A

Abciximab *See*

- Antiplatelet agents.

Abdominal compartment syndrome *See*

- Intra-abdominal hypertension.

Abortion *See*

- Pregnancy.

See also

- Amniotic fluid embolism,
- Antiphospholipid syndrome,
- Immune thrombocytopenic purpura,
- Salpingitis,
- Systemic lupus erythematosus,
- Tetanus.

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Abruptio placentae (placental abruption) *See*

- Trauma in pregnancy – Placental abruption.

See also

- Amniotic fluid embolism,
- Haemolytic–uraemic syndromes,
- HELLP syndrome,
- Pre-eclampsia.

Acanthosis nigricans *See*

- Pigmentation disorders.

See also

- Lung tumours,
- Paraneoplastic syndromes.

ACE *See*

- Angiotensin-converting enzyme.

Acetazolamide *See*

- Carbonic anhydrase inhibitors.

See also

- Benign intracranial hypertension,
- High altitude,
- Periodic paralysis.

Acetylsalicylic acid *See*

- Aspirin.

Achlorhydria

Achlorhydria refers to the lack of secretion of gastric acid. The diagnosis of achlorhydria may be less than rigorous if it is based on the pH of spot samples of gastric contents rather than on formal testing of basal or stimulated gastric secretion.

The absence of gastric acid even after stimulation (i.e. absolute achlorhydria) has a number of associations, including

- gastric carcinoma,
- gastric polyps,
- pernicious anaemia (q.v.),
- iron deficiency (q.v.),
- hypogammaglobulinaemia (see Agammaglobulinaemia),
- increased susceptibility to gastrointestinal infection.

Achlorhydria is of course also seen after

- extensive gastric surgery or irradiation (permanently),
- potent proton pump (H^+/K^+ ATPase) inhibitors (PPIs) (temporarily).

Gastric acid is a prerequisite for peptic ulceration, and **increased acid secretion** is a feature of refractory or recurrent peptic ulceration (see Zollinger–Ellison syndrome).

See also

- Anaemia.

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Acidosis, lactic *See*

- Lactic acidosis.

Acidosis, renal tubular *See*

- Renal tubular acidosis.

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) has become a well-recognized entity throughout all of clinical medicine and beyond. The cumulative worldwide mortality from AIDS pandemic has far exceeded 30 million, with 800,000 deaths still occurring annually, as the overall mortality has been about 40%. Nearly 40 million people currently live with HIV infection, to which are added about 1.7 million new cases each year.

Sophisticated computer modelling of viral phylogenetics has suggested that the causative virus, the **human immunodeficiency virus** (HIV-1), originated in Africa perhaps in 1931, presumably via interspecies transfer

from chimpanzees, though the first positive serology can be dated only from 1959 in Africa and the first cases did not reach the developed world until nearly 10 years later.

HIV infection is now regarded as a chronic condition, and patients in the developed world at least can have a relatively normal lifespan following viral suppression with combined antiretroviral therapy (ART or cART). These ART regimens must be continued indefinitely to prevent viral re-emergence. Current antiviral therapy is so successful that HIV-AIDS control has been effectively achieved even without the development of an effective vaccine. Moreover, treated patients with an undetectable viral load (i.e. <200 copies/mL in blood) do not pose a risk of transmission to others.

Pre-exposure prophylaxis (PrEP) is also available for those at risk, e.g. in serodiscordant sexual partnerships, on either a daily or an episodic basis. PrEP using a combination of tenofovir and emtricitabine has an effectiveness of over 90%, as also is post-exposure prophylaxis with an effectiveness of over 80%. The widespread availability of targeted PrEP has led to a marked fall in new HIV diagnoses, at least in developed countries.

Given the large number of otherwise well patients in the population nowadays with HIV stabilized on ART in developed countries, it is now estimated that most such patients will be cared for in ICUs following surgery, trauma, infection or any of the other conditions that prompt admission to ICU generally. In addition, in patients being treated long term with combined highly active antiretroviral agents, there is an increased occurrence of a range of serious chronic conditions, including accelerated cardiovascular disease, COPD and non-AIDS-defining cancers. For all these patients, special considerations apply in the use of ART if they become critically ill, and there are now published guidelines for this.

The traditionally most common presentation to Intensive Care, namely, **opportunistic infection**, has now been relegated to second place. Patients presenting with these, even if their HIV status is unknown and provided they have no other known immunodeficiency, are generally not difficult to recognize as likely to have AIDS.

These infections are often unusually chronic, recurrent, invasive or multiple. In many such patients presenting with fever and a presumptive diagnosis of infection, a specific microbiological cause is never identified. Although the patient may be a risk to others, particularly if tuberculosis is not promptly recognized, the patient is clearly also at risk of acquiring other, nosocomial infections while in hospital and especially while in Intensive Care.

Respiratory infections are the most common infections suffered by AIDS patients admitted for Intensive Care, but the clinical presentation is dependent on the patient's immune status, most simply assessed by the CD4 count.

- If the CD4 count is normal or nearly so, the infection is most likely to be bacterial or perhaps tuberculosis (TB).
- If the CD4 count is <200/μL, the infection is most likely to be caused by, in order,
  - *Pneumocystis jirovecii (P. carinii)*,
  - bacteria (especially pneumococci, but also legionella, listeria, nocardia, salmonella),
  - mycobacteria (either TB or *Mycobacterium avium* complex (MAC)),
  - fungi (candida, aspergillus),
  - protozoa (toxoplasma),
  - viruses (herpesviruses).

Bacillary angiomatosis and bacillary peliosis hepatis are serious infective complications of cat-scratch disease (q.v.), seen in immunocompromised patients such as those with AIDS.

AIDS-defining **neoplastic conditions** remain a major clinical problem. These cancers include

- Kaposi's sarcoma, due to HSV8 (see Herpesviruses),
- non–Hodgkin's lymphoma and primary cerebral lymphoma.

In disadvantaged communities, presenting features may still occasionally represent the **direct effects** of HIV infection. A very broad collection of such features may be seen, including

- an acute infectious mononucleosis-like illness
  - which commonly persists for several months,
- thrombocytopenia (q.v.),
- wasting,
- neurological disease
  - subacute encephalitis (q.v.),
  - encephalopathy (q.v.),
  - myelopathy (q.v.),
  - peripheral neuropathy (q.v.),
  - aseptic meningitis,
- abnormalities of
  - myocardium,
  - kidneys,
  - gut,
  - thyroid,
  - joints.

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Acromegaly

Acromegaly is a rare condition, produced in adults by excessive growth hormone which is usually derived from a pituitary adenoma. Its incidence is about 4 per million of the population per year, and its prevalence is about 50 per million of the population.

The pituitary adenoma usually arises from somatic mutation of the gene coding for part of a regulatory G protein, thus causing the production of growth hormone to become continuous instead of varying greatly during the day as it normally does in response to many stimuli, including exercise, stress, hypoglycaemia and adrenergic influences. Excessive growth hormone in children may produce **gigantism** as an occasional phenomenon.

Growth hormone (GH, somatotropin, somatropin) is a 191 amino acid peptide, which is secreted by the anterior pituitary and which acts by stimulating the hepatic production of **somatomedin C** (or insulin-like growth factor 1, IGF-1), one of the body's many growth factors which circulate and bind to target cell receptors. IGF, which as an ultimate anabolic agent was called the wonder drug of the late twentieth century, is now described as a system and is the subject of an extensive literature.

The pituitary secretion of growth hormone is regulated by two neuropeptides secreted by the hypothalamus into the pituitary portal circulation, namely, **growth hormone–releasing hormone** (GHRH) which is stimulatory and **somatostatin** (q.v.) which is inhibitory. Acromegaly may thus also occur from excessive pituitary stimulation by GHRH either from the hypothalamus or ectopically from tumours, particularly benign foregut tumours such as bronchial carcinoid (q.v.) or pancreatic adenoma.

The clinical features of acromegaly include both local (mechanical or parasellar) and distal (hormonal) changes, as for all pituitary tumours.

- **Local** (mechanical or parasellar) features include headache and visual impairment (both of fields and of acuity).
- **Distal** (hormonal) features include acral and soft tissue overgrowth (affecting especially the face, hands and feet), increased bodily hair (see Hirsutism), sweating (q.v.) and odour, sleep apnoea (q.v.), husky voice, diabetes and skin tags (fibroma molluscum). Concomitant vascular disease may occur, with both atherosclerosis and microvascular dysfunction (q.v.).

Most patients have sleep apnoea (q.v.), and both the obstructive and central forms of this condition may occur.

Since the hormonal changes of acromegaly which lead to clinical recognition tend to develop slowly, the adenoma is generally a macro-adenoma (i.e. >10 mm) and parasellar features are usual when the diagnosis is made.

Investigations show an elevated plasma growth hormone level which is not suppressed after a glucose load (i.e. >3 μg/L, despite glucose 75 g 1–2 hr previously in a

standard oral glucose tolerance test). The plasma somatomedin C level which reflects average growth hormone activity is increased. The sella itself is best imaged by CT or MRI. If pituitary hyperplasia rather than a discrete adenoma is present, the source of GHRH should be sought either in the hypothalamus or an ectopic site.

Treatment of a pituitary adenoma is usually by transphenoidal ***resection****.*

- *Postoperative* ***radiotherapy*** *is required if the GH and IGF-1 remain elevated, as is often the case.*
- *If GH levels still remain elevated, symptoms may be improved by medical treatment, using agents such as* ***bromocriptine*** *(a dopamine agonist, given in a dose of 2.5–10 mg bd) or* ***octreotide*** *(a synthetic analog of somatostatin, given in a dose of 200 mcg SC bd or tds). Bromocriptine is particularly useful in patients with prolactin-secreting tumours (but see Ergot).*
- *Second-generation* ***dopamine agonists*** *(e.g. cabergoline),* ***somatostatin analogs*** *(e.g. pasireotide) and* ***growth hormone receptor antagonists*** *(e.g. pegvisomant) provide newer pharmacological options for biochemical control when surgery is not feasible or is incomplete. More recently, a long-acting analog of* ***somatostatin-release-inhibitor factor*** *(SRIF) has been found to be effective in resistant cases.*

Pituitary apoplexy is an emergency condition which can complicate any pituitary tumour.

It presents with headache, coma, shock and abnormal eye signs.

It requires urgent treatment with ***corticosteroids*** *and* ***surgery****.*

See also

- Pituitary.

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ACTH *See*

- Adrenocorticotropic hormone.

See also

- Adrenal insufficiency.
- Aldosterone,
- Conn's syndrome,
- Cushing's syndrome,
- Ectopic hormone production,
- Hirsutism,
- Paraneoplastic syndromes.

Actinomycete infections *See*

- Actinomycosis,
- Nocardiosis,
- Whipple's disease.

Actinomycosis

Actinomycosis is due to infection with a Gram-positive bacterium, *Actinomyces israelii*, previously thought to be a fungus because of its filamentous hyphae-like appearance. It is an obligate anaerobe, related to *Nocardia* (q.v.) and often part of the normal oral flora.

Infection arises when there is injury to the mucosal barrier, especially in association with necrotic tissue or a foreign body. Most infections are facio-cervical, but occasionally the infection may involve the lungs or become disseminated. It is also an uncommon cause of pelvic inflammatory disease in women.

It is a chronic deep granulomatous infection with sinus formation. Inspection of exuded material may show the characteristic 'sulphur granules', tiny pale particles which on microscopy are masses of filaments.

Laboratory identification can sometimes be difficult, as the organisms on smear may fragment to give coccobacilli appearing like diphtheroids and on culture they are slowly growing under anaerobic conditions.

Treatment is with ***penicillin*** *7.2–14.4 g (12–24 million U) IV per day in divided doses for 2–4 weeks, then orally in reduced dose for 3–6 months. In penicillin-sensitive patients,* ***tetracycline*** *may be used.*

- ***Surgical clearance*** *may be required, and* ***hyperbaric oxygen*** *should be considered in severe infections.*

The prognosis is generally good.

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Acute brain syndrome *See*

- Delirium.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare and potentially fatal condition of the third trimester and is usually associated with pre-eclampsia. It presents with nausea, vomiting, abdominal pain and jaundice.

Liver function tests are abnormal, and there is usually a coagulopathy. Hypoglycaemia can be severe and sustained. The liver biopsy shows diffuse panlobular fatty change (i.e. steatosis).

*Treatment is with emergency **delivery** and Intensive Care support.*

See also

- HELLP syndrome,
- Pre-eclampsia.

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Acute flaccid myelitis *See*

- Poliomyelitis.

Acute lung irritation

Acute lung irritation can be produced by a large number of chemical pollutants in the form of noxious gases and fumes (see Occupational lung diseases). Irritation generally occurs in the upper respiratory tract (and often elsewhere, such as the skin), as well as in the lung. Water-soluble gases (e.g. ammonia, sulphur dioxide) particularly affect the upper airway and produce immediate symptoms, whereas less soluble gases (e.g. oxides of nitrogen, ozone) primarily affect the peripheral airways and may produce delayed symptoms (i.e. about 12 hr later). Heavy exposure to any agent causes effects throughout the entire respiratory system.

Clinical features of acute lung irritation thus include
- sneezing, rhinorrhoea, lacrimation,
- stridor (q.v.),
- cough,
- wheeze,
- dyspnoea.

Systemic effects may also be seen on occasion, including
- fever,
- chills,
- leukocytosis.

Bronchiolitis (q.v.), pulmonary oedema (q.v.) and subsequent bronchopneumonia are possible consequences of acute lung irritation.

Toxic gases and fumes include
- ammonia,
- chlorine (q.v.),
- sulphur dioxide,
- oxides of nitrogen,
- ozone,
- hydrogen sulphide (q.v.),
- isocyanates
  - which may also cause occupational asthma (q.v.),
- osmium tetroxide,
- metal fumes
  - especially oxides of copper (q.v.), magnesium (q.v.) and zinc (q.v.),
  - also oxides of antimony, beryllium (q.v.), cadmium (q.v.), cobalt (q.v.), iron (q.v.), manganese (q.v.), nickel, selenium (q.v.), tin, tungsten and vanadium,
- mercury (q.v.),
- platinum salts,
- polymer fumes (Teflon degradation products),
- warfare agents (q.v.).

The treatment of toxic gas exposure is focussed on airway protection, intubation and lung protective modes of mechanical ventilation. Corticosteroids have not been of value acutely, though benefit has been reported during the later reparative phase. Interestingly, simple drugs such as aminophylline, ibuprofen, N-acetylcysteine, nebulized heparin and salbutamol have been recommended, but formal documentation of their efficacy is lacking.

Systemic abnormalities are also produced following the inhalation of
- carbon monoxide (q.v.),
- cyanide (q.v.).

Asphyxia may be caused by excess
- carbon dioxide,
- nitrogen,
- methane.

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Acute pulmonary oedema

Pulmonary oedema is defined as an increased amount of extravascular fluid (water and solute) in the lung, where it may be interstitial or alveolar or both.

Pulmonary oedema is one of the commonest respiratory disorders and may follow a wide variety of local and systemic insults. Although pulmonary oedema due to left heart failure is the classical clinical picture, pulmonary oedema also occurs in a number of other common settings. In these, the left atrial pressure may be normal or even low.

These non-cardiac settings include

- serious medical or surgical illness in the form of the **acute respiratory distress syndrome** (ARDS) (q.v.),
- an important component in
  - viral pneumonia,
  - aspiration pneumonitis (q.v.),
  - respiratory burns (q.v.),
  - uraemia,
  - endotoxaemia (a systemic inflammatory response syndrome),
  - drowning (q.v.),
  - head injury,
  - severe upper airway obstruction (see Asthma),
  - altitude-related illness (see High altitude).

Pulmonary oedema may therefore present in diverse settings with different pathogenetic mechanisms and thus with different therapeutic implications.

The causes of pulmonary oedema are

1. **Increased capillary hydrostatic pressure**
   - cardiogenic (left heart failure),
   - blood volume overload,
   - pulmonary veno-occlusive disease (q.v.).
2. **Increased capillary permeability**
   - acute respiratory distress syndrome (ARDS)(q.v.),
   - viral and other pneumonia,
   - inhaled toxic substances (including oxygen),
   - circulating toxic agents (including sepsis),
   - disseminated intravascular coagulation (q.v.),
   - uraemia, radiation (q.v.), burns (q.v.), non-fatal downing (q.v.),
   - vaping-associated respiratory disease after using e-cigarettes (see Vaping).
3. **Decreased plasma oncotic pressure**
   - hypoalbuminaemia.
4. **Decreased tissue hydrostatic pressure (i.e. negative-pressure pulmonary oedema)**
   - rapid lung re-expansion, after
     - drainage of a pneumothorax or large pleural effusion,
     - pneumonectomy,
   - laryngospasm (and other causes of acute upper airway obstruction, when associated with strong inspiratory effort).
5. **Decreased lymphatic drainage**
   - lymphangitis carcinomatosa,
   - lymphangioleiomyomatosis (q.v.),
   - lung transplantation.
6. **Uncertain mechanisms**
   - high altitude (q.v.),
   - neurogenic (raised intracranial pressure),
   - drug overdose (especially IV heroin),
   - pulmonary embolism,
   - maximal exercise (occasionally),
   - scuba diving, usually in cold water (occasionally).

In practice,

- the first two groups of causes are by far the most commonly encountered,
- the third group is probably not a cause in its own right, but lowers the threshold for pulmonary oedema from other causes,
- groups four, five and six are less common.

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Acute respiratory distress syndrome

Acute respiratory distress syndrome (adult respiratory distress syndrome, ARDS) has been recognized as the hallmark respiratory complication of critical illness since its first description in 1967. Its pathogenesis, clinical features, diagnosis and management have been extensively described, studied and reviewed in the literature over the past four decades.

It has become apparent that there has been a major decline (about 4-fold) in the incidence and mortality of ARDS over the past 20 years. This decline has been attributed to improved resuscitation and early treatment of sepsis, trauma and other precursor conditions, to more restrictive fluid and blood product practices, and to improved ventilator protocols focussed on lung protection. This improvement has occurred despite the failure of any specific pharmacological measure to alter its outcome.

It should be remembered that even later definitions of ARDS (e.g. Berlin 2012) have limited accuracy and that its differential diagnosis includes a number of other conditions associated with diffuse alveolar changes (see Pulmonary infiltrates). The syndrome thus incorporates considerable heterogeneity.

See

- Acute pulmonary oedema.

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Acyclovir

Acyclovir (aciclovir) is one of the most important antiviral drugs. It replaced vidarabine (ara-A), the first available antiviral agent for systemic use in serious infections. It is a synthetic purine nucleoside analog, structurally related to guanosine. Its unique mechanism of action inhibits DNA synthesis and thus viral replication, so that it does not affect the latent virus. There is a low incidence of development of resistance, but unwarranted use is unwise.

The antiviral effects of acyclovir are particularly relevant for herpesviruses (q.v.), as follows. It is

- especially effective against **herpes simplex virus** (HSV) types 1 and 2,
- less effective but still very useful for **varicella-zoster virus** (VZV) (q.v.),
- of intermediate efficacy against **Epstein–Barr virus** (EBV) (q.v.),
- ineffective against **cytomegalovirus** (CMV) (q.v.), but the related agent, **ganciclovir**, is however effective against CMV – see below.

The greatest value of acyclovir is in **HSV encephalitis**, in which trial results have shown a survival rate of about 80% and complete neurological recovery in about 50%.

It is also of value in oral-labial, genital, rectal and neonatal HSV infections.

In **VZV infections**, it is helpful in

- the elderly, especially those with widespread lesions or trigeminal involvement,
- herpes zoster encephalitis,
- varicella pneumonia,
- immunocompromised patients (in whom interferon alpha and/or VZV immune globulin are also useful).

Acyclovir

- is not indicated in **infectious mononucleosis**, except perhaps in severe cases,
- is not indicated in **cytomegalovirus infections**, except for prophylaxis after bone marrow transplantation in seropositive patients, in whom it is effective when given in high dosage, i.e. 500 mg/m^2 tds IV for the first month),
- is not effective in the **chronic fatigue syndrome** (q.v.).

Acyclovir is not protein-bound but is distributed evenly throughout the total body water, except in the CSF in which the level is 25–50% of that in plasma. The urinary concentration is about 10 times the plasma concentration. It has a half-life of about 3 hr, which rises 6-fold in severe renal failure, since it is primarily excreted in the urine. It is 60% removed by dialysis. It is probably not mutagenic or carcinogenic. Although fetal risk has not been shown, it crosses the placenta and should be used in pregnancy only if there is a strong maternal indication. It is excreted into breast milk.

It is available as a powder for IV administration, as capsules for oral use and as an ointment for mucocutaneous lesions or keratitis. Intravenously, it is given as 5–10 mg/kg 8 hrly for 5–10 days. Typically, 500 mg are reconstituted in 20 mL, diluted to 100 mL and administered over 1 hr, giving a mean steady-state peak plasma concentration of 20 mcg/mL.

Although the solution is widely compatible, it undergoes irreversible crystallization if refrigerated. Intravenous acyclovir is normally well tolerated, but it is potentially phlebitic because of its alkaline nature unless given diluted and slowly, and it can sometimes give rise to nausea or a rash. Rarely, reversible encephalopathy or renal dysfunction may occur from very high concentrations.

Later nucleoside analogs include

- **valacyclovir** (a prodrug of acyclovir) and **famciclovir**, which are useful alternative agents,
- **foscarnet**, which may be used in chronic acyclovir-resistant HSV type 2 infections.

Ganciclovir is structurally similar to acyclovir and is given in similar dosage. Its chief difference is that it is active against cytomegalovirus (q.v.). It is therefore used, often with immune globulin, in CMV retinitis or pneumonia, for example after bone marrow transplantation. Unlike acyclovir, it can produce bone marrow depression. It is teratogenic and mutagenic in animals. The usual dosage is 5 mg/kg IV 12 hrly.

Valganciclovir is a prodrug of ganciclovir with much higher bioavailability.

See also

- Bell's palsy,
- Encephalitis.

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Addison's disease *See*

- Adrenal insufficiency.

Adenosine

Adenosine is an autacoid (q.v.). It is an endogenous purine nucleoside of molecular weight 267 Da, and it has receptors (A1 or A2) on most cell membranes. It is released when ATP is used and may thus help maintain the balance between oxygen availability and utilization. It is involved in many local regulatory processes, and in particular it is a vasodilator and an inhibitor of neuronal discharge. Adenoreceptors are present on phagocytes as well as in cardiac myocytes, and there is evidence that

their modulation may prevent tissue injury in ischaemia and sepsis.

Its cardiac effects were first recognized in 1929 and are extensive. They especially involve decreased conduction and ventricular automaticity, coronary vasodilatation and the blunting of the effects of catecholamines. On balance, it is thus 'cardioprotective'. Both A1 and A2 receptors are present in the heart – A1 in the cardiomyocytes and A2 in the endothelial cells and vascular smooth muscle cells.

Clinically, its particular use is in the diagnosis and treatment of **tachyarrhythmias**.

- It is of most value in the treatment of supraventricular tachycardia, especially that associated with the WPW syndrome, with an average time to termination of arrhythmia of 30 sec.
- It has no effect in atrial fibrillation or atrial flutter.
- It is not of value in ventricular tachycardia unless catecholamine induced.

Its effects are antagonized by theophylline and potentiated by dipyridamole, but it may be administered without altered efficacy in the presence of other cardiac drugs or in liver or renal disease.

It is of potential clinical use in electrophysiological studies, in cardiac stress testing and in the assessment of coronary blood flow reserve. It has no useful effect on coronary ischaemia.

Since its half-life is only 10 sec, it is given as a rapid IV bolus of 3–6 mg. A further bolus of up to 12 mg may be given 1–3 min later if necessary.

It can produce unpleasant and marked though transient side-effects, including flushing (q.v.), sweating (q.v.), tingling, headache, light-headedness, nausea and apprehension. Bronchospasm may be precipitated in asthmatics. It can also produce cardiac pain, which is angina-like but not in fact ischaemic.

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Adrenal insufficiency

Acute adrenal insufficiency is an uncommon condition and is usually due to haemorrhage (especially from heparin – q.v.), hypotension or shock (as in the Waterhouse–Friderichsen syndrome – q.v.).

It thus occurs mostly in seriously ill patients, in whom it should remembered as an uncommon cause of the **hyperdynamic state** (q.v.).

The clinical features include nausea, weakness and abdominal pain, as well as circulatory failure. Typically, there is hyponatraemia (q.v.) with hyperkalaemia, and the plasma urea may be elevated.

Relevant investigations include failure of the plasma cortisol level to increase after the injection of synthetic ACTH (see below) and direct imaging with CT.

*Treatment is with physiological doses of **hydrocortisone** IV.*

Relative adrenal insufficiency (RAI) refers to a clinical scenario that has been increasingly recognized in seriously ill patients since the 1990s, though there remains controversy about its definition, its relevance and even its existence. Unlike (absolute) acute adrenal insufficiency (see above), it is probably frequent, but it has no particular set of clinical features. Instead, it represents an exacerbation of the responses to severe illness or injury and is chiefly manifest in retrospect as circulatory improvement in catecholamine-dependence after physiological doses of hydrocortisone, particularly in sepsis. Presumably, like other organs and pathways, the hypothalamic–pituitary–adrenal (HPA) axis (q.v.) has been impaired in this setting, although paradoxically the basal cortisol levels in critically ill patients are generally high and independent of the usually low ACTH level at this time (probably because some cytokines have ACTH-like activity).

A task force developing consensus guidelines in 2008 (and updated in 2017) coined the term **critical illness–related corticosteroid insufficiency** (CIRCI) to reflect the additional concept of an inadequate cellular or tissue response to endogenous corticosteroid contributing to the severity of the patient's illness. However, since the diagnosis of tissue corticosteroid resistance remains difficult, practical diagnosis relies on the principles described below.

The identification of relative adrenal insufficiency requires a high level of suspicion and the demonstration of an abnormal synthetic ACTH test (see below). However, like most laboratory tests which have been developed in well subjects or stable patients, the interpretation of this test can be controversial, especially in seriously ill patients, i.e. the very ones in whom the test is most important. This difficulty is compounded by

- hypoalbuminaemia, because most circulating total cortisol is protein-bound and it is the free cortisol

which is active (but which is not currently measurable in most laboratories), and
- a commonly blunted ACTH response, presumably because of existing maximal stimulation.

Nevertheless, the practical implication is that physiological doses of glucocorticoid appear to be of therapeutic benefit, especially in improving inotrope responsiveness in circulatory failure. This is an area of ongoing clinical research. A common practice has been that if the synthetic ACTH is not clearly normal (see below), a therapeutic trial of hydrocortisone (e.g. 100 mg IV 8 hrly or 200 mg per day by IV infusion) can be warranted. However, given the controversy about the ACTH test in this situation (see above), those who prescribe hydrocortisone in such cases most commonly do so empirically and without a prior ACTH test. Such cases include septic shock, ARDS, trauma, community-acquired pneumonia, bacterial meningitis, cardiopulmonary bypass and after cardiac arrest. However, given the heterogeneity of steroid-responsiveness among patients with these conditions, it is likely that genomic studies will be needed to clarify optimal treatment regimens.

An additional point of interest in this area is that the greatly increased risk of relative adrenal insufficiency in patients who have been given the sedative agent, **etomidate**, now provides a contraindication to the use of that drug in Intensive Care practice.

Chronic adrenal insufficiency (Addison's disease) is due to
- autoimmune disease (sometimes polyglandular),
- a space-occupying lesion, typically a metastasis or granuloma (e.g. TB),
- pituitary deficiency, due to
  - global hypopituitarism (when hypothyroidism (q.v.) is also typically present), or
  - previous administration of corticosteroids in pharmacological doses (when diabetes is commonly associated),
- HIV infection (q.v.), with associated CMV adrenal infection,
- drugs, such as ketoconazole, rifampicin.

Clinical features comprise
- weakness,
- weight loss,
- pigmentation (q.v.), especially in body creases,
- hypotension,
- hypovolaemia (except that blood volume remains normal in pituitary deficiency (q.v.), since aldosterone secretion is primarily controlled by the renin–angiotensin system (q.v.)).

Investigations show mild hyperkalaemia and proneness to hyponatraemia (q.v.) from water overload. In patients who are sufficiently hypovolaemic to have prerenal renal failure, there is more marked hyperkalaemia with hypoglycaemia, raised plasma urea and raised haematocrit.

Specific testing shows a low plasma cortisol, which fails to rise after **synthetic ACTH** 250 mcg IV (normal >150 nmol/L and a rise at 30 min by at least 300 nmol/L to a peak of >550 nmol/L). This short synthetic ACTH stimulation test is simple and safe. In septic patients, the cortisol rise rather than the basal level has correlated best with outcome (but see above).

If adrenal insufficiency is clinically overt and corticosteroids have been commenced, confirmatory testing is very difficult, unless dexamethasone can be temporarily substituted and then ceased pending a long (i.e. 3-day) synthetic ACTH stimulation test.

The plasma ACTH level is >20 pmol/L in primary adrenal failure, but in hypopituitarism it is low (as are the other pituitary hormones – q.v.). A rise in plasma cortisol still occurs in hypopituitarism following ACTH, though this may be subnormal due to chronic ACTH deficiency.

*Treatment of adrenal insufficiency is urgent if there is circulatory failure (i.e. adrenal crisis), with **hydrocortisone** 100 mg IV then 10–15 mg/hr, together with fluids, electrolytes and glucose. Chronic treatment requires maintenance therapy with cortisone (approximately 35 mg per day given about 2/3 in the morning and 1/3 in the evening), together with fludrocortisone 100 mcg per day.*

Patients with adrenal insufficiency exposed to stress require increased doses of corticosteroids.

Typically, double the usual dose is used for minor stress and hydrocortisone 100 mg IV 8 hrly for severe stress, though recently it has become recognized that these doses are excessive. In fact, doses of 25–150 mg of hydrocortisone per day for a maximum of 3 days are adequate.

Hypothalamic–pituitary–adrenal (HPA) (q.v.) function is suppressed by previously administered corticosteroids in pharmacological doses (even in the inhaled form in children).
- This may not recover for a year or more after such steroids are ceased.
- There is no simple and accurate prediction of hormonal reserve function, based on the previous dose or duration of steroid treatment.
- Prophylactic hydrocortisone (as above) is also routinely recommended in such patients exposed to