clinical picture and be life-threatening as a consequence of dehydration and renal failure. The features of hypercalcaemia and its general management are discussed elsewhere (see Chapter 13.4). Oncogenic osteomalacia, an acquired phenotype, is a rare syn- drome characterized clinically by reduced mineralization of newly formed bone and the features of osteomalacia (including fractures, bone pain, and muscle weakness). It is usually associated with benign mesenchymal or mixed connective tissue tumours (par- ticularly haemangiopericytomas) that have a propensity to arise in the head and neck. The use of imaging (including octreotide scintigraphy or PET) is important in the localization of such tu- mours. Biochemical features of oncogenic osteomalacia include an excessive renal loss of phosphate that results in phosphaturia and hypophosphataemia. The serum calcium level is usually normal and serum alkaline phosphatase is usually elevated. Circulating levels of 1,25-dihydroxyvitamin D3 are usually suppressed (des- pite ambient hypophosphataemia). Circulating levels of fibroblast growth factor 23 (FGF-23), a secretory product of tumours associ- ated with oncogenic osteomalacia, are usually elevated. It is possible

 that FGF-23 plays an important role in renal phosphate wasting or impairs regulation of vitamin D metabolism, although there may be other unknown phosphaturic factors which also inhibit the 1α-hydroxylase enzyme. Removal of the causative tumour is the treatment of choice. Syndrome of inappropriate antidiuresis (SIAD) Syndrome of inappropriate antidiuresis is a disorder of sodium and water balance characterized by impaired water excretion, with re- sultant hyponatraemia, reduced plasma osmolality, and inappropri- ately high urine osmolality. A diagnosis of this syndrome requires the absence of hypovolaemia, hypotension, deficiency of cardiac, renal, thyroid, or adrenal function, or any known stimulus for the secretion of AVP, an antidiuretic hormone. The syndrome is usually, but not invariably, associated with high levels of circulating AVP, al- though other, as yet unidentified antidiuretic substances are some- times involved. Inappropriate secretion of AVP can either be from an ectopic

or eutopic (posterior pituitary) source. The most common ec- topic source of AVP associated with a syndrome of inappropriate antidiuresis is bronchogenic carcinoma. Inappropriate eutopic se- cretion of AVP can be induced by a wide variety of diseases and drugs. Thus, although a syndrome of inappropriate antidiuresis in association with malignancy may be due to inappropriate ectopic secretion of AVP from the tumour itself, it may also result from inappropriate eutopic AVP secretion. The latter may be caused by treatment of the tumour (e.g. chemotherapy such as cyclophospha- mide), an intercurrent illness such as pneumonia, a complication such as hydrocephalus or cerebrovascular accident, or even by the tumour itself (see Table 13.10.1). The treatment of this syndrome is often restriction of fluid intake (e.g. 500 ml/24 h). Occasionally, it may also be necessary to administer hypertonic saline. Use of aquaretic agents such as tolvaptan, which increase excretion of free water through antagonism of the V2 receptor, thereby blocking the action of AVP within the distal nephron, is an important develop- ment in the management of SIAD and a useful addition to our treat- ment options for this condition. In a small number of individuals, the syndrome of inappropriate antidiuresis occurs in the absence of ADH secretion and is attribut- able to activating mutations in the arginine vasopressin receptor 2 (AVPR2). Ectopic ACTH secretion Pro-opiomelanocortin (POMC) is a 31-kDa precursor for both ACTH and β-lipotropin as well as for other polypeptides derived from it, including γ-lipotropin and β-endorphin. A variety of non- pituitary tumours are capable of secreting POMC-derived pep- tides. Approximately 50% of ectopic ACTH-producing tumours are in the lung and the rest are present in a variety of other tissues (Table 13.10.2). Some tumours, particularly pancreatic islet cell tumours which are seldom (<5%) associated with Cushing’s syn- drome, can, in addition to ACTH, also secrete many other hor- mones that include insulin, gastrin, and glucagon. This accounts for the usefulness, when screening for ectopic ACTH, of measuring other hormones (e.g. calcitonin, hCG) which may be cosecreted, the presence of which raises the suspicion of an ectopic hormone- secreting tumour. Very rarely, CRH is secreted ectopically in asso- ciation with ACTH. Neuroendocrine tumours are the most common source of ectopically-derived ACTH. These include bronchial carcinoid tu- mours most frequently, but also include carcinoids at other sites including the foregut, pancreas, and thymus. Other endocrine and nonendocrine tumours that can secrete ectopic ACTH include small cell lung carcinoma, phaeochromocytoma, medullary carcinoma of the thyroid, mesothelioma, and small cell colorectal carcinoma (see Table 13.10.2). The exact mechanism of synthesis of ectopic POMC- derived peptides is still debated. POMC mRNA can be found in most tu- mours, but ACTH secretion is much less common, probably due to the lack of the signal sequence required for translocation. Changes Table 13.10.1 Conditions associated with the syndrome of inappropriate antidiuresis (SIAD) Malignancies Small cell lung Pancreas—islet cell Duodenum Colon Bladder Prostate Thymus Cervix Lymphoma Lung diseases Pneumonia • Viral • Bacterial • Fungal Tuberculosis Lung abscess Asthma Pneumothorax Chest wall injury Mechanical ventilation Central nervous system diseases Cerebral trauma Cerebrovascular accident Meningitis Encephalitis Cerebral abscess Brain tumours—primary or secondary Hydrocephalus Guillain-Barré syndrome Delirium tremens Acute intermittent porphyria General surgery Drugs Vasopressin Desmopressin (DDAVP) Oxytocin Thiazides Vincristine, vinblastine Cyclophosphamide Phenothiazines Tricyclic antidepressants Carbamazepine Chlorpropamide Clofibrate Serotonin-reuptake inhibitors Metabolic causes Porphyria

 in promoter usage and also in POMC processing may lead to ec- topic secretion of ACTH. In addition, many tumours associated with ectopic ACTH secretion are of neuroendocrine morphology and may arise from progenitor cells

associated with ACTH secre- tion. Differential gene expression profiles have been demonstrated in surgical tissue specimens taken from carcinoid tumours causing ectopic ACTH syndrome and pituitary tumours causing Cushing's disease. These include more abundant mRNA expression in ectopic ACTH syndrome compared with Cushing's disease from genes such as Ikaros family zinc finger protein 1 (IKZF1, a DNA-binding pro- tein), proprotein convertase 2 (PC2) and somatostatin receptors 2 and 5 (SSTR-2 and -5). Enhanced SSTR-2 and -5 expression in tu- mours associated with ectopic ACTH syndrome has therapeutic im- plications for use of more selective somatostatin agonists in these patients. Presentation The clinical picture is variable and independent of the mass of the ectopically ACTH-secreting tumour. In patients with small cell lung cancer who have a rapidly progressive tumour, the physical features of Cushing's syndrome may not have time to develop. The major fea- tures are weight loss, proximal muscular weakness, polyuria, thirst, oedema, carbohydrate intolerance with glycosuria, and sometimes pigmentation due to melanocyte-stimulatory effects of ectopically produced POMC-related peptides. Hypokalaemic alkalosis is a characteristic finding; the plasma potassium is typically less than 3.2 mmol/litre and plasma bicarbonate more than 30 mmol/litre, urinary potassium loss being an important contributor to these bio- chemical features. This hypokalaemia is in part due to the very high cortisol levels, which have a mineralocorticoid action, and cortico- sterone and 11-deoxycorticosterone, which may also be produced in excess. The 11β-hydroxysteroid dehydrogenase enzyme may also function abnormally, causing decreased inactivation of cortisol and corticosterone. The serum cortisol level is usually greatly ele- vated (>1000 nmol/litre) and the plasma ACTH level is also raised (>200 μg/litre). These high levels do not usually occur in pituitary- dependent Cushing's disease. However, there is some overlap in plasma ACTH levels between patients with ectopic ACTH secretion and patients with Cushing's disease, with very high ACTH levels having been reported in a cohort of patients with Cushing's disease originating from pituitary macroadenomas. When ectopic sources of ACTH originate from tissues other than small cell lung cancer, the clinical manifestations may be quite in- distinguishable from Cushing's disease, and cushingoid features (including proximal myopathy, thinning of the skin, bruising, and psychiatric disorders) may antedate by months or years any evidence of a tumour causing ectopic ACTH secretion. The de- gree of elevation of ACTH is less marked than with small cell lung cancer and is proportional to tumour size. Some carcinoid tu- mours may be small and difficult to locate. The real problem is to differentiate ectopic ACTH secretion from pituitary-dependent disease (Table 13.10.3). The presence of a hypokalaemic alkalosis (K<3.2 mmol/litre) is a very useful test in the differential diagnosis. Lack of suppression on high-dose dexamethasone testing is found in 90% of patients with ectopic ACTH production, but also in up to 20% with Cushing's disease. However, the CRH test is very useful in differentiation as patients with ectopic ACTH secretion show an absent rise in cortisol whereas pituitary-dependent Cushing's dis- ease is associated with an exaggerated response in 95% of patients. Because most tumours that ectopically secrete POMC are located either within the chest or abdomen, MRI or CT scans will often re- veal the source of ectopic hormone secretion. In patients in whom the lesion is not readily visible by imaging techniques, selective venous catheterization and sampling may help to determine the ec- topic source of ACTH secretion by comparing levels at various sites within the venous system. Such sampling should include inferior pe- trosal sinuses in case of pituitary-dependent disease. Radionuclide imaging (including octreotide scintigraphy) may occasionally be helpful in localizing the source of ectopic ACTH secretion. In a sig- nificant minority of patients with presumed ectopic ACTH secre- tion, the source of ACTH cannot be identified. Treatment Rapid control of hypercortisolaemia is the initial aim of manage- ment following diagnosis. Removal or debulking of the primary tu- mour or its

control with radiotherapy, chemotherapy or, in the case Table 13.10.2 Types of neoplasm causing ectopic pro- opiomelanocortin (ACTH) secretion Small cell carcinoma of the bronchus Bronchial carcinoid Thymic carcinoid Islet cell pancreatic tumour Phaeochromocytoma Medullary carcinoma of the thyroid Breast carcinoma Tracheal carcinoma Oesophageal carcinoma Gastric carcinoma Ileal carcinoma Appendicular carcinoma Colonic carcinoma Ovarian carcinoma Prostatic carcinoma Squamous carcinoma of the cervix Adrenal medullary paraganglioma Melanoma Mesothelioma Table 13.10.3 Response to tests used to differentiate ectopic ACTH secretion from Cushing's disease (from Howlett et al., 1986) Ectopic ACTH
(% of cases) Cushing's disease
(% of cases) Hypokalaemia <3.2 mmol/litre 100 10 Diabetes mellitus 78 38 Dexamethasone 8 mg/day
(no suppression) 89 22 CRH test excessive response 0

> 90 CRH, corticotrophin-releasing hormone.

section 13 Endocrine disorders 2546 of neuroendocrine tumours, 131I-m-iodobenzylguanidine therapy, will relieve the endocrine manifestations. A relapse may occur if metastases develop because these, too, usually secrete ACTH. When it proves impossible to control a primary tumour, or when the source of ectopic ACTH cannot be identified, adrenocortical hypersecretion may be reduced by medical adrenalectomy. This can usually be achieved through the administration of steroidogenesis inhibitors, including metyrapone (500–4000 mg/day), an 11β- hydroxylase inhibitor of the conversion of 11-deoxycortisol to cor- tisol. Aminoglutethimide (1000–1500 mg/day) may also be used but frequently causes a skin rash. Ketoconazole (400–800 mg/ day), which can cause fatal liver damage, and the adrenolytic drug mitotane are also useful. Mifepristone (RU-486), a glucocorticoid antagonist at the receptor level, has been used as palliative therapy for some patients (10–30 mg/kg per day). Lastly, the long-acting somatostatin analogue, octreotide (0.3 mg/day, subcutaneously), has also been used in the treatment of ectopic ACTH syndrome. Bilateral adrenalectomy is an alternative approach, but frequently it is not practical for patients with rapidly progressive metastatic disease. It may be possible to embolize the arterial supply of the adrenal gland if patients are not suitable surgical candidates for adrenalectomy. Medical treatment needs to be monitored carefully so that adrenal insufficiency is avoided. The prognosis of patients with ectopic ACTH secretion is poor in patients with small cell lung carcinoma but can be excellent in patients with neuroendocrine tumours, depending on tumour hist- ology and the presence of lymph node metastases. Ectopic secretion of insulin-like growth factors The insulin-like growth factors, IGF-1 and IGF-2, share some sequence homology and actions of insulin. IGF-2 is important in fetal growth, whereas IGF-1, synthesized in the liver, mediates most of the actions of GH. IGFs circulate bound to one of six binding pro- teins (IGFBPs). Of these, the most important is IGFBP3, which itself is GH-dependent and binds 75% of IGF-1 and IGF-2. IGF-2 secretion from tumours may be associated with hypo- glycaemia. Usually the tumour is large and of mesenchymal origin, arising in the abdomen or thorax. Symptoms are those of neuroglycopenia—sweating, tachycardia, disorientation, drowsi- ness, fits, and coma. Histology shows a mesothelioma, a fibrosar- coma, or other sarcoma such as a leiomyosarcoma. Other neoplasms associated with hypoglycaemia are haemangiopericytoma, hepa- toma, adrenal carcinoma, lung carcinoma, Wilms' tumour, and co- lonic carcinoma. IGF-2 secretion leads to suppression of GH and insulin, and re- duced production

of IGFBP3, IGF-1, and acid-labile subunit (ALS), leading to reduced formation of the IGF–IGFBP3–ALS complex which protects the IGFs from degradation. IGF-2 circulates as a smaller complex which has enhanced tissue and receptor bioavail- ability, allowing access to the insulin receptor. There is also an in- crease in the large molecular weight molecules and increased levels of big IGF-2 not detected on radioimmunoassay. GH deficiency, decreased gluconeogenesis, and increased glucose metabolism by the tumour, which is usually large, may also contribute to hypogly- caemia. Treatment of these tumours is difficult. The hypoglycaemia is often not responsive to diazoxide, glucagon, octreotide, or cor- ticosteroids. However, administration of GH may be effective—increasing IGFBP3 and IGF-1 and antagonizing the effect of excess IGF-2. The underlying tumour may be resistant to radiotherapy; surgery, although effective when possible, is not always feasible. IGF-1 and IGF-2 may also play an important role in tumour pro- gression. Studies of breast cancer cells have suggested that IGF-1 may have local mitogenic effects, and a role for IGF-2 has recently been proposed in hepatocellular, colorectal, and adrenocortical tumours. Ectopic hCG secretion hCG is a glycoprotein consisting of an α and a β subunit. The α sub- unit is species specific and is the same for all glycoprotein hormones— luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH). The β-subunit determines re- ceptor interaction and specific hormone activity. The β subunit of hCG is very similar to that of LH and this can cause problems with cross-reaction in assays: the LH value may be spuriously elevated in the presence of increased hCG levels. Clinically silent, ectopic secre- tion of hCG, with or without its free α and β subunits, occurs in many patients (Table 13.10.4). Patients with ectopic secretion of gonadotrophins usually pre- sent with abnormalities in the reproductive system. In the first decade of life, ectopic hCG production may cause isosexual preco- cious puberty in boys with hepatoblastoma or a germ cell tumour. hCG, through its LH-like action, causes Leydig cell stimulation in the testes. In turn, testosterone levels reach those of a normal adult, and secondary sexual characteristics develop together with prema- ture skeletal maturity. The testes remain small because there is no seminiferous tubule growth as this is dependent on FSH. Precocious puberty is rare in girls. Intracranial teratoma, choriocarcinoma, and pinealoma are as- sociated with ectopic hCG secretion. In some patients, cosecretion of ectopic hCG with oestrogen may be associated with gynaeco- mastia in men, and with dysfunctional uterine bleeding in women. Hirsutism and amenorrhoea are also presenting features of women with ectopic hCG secretion. Other tumours associated with ectopic Table 13.10.4 Human chorionic gonadotrophin (hCG) in sera of patients with malignant tumours (from Vaitukaitis, 1991) Tissue Percentage of cases with ectopic secretion of hCG Breast 21 Lung 10 Gastrointestinal tract 18 Pancreas (more commonly hCG -α) 33 Stomach 22 Liver 21 Small intestine 13 Large intestine 12 Biliary tract 11 Ovary (adenocarcinoma) 40 Testis 62 Seminoma 38 Embryonal cell carcinoma 58 Choriocarcinoma 100 Mixed 73

 hCG secretion include dysgerminomas, testicular tumours, ovarian adenocarcinoma, and stomach, pancreatic, bronchogenic, hep- atic, and renal cell carcinomas. Rarely, ectopic LH secretion has been described in adrenal tumours and pancreatic neuroendocrine tumours. hCG is a useful tumour marker in gestational trophoblastic dis- ease (choriocarcinoma) and in some men with testicular tumours, and provides an early warning of recurrent disease. However, it is important to measure other tumour markers (e.g. α-fetoprotein), which may also be secreted by nonseminomatous germ cell tu- mours. Discordance of marker levels and tumour progress may be seen. In central nervous system disease, cerebrospinal fluid/plasma ratios may help in the correct localization of tumours, as hCG does not cross the blood–brain barrier and levels in cerebrospinal fluid remain undetectable in

pregnancy. Thus, cerebrospinal fluid con- centrations higher than plasma suggest primary central nervous system disease. In some patients, most commonly with choriocarcinoma and massive elevation of hCG, the latter, through its weak TSH ac- tivity, due to its biochemical similarity to TSH, may cause goitre and hyperthyroidism. This most frequently occurs in women, is not associated with eye signs, and is usually associated with modest biochemical abnormalities. Treatment of the tumour results in a re- sumption of a euthyroid state but, if this is not possible, carbimazole or propylthiouracil may be required. Ectopic human placental lactogen Human placental lactogen (hPL), also called human chorionic somatomammotropin (hCS), is a trophoblastic hormone which may be secreted ectopically in association with lung tumours, testicular tumours, and trophoblastic disease. It is usually associated with gy- naecomastia in men, and these tumours may also be associated with increased levels of oestradiol and hCG. Ectopic GHRH and GH secretion Most patients with acromegaly (98%) have benign GH-producing pituitary adenomas. Less than 2% of patients with acromegaly have ectopic growth hormone-releasing hormone (GHRH) production which causes hyperstimulation of the somatotroph cells within the anterior pituitary, and consequently increased GH secretion. Indeed, the presence of anterior pituitary somatotroph hyperplasia differentiates histologically the minority of acromegalic patients with ectopic GHRH syndrome from those with GH-producing pitu- itary adenomas. A patient with a carcinoid tumour of the pancreas producing GHRH enabled the final elucidation of the structure of this important hypothalamic peptide. Ectopic GHRH syndrome is caused most frequently by carcinoid tumours, especially of the lung and gastrointestinal tract. Although many carcinoid tumours ex- press immunoreactive GHRH, the development of acromegaly is uncommon (although many of these patients may display abnormal GH secretory dynamics). Other tumours reported to secrete GHRH ectopically include small cell lung cancer, adrenal adenomas, endo- metrial tumours, and phaeochromocytoma. GHRH can also be se- creted by hypothalamic hamartomas which also result in anterior pituitary somatotroph hyperplasia. Determination of the cause of acromegaly (pituitary GH excess versus ectopic GHRH syn- drome) is extremely important in the management of acromegaly. Ectopically GHRH-secreting tumours are usually clinically apparent and GHRH levels in the circulation are elevated. Surgical resection of such tumours is the logical approach to management. Long- acting somatostatin analogues can also be used in those patients with ectopic GHRH syndrome caused by disseminated or recurrent carcinoid tumours. Ectopic GH secretion has been reported in patients with bron- chial, pancreatic, and gastrointestinal carcinoma, and cells cultured from an undifferentiated lung cancer have been shown to synthesize GH in vitro. Breast carcinoma and ovarian tumours may also occa- sionally secrete GH but no clinical syndrome has been clearly iden- tified as caused by ectopic GH. Ectopic prolactin secretion Prolactin may be secreted by bronchial carcinoma and renal cell carcinoma; the usual endocrine manifestation is galactorrhoea and there may be marked hyperprolactinaemia. These abnormalities are reversed if the tumour is controlled or removed. Difficulties in differential diagnosis may arise unless the underlying abnormality is clinically obvious or suspected, because in most instances the hyperprolactinaemia will be attributed to a prolactin-secreting ad- enoma. Suspicion of an ectopic source may only arise when the pro- lactin level is not lowered by treatment with dopamine agonists. An autocrine role for prolactin in breast and prostate cancer has recently been postulated. Ectopic calcitonin secretion Increased serum calcitonin levels are encountered in a variety of cancers apart from medullary carcinoma of the thyroid. The most common of these are small cell lung cancer, leukaemia, and neo- plasms of the breast and pancreas. It is often produced as part of a multihormonal profile in conjunction with gastrin, ACTH, and somatostatin, among others. Ectopic calcitonin may differ from the normal hormone in having more components of high

molecular weight; it does not cause any apparent symptoms and does not pro- duce hypocalcaemia. Ectopic renin secretion Although hypertension associated with hyperreninism and in- creased aldosterone production is usually due to a renal lesion, ec- topic secretion of renin has also been described in association with cancer of the lung, pancreas, ovary, and, rarely, testicle. The clinical picture is usually dominated by the underlying neoplasm, but the patient has hypertension and the cause of this may be suspected from the associated hypokalaemia and its accompanying muscle weakness. Effective treatment of the primary lesion will reduce the increased renin and aldosterone levels and hence the raised blood pressure. When the underlying cause cannot be eradicated, the use of an angiotensin-converting enzyme inhibitor will control the hypertension. Ectopic aldosterone secretion Hypertension and hypokalaemia related to ectopic secretion of al- dosterone from a nonadrenal neoplasm have been described in pa- tients with ovarian tumours. Its pathogenesis is different from the others described in this section. The aberrant production of a steroid, aldosterone, rather than a peptide, is presumably due to biochemical change within the ovarian steroidogenic cells. Attention is likely to be focused on a suspected lesion of the adrenal zona glomerulosa

section 13 Endocrine disorders 2548 because the hyperaldosteronism is associated with low plasma renin activity. The ovarian lesion may initially be clinically silent and only revealed by pelvic imaging. Endocrine manifestations of nonmalignant, nonendocrine diseases Systemic disease of nonendocrine glands may influence endocrine function due to a specific effect of the disease itself, due to a general response to either acute or chronic illness, or due to drug therapy used to treat the illness itself (Table 13.10.5). Often, hormonal per- turbations may be a complex mixture of all of these mechanisms, as may be seen in AIDS or critically ill patients on intensive therapy units. This section includes examples of systemic disease-causing endocrine disorders. A commonly observed hormonal disturbance encountered in many hospital inpatients is the sick euthyroid syndrome. Peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) is reduced, and typical thyroid function tests in this syndrome are a normal or reduced TSH in association with reduced T3 and T4 (and in- creased reverse T3 if measured). Severe illness may also interfere with hypothalamopituitary function and lead to hypogonadotropic hypogonadism. Possible mechanisms include increased cortisol levels, stress, cytokines, or opioids given as analgesia. Disorders influencing hypothalamopituitary function Anorexia nervosa is associated with complex changes in hypothalamopituitary function, with reduction in GnRH and gonadotrophin secretion leading to hypogonadotropic hypo- gonadism, and increased GH secretion which is associated with in- creased peripheral resistance to GH. Iron overload due to haematological conditions such as β-thalassaemia major and to haemochromatosis may cause iron deposition in the anterior pituitary gland, and in particular in the gonadotrophs. This leads to hypogonadotropic hypogonadism, which may be ameliorated to a degree by venesection and iron che- lation therapy. Haemochromatosis may also lead to other hormonal changes due to pancreatic involvement causing diabetes mellitus, and cirrhosis associated with secondary hyperaldosteronism and hypogonadism. Thyroid Morning sickness in the first trimester of pregnancy may be asso- ciated with clinical and biochemical features of thyrotoxicosis, as the molecules hCG and TSH share very similar β subunits, allowing cross-reactivity when high levels of hCG occur. Opportunistic infections of the thyroid gland may occur, in conditions associated with immunosuppression such as AIDS. Infections with cytomegalovirus, cryptococcus, and pneumocystis have been described. In addition, some patients with HIV infec- tion have increased T4 and T3 due to increased thyroid-binding globulin. As the disease progresses, T4 and T3 levels fall as patients develop biochemical features of sick

euthyroidism. Adrenal Opportunistic infections (cytomegalovirus, atypical mycobac- teria, cryptococci, toxoplasma, and pneumocystis), lymphoma, and Kaposi's sarcoma may involve the adrenal glands in HIV and AIDS. The adrenal gland is the most commonly involved endo- crine gland at autopsy. However, frank adrenal insufficiency is rare because this requires destruction of over 90% of the adrenal cortex. Gonads Chemotherapy and irradiation may be associated with gonadal failure due to hypothalamopituitary gonadotrophin deficiency (e.g. following cranial irradiation or due to testicular/ovarian damage following cytotoxic drug therapy such as cyclophospha- mide, cisplatin, and busulfan). Table 13.10.5 Hormonal abnormalities associated with nonendocrine disorders Disease Endocrine abnormality Severe illness Sick euthyroid syndrome (↓TSH ↓T4 ↓T3 ↑rT3) Hypogonadism (↓LH ↓testosterone/oestradiol) Anorexia nervosa Hypogonadotropic hypogonadism (↓GnRH ↓LH/FSH ↑GH) Iron overload Hypogonadotropic hypogonadism (↓LH/FSH ↓T or E2) Hyperemesis gravidarum Thyrotoxicosis (↓TSH ↑T4, ↑hCG) HIV infection and AIDS ↑T4 ↑T3 ↑TBG(HIV) Opportunistic infections may cause goitre, hypo- or hyperthyroidism Adrenal infiltration (infection, lymphoma, and Kaposi's sarcoma), however Addison's rare Impaired aldosterone and adrenal androgen secretion, with preferential glucocorticoid production Cytotoxic chemotherapy and radiotherapy Hypogonadotropic hypogonadism (↓ LH/FSH ↓T/E2) Premature ovarian and testicular failure due to direct cytotoxic effect Coeliac disease Reversible androgen resistance (↑FSH/LH ↓testosterone) Alcoholic liver disease Androgen deficiency (↓testosterone ↑SHBG ↑E2) Sarcoidosis and other granulomatous disorders ↑1,25 DHCC ↑calcium HTLV-1 infection ↑PTHrP ↑calcium

13.10 Hormonal manifestations of nonendocrine disease 2549 Coeliac disease is associated with reversible male infertility due to androgen resistance, and improves on a gluten-free diet. Alteration of gonadal steroid metabolism may occur in chronic liver dis- ease, particularly if alcohol related. Elevated sex hormone-binding globulin and oestradiol levels are associated with a reduction in bio- available testosterone leading to testicular atrophy, gynaecomastia, and erectile impotence. Gynaecomastia Palpable breast glandular tissue is prevalent in population studies of men and boys. Subareolar glandular tissue of more than 2 cm in diameter is found in 35 to 60% of men. Gynaecomastia may occur as a result of various underlying conditions (Table 13.10.6) as well as drug therapy, and results from an alteration in the ratio of oes- trogen to androgen. Gynaecomastia can occur in association with testicular and adrenal neoplasms, Klinefelter's syndrome, thyrotoxi- cosis, cirrhosis, primary hypogonadism, malnutrition, and ageing (see Table 13.10.6). An increase in levels of free oestrogen, reduced levels of free endogenous androgens and androgen receptor defects may underlie these changes. Increased aromatization of oestrogen precursors occurs in patients with obesity, liver disease, and hyper- thyroidism, and as a result of ageing. Calcium Hypercalcaemia in sarcoidosis is due to increased circulating 1,25-dihydroxyvitamin D3, which undergoes dysregulated over- production in alveolar macrophages in a dose-dependent fashion, stimulated by γ-interferon, which is one factor responsible for the maintenance of the inflammatory process in sarcoidosis. Other granulomatous disorders (tuberculosis, histoplasmosis, coccidiomycosis, ruptured silicone breast implants) may rarely be associated with hypercalcaemia due to the same mechanism. Treatment with glucocorticoids or hydroxychloroquine are effective in lowering 1,25-dihydroxycholecalciferol and calcium. HTLV1 infection may be associated with hypercalcaemia, due to transactivation of the PTHRP gene on chromosome 12. Endocrine manifestations of obesity Our understanding of adipose tissue has been transformed from a role of fat storage to one that incorporates a complex interplay of hormones with both endocrine and paracrine effects, and plays important roles in the regulation of appetite,

energy expenditure, and body fat mass. A detailed description of the complexities of the endocrine manifestations of obesity is beyond the scope of this chapter (see Chapter 11.6), but the major endocrine manifestations are outlined. Leptin is an adipokine, levels of which increase with weight gain. Leptin has effects within the hypothalamus to sup- press food intake and promote energy expenditure pathways. Leptin may also have direct effects on ovarian function in women, which may play a role in the link between menstrual cyclicity and fer- tility with optimum weight. Other adipokines such as visfatin and resistin play important roles in reducing insulin sensitivity and pro- moting a proinflammatory state in obesity. Levels of adiponectin (which has anti-inflammatory and immunoregulatory effects and improves insulin sensitivity) are reduced in obesity. Increased aromatase expression within the adipocyte in obesity may explain in part the association of male obesity with feminizing effects and, through suppression of the hypothalamo-pituitary regulation of the gonadal axis through oestradiol, the association of male obesity with hypogonadotropic hypogonadism. Finally, there has been much interest in the effects of obesity on steroid hormone regu- lation within the adipocyte, including the effects on the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) that inter- converts inactive cortisone and active cortisol. Inhibition of 11β- HSD1 remains an exciting therapeutic strategy for patients with obesity, to improve the associated dysmetabolic sequelae. Drug-induced endocrine manifestations Several pharmaceutical drugs may induce manifestations of endo- crine disease. More commonly they may influence the results of hor- monal assays and lead to mistaken diagnosis. It may not be a major problem when it is known that the patient is taking a particular com- pound and, from its molecular structure, it is appreciated that such a substance could influence the endocrine system or the results of hormonal assays. The problem is greater, however, when the drug in question has no clear relationship to a hormone and the mechanism Table 13.10.6 Nonendocrine conditions associated with gynaecomastia Neoplasms Ectopic production of human chorionic gonadotrophin or human placental lactogen Liver disease (18%) Starvation during recovery phase (refeeding) Renal disease and dialysis (1%) Drugs (10–20%) Antiandrogens/inhibitors of androgen synthesis Cyproterone Flutamide Spironolactone Antibiotics Ketoconazole Antiulcer medication Cimetidine Omeprazole Ranitidine Cancer chemotherapeutic agents Alkylating agents Cardiovascular drugs Captopril Digoxin Methyldopa Nifedipine Psychoactive drugs Haloperidol Phenothiazines Drugs of abuse Cannabis

section 13 Endocrine disorders 2550 by which it induces an endocrine manifestation, or interferes with an assay procedure, is not readily apparent. Thyroid Abnormalities of thyroid function test measurements Drugs can interfere with thyroid function tests. Some act by inhibiting the conversion of T4 to T3, others by increasing thyroid- binding globulin. β-Blockers with membrane stabilizing proper- ties, such as propranolol, inhibit peripheral conversion of T4 to T3. Oral cholecystographic agents and amiodarone, a heavily iodinated antiarrhythmic agent, are also potent inhibitors of T4 to T3 conver- sion and produce decreased serum T3 concentrations and an in- crease in reverse T3. Oestrogen increases thyroid-binding globulin, due to an increase in the sialic acid content of thyroxine-binding globulin, which prolongs its half-life in the circulation. Thus, women on oestrogens (e.g. the contraceptive pill) have high total T4 concen- trations but are euthyroid. Such results may also be seen in patients on tamoxifen. Heroin and methadone addicts also have raised levels of thyroxine-binding globulin, as do patients on the lipid-lowering agent, clofibrate. A decreased serum T4 does not necessarily indicate the presence of hypothyroidism. Many pharmacological agents lower the total T4 concentration by interfering with the binding of T4 to one or more of the thyroid-binding proteins. Therapeutic levels of pheny- toin lower the level of

serum T4 and high concentrations are capable of inhibiting the binding of T4 and T3 to thyroid-binding globulin. High doses of salicylates have the same effect. Diclofenac, a non- steroidal anti-inflammatory drug structurally similar to thyroxine, also interferes with thyroid hormone binding. Phenylbutazone, anabolic steroids, and glucocorticoids may also be associated with a low total T4 and normal thyroid function. Measurement of free thyroxine (FT4) will obviate the problems of misleading results from the measurement of total T4. Drug-induced hyperthyroidism Amiodarone may cause hyperthyroidism due to its high iodine con- tent, or due to a destructive thyroiditis. Biochemically, there may be a marked elevation of total thyroxine, a relatively normal level of T3, and a suppressed TSH. Often, thyrotoxicosis is masked by the β-blocking effect of the drug. Because of the large iodine load, it may be very difficult to treat with antithyroid drugs, and steroids may also be necessary to suppress thyroid hormone levels into the normal range. Even if amiodarone is stopped, its effects continue for many weeks because it is predominantly stored in adipose tissue. Contrast media and iodine-containing cough medicines may simi- larly induce hyperthyroidism (Jod–Basedow phenomenon). Drug-induced hypothyroidism Increased iodide intake may also lead to decreased iodide trapping and a decrease in synthesis of thyroid hormones, hypothyroidism, and goitre. Iodine is contained in several tonics and cough medi- cines. Amiodarone, besides producing thyrotoxicosis, may cause iodine-induced hypothyroidism in patients replete with iodine. Lithium blocks iodine uptake and the release of thyroid hormones. It also interferes with cAMP formation and thus inhibits the effects of TSH stimulation and may lead to goitre, although only 2% of patients on lithium actually develop clinical features of hypothyroidism. Adrenal cortex Abnormalities of adrenal hormone measurements Drugs may interfere with tests of adrenal function. Thus, the drug phenytoin accelerates metabolism of dexamethasone, and patients on phenytoin may not suppress cortisol normally during dexa- methasone suppression tests. Furthermore, during the assessment of adrenal reserve, chronic topical application of steroids, as well as inhalation of steroids for asthma, may suppress adrenal function. Oestrogens, by enhancing hepatic production of cortisol-binding globulin, which binds between 90 and 97% of circulating cortisol, increases cortisol-binding globulin two- to threefold. Thus, assess- ment of glucocorticoid replacement in patients on oestrogens is in- fluenced by this effect and oestrogens should be stopped 6 weeks prior to the test. Drug-induced Cushing’s syndrome Chronic, excessive intake of alcohol causes alcoholic pseudo- Cushing’s syndrome. These patients behave biochemically as if they have Cushing’s syndrome with absent dexamethasone suppres- sion. This occurs through a centrally mediated mechanism with hypersecretion of pituitary ACTH and secondary secretion of cor- tisol by the adrenals. Drug-induced primary aldosteronism Primary aldosteronism can be mimicked by the mineralocorticoid effect of glycyrrhizic acid contained in both carbenoxolone and li- quorice. Cortisol is normally inactivated by conversion to the in- active metabolite, cortisone, by the enzyme 11β-hydroxysteroid dehydrogenase but these compounds inhibit the enzyme, which is important in the kidney because it protects renal mineralocorticoid receptors from cortisol. This can result in the syndrome of apparent mineralocorticoid excess in which renal mineralocorticoid recep- tors are stimulated locally by cortisol. Drug-induced adrenal insufficiency The antifungal agent, ketoconazole, and the short-acting anaes- thetic, etomidate, are imidazole derivatives with significant inhibi- tory effects on 11β-hydroxylase. While they do not usually produce clinical insufficiency, they may do so in subjects with limited pi- tuitary or adrenal reserve. Rifampicin and phenytoin, which both accelerate the metabolism of cortisol by inducing hepatic mixed- function oxygenase enzymes, can also provoke adrenal insufficiency in similar patients with limited pituitary or adrenal reserve. In such patients, increased doses of replacement therapy are necessary. Gonads Several drugs can affect testicular function, leading to

hypogonadism and infertility. Mechanisms include the direct inhibition of testos- terone synthesis or competitive inhibition of androgen action at receptor level. Spironolactone acts as a partial androgen receptor antagonist. Alcohol reduces testosterone levels acutely and chronic- ally, by both a central and a gonadal effect on testosterone synthesis, secretion, and metabolism. Cimetidine has antiandrogen effects due to direct interaction with the androgen receptor and it may also exert antiandrogen effects at the pituitary and hypothalamus leading to gynaecomastia and impotence in males. Anticonvulsants (e.g. phenytoin) increase sex hormone-binding globulin and therefore

 decrease free testosterone levels. They also enhance conversion of testosterone to oestradiol. Sulfasalazine causes reversible male infer- tility associated with oligospermia. Infertility may occur as a result of cytotoxic therapy, caused in particular by alkylating agents such as cyclophosphamide. These produce depletion of the germinal epithelium and lead to a raised FSH level, and oligo- or azoospermia, but normal LH and testos- terone levels in males, and may lead to premature ovarian failure in women. In women, hirsutism can be caused by several drugs, including danazol, phenytoin, diazoxide, and minoxidil. Pharmacological doses of glucocorticoids may lead to hypo- gonadism because of inhibited gonadotrophin release. Drugs such as tricyclics, benzodiazepines, antihypertensives, and antipsychotics may also lead to hypogonadotropic hypogonadism in both sexes. Prolactin Prolactin is controlled predominantly by a hypothalamic inhibitory mechanism through dopamine secretion. Some drugs can cause hyperprolactinaemia and galactorrhoea, usually acting through a dopaminergic mechanism. They may elevate prolactin to a suf- ficient extent to cause a clinical suspicion of prolactinoma, and in such patients a careful drug history is particularly important. Metoclopramide, pimozide, and sulpiride all act as dopamine ant- agonists and may considerably elevate prolactin, with all the at- tendant effects thereof. Fluoxetine may also lead to elevated serum prolactin, although tricyclic antidepressants are not usually associ- ated with hyperprolactinaemia. Phenothiazines, chlorpromazine, perphenazine, and trifluo- perazine also act as dopamine antagonists, as do haloperidol and butyrophenone. Reserpine and methyldopa both decrease dopa- mine stores and may cause hyperprolactinaemia. Oestrogens, in high doses, may slightly elevate prolactin but normal contraceptive pills do not. Verapamil, by decreasing dopaminergic tone, may also increase prolactin levels. Gynaecomastia Gynaecomastia may occur due to treatment with various drugs (see Table 13.10.6). Drugs such as spironolactone and ketoconazole, which can displace steroids from sex hormone-binding globulin, displace oestrogens more easily than androgens. Activation of the oestrogen receptors in breast tissue may take place with drugs that have structural homology with oestrogen, such as digoxin; griseofulvin and cannabis may have the same effect. A decrease in androgen levels occurs in older men and with drugs such as spir- onolactone and ketoconazole that inhibit the biosynthesis of tes- tosterone. The mechanism for the induction of gynaecomastia by captopril and calcium channel blockers (nifedipine) is unclear. With cimetidine and omeprazole, this effect may be due to a direct antiandrogen effect or the inhibition of liver cytochrome P450. Posterior pituitary The syndrome of inappropriate antidiuresis is characterized by normovolaemic hyponatraemia with persistent secretion of AVP, despite a reduced plasma osmolality. Several drugs can cause this syndrome through the inappropriate stimulation of eutopic AVP secretion. These include thiazide diuretics, vincristine, vin- blastine, cyclophosphamide, chlorpropamide, phenothiazines, carbamazepine, clofibrate, tricyclic antidepressants, and serotonin- reuptake inhibitors (see Table 13.10.1). The syndrome of inappro- priate antidiuresis can also be caused by the administration of desmopressin

(a V2 selective analogue of AVP) or oxytocin. Nephrogenic diabetes insipidus can be induced by lithium in the therapeutic range, and up to 20% of patients receiving long-term therapy may develop this complication. Demethylchlortetracycline produces dose-dependent nephrogenic diabetes insipidus, and both the concentrating defect and the unresponsiveness to vasopressin are reversible on cessation of the drug. Parathyroid Lithium therapy can cause an increase in parathyroid gland size, either with hyperplasia or adenoma. This hyperparathyroidism leads to mild hypercalcaemia and sometimes osteoporosis. Thiazide diuretics, by causing haemoconcentration and hypocalciuria, may also result in mild hypercalcaemia but this is usually transient (4–6 weeks); after this time, other causes of hypercalcaemia should be sought. Vinblastine and colchicine inhibit parathyroid hormone secretion which may result in hypocalcaemia. FURTHER READING Alexandraki KI, Grossman AB (2010). The ectopic ACTH syndrome. Rev Endocr Metab Disord, 11, 117–26. Bell NH (1991). Endocrine complications of sarcoidosis. Endocrinol Metab Clin North Am, 20, 645–54. Braunstein GD (1993). Current concepts: gynecomastia. N Engl J Med, 328, 490–5. Carpenter TO (2003). Oncogenic osteomalacia—a complex dance of factors. N Engl J Med, 348, 1705–8. Chattopadhyay N (2006). Effects of calcium-sensing receptor on the secretion of parathyroid hormone-related peptide and its impact on humoral hypercalcemia of malignancy. Am J Physiol Endocrinol Metab, 290, E761–70. Chopra IJ (1997). Clinical review 86: euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab, 82, 329–34. Daughaday WH, Deuel TF (1991). Tumour secretion of growth fac- tors. Endocrinol Metab Clin North Am, 20, 539–63. Docter R, et al. (1993). The sick euthyroid syndrome: changes in thy- roid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf), 39, 499–510. Gola M, et al. (2006). Neuroendocrine tumors secreting growth hormone-releasing hormone: pathophysiological and clinical aspects. Pituitary, 9, 221–9. Grinspoon SK, Bilezikian JP (1992). HIV disease and the endocrine system. N Engl J Med, 327, 1360–5. Guise TA, Mundy GR (1998). Cancer and bone. Endocr Rev, 19, 18–54. Hayes AR, Grossman AB (2018). The ectopic adrenocorticotropic hor- mone syndrome: rarely easy, always challenging. Endocrinol Metab Clin North Am, 47, 409–25. Hirshberg B, et al. (2003). Ectopic luteinizing hormone secretion and anovulation. N Engl J Med, 348, 312–17. Howlett TA, et al. (1986). Diagnosis and management of ACTH- dependent Cushing's syndrome: comparison of the features in
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