

4 Point of care testing

The methods for measuring some biological compounds in blood and urine have become so robust and simple to use that measurements can be made away from the laboratory – by the patient's bedside, in the ward sideroom, at the GP's surgery, at the Pharmacy or even in the home. Convenience and the desire to know results quickly, as well as expectation of commercial profit by the manufacturers of the tests, have been the major stimuli for these developments. Experience has shown that motivated individuals, e.g. diabetic patients, frequently perform the tests as well as highly qualified professionals.

The immediate availability of results at the point of care can enable the appropriate treatment to be instituted quickly and patients' fears can be allayed. However, it is important to ensure that the limitations of any test and the significance of the results are appreciated by the tester to avoid inappropriate intervention or unnecessary anxiety.

Outside the laboratory

Table 4.1 shows what can be commonly measured in a blood sample outside the normal laboratory setting. The most common blood test outside the laboratory is the determination of glucose concentration in a finger stab sample, at home or in the clinic. Diabetic patients who need to monitor their blood glucose on a regular basis can do so at home or at work using one of many commercially available pocket-sized instruments.

Figure 4.1 shows a portable bench analyser. These analysers may be used



Fig 4.1 A portable bench analyser.

to monitor various analytes in blood and urine and are often used in outpatient clinics.

Table 4.2 lists urine constituents that can be commonly measured away from the laboratory. Many are conveniently measured, semi-quantitatively, using test strips which are dipped briefly into a fresh urine sample. Any excess urine is removed, and the result assessed after a specified time by comparing a colour change with a code on the side of the test strip container. The information obtained from such tests is of variable value to the tester, whether patient or clinician.

The tests commonly performed away from the laboratory can be categorized as follows:

A. *Tests performed in medical or nursing settings.* They clearly give valuable information and allow the practitioner to reassure the patient or family or initiate further investigations or treatment.

B. *Tests performed in the home, or non-clinical setting.* They can give valuable information when properly and appropriately used.

C. *Alcohol tests.* These are sometimes used to assess fitness to drive. In clinical practice alcohol measurements need to be carefully interpreted. In the Accident and Emergency setting extreme caution must be taken before one can fully ascribe confusion in a patient with head injury to the effects of alcohol, a common complicating feature in such patients.

Table 4.1 Common tests on blood performed away from the laboratory

Analyte	Used when investigating
Blood gases	Acid-base status
Glucose	Diabetes mellitus
Urea	Renal disease
Creatinine	Renal disease
Bilirubin	Neonatal jaundice
Therapeutic drugs	Compliance or toxicity
Salicylate	Detection of poisoning
Paracetamol	Detection of poisoning
Cholesterol	Coronary heart disease risk
Alcohol	Fitness to drive/confusion, coma

Table 4.2 Tests on urine performed away from the laboratory

Analyte	Used when investigating
Ketones	Diabetic ketacidosis
Protein	Renal disease
Red cells/haemoglobin	Renal disease
Bilirubin	Liver disease and jaundice
Urobilinogen	Jaundice/haemolysis
pH	Renal tubular acidosis
Glucose	Diabetes mellitus
Nitrates	Urinary tract infection
HCG	Pregnancy test

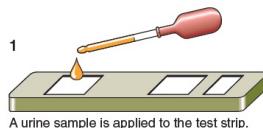
Methodology

It is a feature of many sideroom tests that their simplicity disguises the use of sophisticated methodology. One type of home pregnancy test method involves an elegant application of monoclonal antibody technology to detect the human chorionic gonadotrophin (HCG), which is produced by the developing embryo (Fig. 4.2). The test is simple to carry out; a few drops of urine are placed in the sample window, and the result is shown within 5 minutes. The addition of the urine solubilizes a monoclonal antibody for HCG, which is covalently bound to tiny blue beads. A second monoclonal antibody specific for another region of the HCG molecule, is firmly attached in a line at the result window. If HCG is present in the sample it is bound by the first antibody, forming a blue bead–antibody–HCG complex. As the urine diffuses through the strip, any HCG present becomes bound at the second antibody site and this concentrates the blue bead complex in a line – a positive result. A third antibody recognizes the constant region of the first antibody and binds the excess, thus providing a control to show that sufficient urine had been added to the test strip, the most likely form of error.

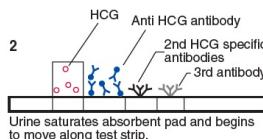
General problems

The obvious advantages in terms of time saving and convenience to both patient and clinician must be balanced by a number of possible problems in the use of these tests. They include:

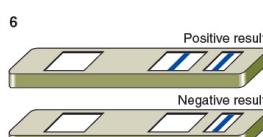
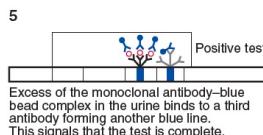
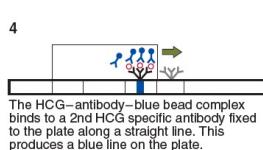
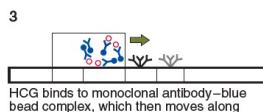
■ **Cost.** Many of these tests are expensive alternatives to the traditional methods used in the laboratory. This additional expense must be justified, for example, on



A urine sample is applied to the test strip.



Urine saturates absorbent pad and begins to move along test strip.



A positive result is shown by 2 blue lines; a negative result is shown by 1 blue line.
Fig 4.2 How a pregnancy test kit works.

the basis of convenience or speed of obtaining the result.

■ **Responsibility.** The person performing the assay outside the laboratory (the operator) must assume a number of responsibilities that would normally be those of the laboratory staff. There is the responsibility to perform the assay appropriately and to provide an answer that is accurate, precise and meaningful. The operator must also record the result, so that others may be able to find it (e.g. in the patient's notes), and interpret the result in its clinical context.

Analytical problems

Many problems under this heading will have little to do with the assay technology but will be due to operator errors. Tests designed for use outside the laboratory are robust but are by no means foolproof. Most operators will not be trained laboratory technicians but patients, nurses or clinicians. If an assay is to be performed well these individuals must be trained in its use. This may require the reading of a simple set of instructions (e.g. a home pregnancy test) or attending short training sessions (e.g. the ward-based blood gas analyser). The most commonly encountered analytical errors arise because of failure to:

- calibrate an instrument
- clean an instrument
- use quality control materials
- store reagents or strips in appropriate conditions.

All of these problems can be readily overcome by following instructions carefully. Regular maintenance of the equipment may be necessary, and simple quality control checks should be performed. It should always be possible to arrange simple quality control cross checks with the main biochemistry laboratory.

Interpretive problems

Even when analytically correct results are obtained, there are other problems

which must be overcome before the exercise can be considered a success. The general appropriateness of the test must be considered. If an assay is performed in an individual of inappropriate age, sex, or at the wrong time of day, or month, then the result may be clinically meaningless. Similarly, the nature of the sample collected for analysis should be considered when interpreting the result. Where the results seem at odds with the clinical situation, interference from contaminants (e.g. detergents in urine containers) should be considered as should cross reactivity of the assay with more than one analyte (e.g. haemoglobin and myoglobin).

Any biochemical assay takes all these potential problems into account. However, with extra-laboratory testing, correct interpretation of the result is no longer the laboratory's responsibility but that of the operator.

The future

There is no doubt that in the future, biochemical testing of patients at the point of care will become practical for many of the analytes currently measured in the laboratory. There is, however, likely to be much debate about costs and the clinical usefulness of such non-laboratory-based analyses.

Case history 2

At a village fete, a local charity group was fundraising by performing certain sideroom tests. An 11-year-old boy was found to have a blood glucose of 14.4 mmol/L. His family was concerned, and an hour later his cousin, a recently diagnosed diabetic, confirmed the hyperglycaemia with his home monitoring equipment, and found glycosuria +++.

- What is the significance of these findings?

Comment on page 164.

Point of care testing

- Many biochemical tests are performed outside the normal laboratory setting, for the convenience of patient and clinician.
- Although apparently simple, such tests may yield erroneous results because of operator errors.
- It is important that advice be readily available to interpret each result in the clinical context.

Fig 4.1 A portable bench analyser.

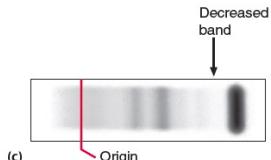
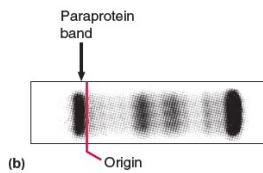
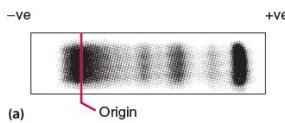


Fig 26.2 Electrophoresis of serum proteins. (a) Normal pattern; (b) paraprotein band; (c) α_1 -antitrypsin deficiency.

significance, but such a diagnosis should be made only after the possibility of myeloma has been excluded by the failure of the disease to progress, as gauged by no increase in the concentration of the paraprotein in serum with time. Regular and careful follow-up of such patients is required.

Deficiencies or absence of immunoglobulins

Deficiencies or absence of immunoglobulins can occur as a result of infection, genetic abnormalities or the effects of therapy (Table 26.2). Where the situation is irreversible, replacement therapy has been used, either by addition of immunoglobulin-rich plasma or by the transplantation of bone-marrow-containing competent plasma cells.

Table 26.2 Causes of hypogammaglobulinaemia

Type	Specific causes
Physiological	Levels of IgA and IgM are low at birth
Genetic	Bruton's X-linked agammaglobulinaemia
	Severe combined immunodeficiency (SCID)
Acquired	Malnutrition
	Malignancy
	Infections, e.g. HIV, measles
	Immunosuppressant drugs, e.g. azathioprine, cyclosporin

Case history 20

A 45-year-old man presented with severe back pain and malaise. He had lost 3 kg weight in 3 months. His blood film showed many primitive RBCs and WBCs. His bone marrow biopsy showed an excess of plasma cells. He did not have a paraprotein band on serum electrophoresis. Analysis of concentrated urine revealed an excess of free monoclonal light chains.

- What is the diagnosis?

Comment on page 166.

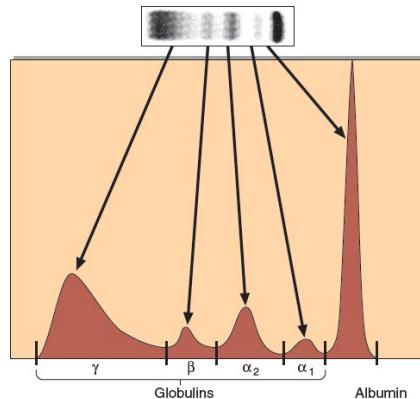


Fig 26.3 Scan of an electrophoresis strip.



Clinical note

The diagnosis of myeloma requires that two of the following are present:

- a paraprotein in serum or urine
- plasma cell infiltration in bone marrow
- myeloma-related end-organ damage, including skeletal lesions (Fig 26.4).



Fig 26.4 Skull X-ray showing osteolytic lesions of myeloma.

Immunoglobulins

- Electrophoresis of serum may confirm the presence of a paraprotein in a specimen from a patient with a raised globulin fraction.
- Some myelomas produce immunological light chains only. These are best demonstrated by urine electrophoresis.
- Immunoglobulin measurements can give information on immune deficiency and response to infection
- Serial study of immunoglobulin levels can be of help in following the progression of disease or in monitoring of treatment.

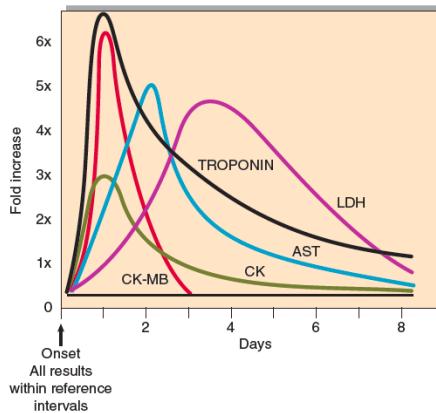


Fig 27.3 Enzymes in serum following an uncomplicated MI.

Diagnosis

The essential components of diagnosis are the history, the characteristic ECG changes and the detection in blood of biochemical markers of myocardial injury. Patients experiencing MI classically complain of severe crushing central chest pain. However, such a characteristic history is not always obtained, and a minority of patients may even have a 'silent' MI. When present, the characteristic ECG changes (Fig 27.2) are specific to MI, but they are equivocal or absent in up to 30% of patients. It is in this group of patients that cardiac markers are most useful.

Cardiac biomarkers

When myocardial cells die, they break up and release their contents. This is the basis for the role of cardiac biomarkers in MI diagnosis. Historically, various 'cardiac enzymes' have been used (Fig 27.3); however, at present, cardiac troponins are used in the diagnosis of MI. Troponin is a complex contractile protein comprising of three subunits: C, T and I. Troponin T and I are cardiospecific (therefore used in MI diagnosis; Tables 27.2 and 27.3), whereas C is also present in skeletal muscle. Troponins rise within a few hours on onset of symptoms and remain elevated for 1–2 weeks. This property enables early as well as late diagnosis. The diagnostic sensitivity of troponin reaches 100% 12 hours after onset of symptoms, i.e. MI can be excluded with confidence with a negative (undetectable) troponin

Table 27.2 Potential roles for troponin measurement

- Diagnosis of acute myocardial infarction (MI)
- Prognosis in acute coronary syndrome
- Diagnosis of perioperative MI (where there is coexistent skeletal muscle damage)
- Monitoring thrombolytic therapy
- Identification of patients who will respond to interventions, e.g. low-molecular-weight heparins, platelet glycoprotein IIb/IIIa antagonists, angioplasty

Table 27.3 Troponins T and I contrasted

	Troponin T	Troponin I
Molecular weight	37 kDa	22.5 kDa
Nature of protein	Structural	Catalytic
Kinetics of release	Biphasic	Only a single peak
Duration of elevation	Up to 14 days	5–7 days
Number of assays	One	Several
Ontogeny	May be expressed in skeletal muscle in utero	Only ever expressed in myocardium

cardiovascular pathologies such as myocarditis, pulmonary embolism and stroke and non-cardiac conditions such as severe sepsis.



Clinical note

The classical feature of an MI is crushing chest pain radiating down the left arm. Not all patients with an MI experience this. In addition to the many variants of angina-like pain, it is recognized that a sizeable proportion of MIs are 'silent', and are subsequently only detected by ECG and/or cardiac markers.

In one European heart study, 2% of middle-aged men showed definite ECG evidence of a previously unrecognized MI.

Case history 21

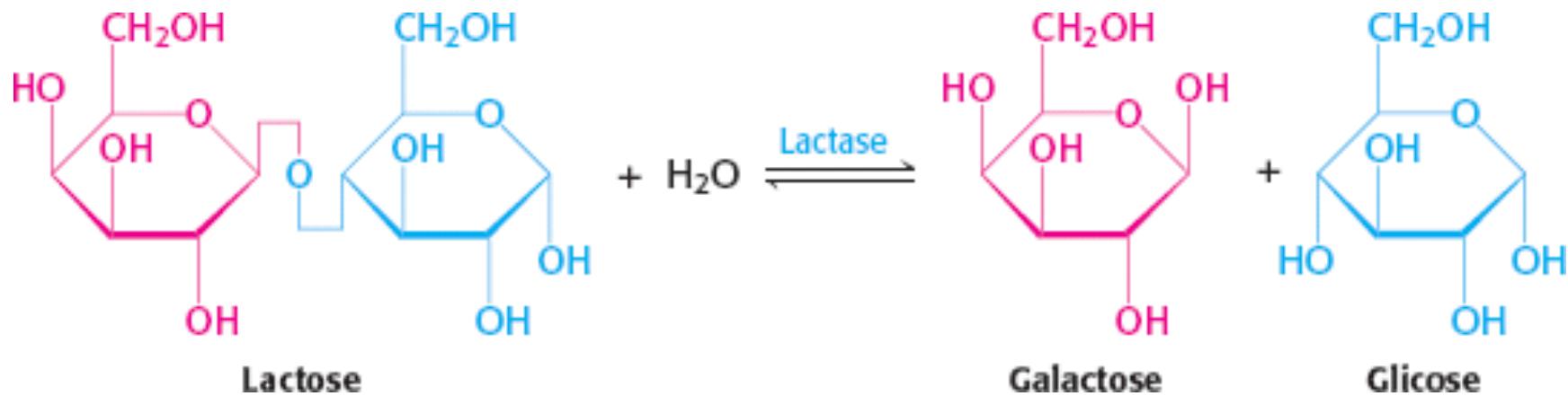
A 52-year-old man presented at the Accident and Emergency department with severe chest pain which had been present for the past hour. He had previously attended the chest pain clinic and had a 2-year history of angina of effort.

- What specific tests would you request from the biochemistry laboratory?
- Comment on page 166.

Myocardial infarction

- A new universal diagnosis of myocardial infarction (MI) has been adopted.
- The cardiac enzymes historically were creatine kinase, aspartate aminotransferase and lactate dehydrogenase.
- Cardiac troponins are considered very specific markers in the diagnosis of AMI and in the monitoring of ACS, but they can also increase in other cardiovascular pathologies, as well as non-cardiac conditions such as severe sepsis.
- Early diagnosis of MI is important so that therapy can be started promptly.
- The finding of a very high serum CK is not usually consistent with AMI and should prompt investigation for an alternative diagnosis such as rhabdomyolysis (skeletal muscle breakdown).

Tema glicólise e gliconeogénese



Quando as crianças são desmamadas e o leite se torna menos importante em suas dietas, a atividade da lactase normalmente diminui para cerca de 5 a 10% do nível por ocasião do nascimento.

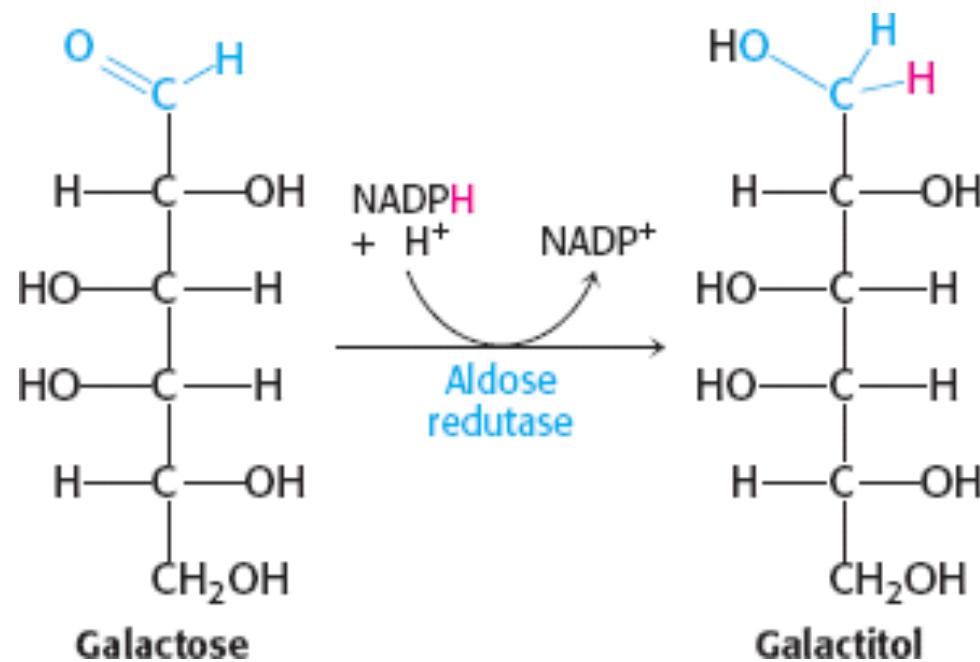
O que acontece com a lactose no intestino de um indivíduo com deficiência em lactase? A lactose é uma boa fonte de energia para os microrganismos do cólon, e estes fermentam a lactose em ácido láctico, enquanto também geram metano (CH_4) e gás hidrogênio (H_2). O gás produzido provoca a desconfortável sensação de distensão abdominal e o problema irritante de flatulência. O lactato produzido pelos microrganismos é osmoticamente ativo e “puxa” água para o lúmen intestinal, como a lactose não digerida, resultando em diarreia. Se intensos o suficiente, o gás e a diarreia impedem a absorção de outros nutrientes, como lipídios e proteínas. O tratamento mais simples é evitar o consumo de produtos contendo muita lactose. Uma opção é usar formulações da enzima lactase ao consumir laticínios.

Tema glicólise e gliconeogénese

Menos comuns do que a intolerância à lactose são os distúrbios que interferem no metabolismo da galactose. O distúrbio do metabolismo da galactose é denominado *galactosemia*. A forma mais comum, a galactosemia clássica, é uma deficiência hereditária na atividade da galactose 1-fosfato uridil transferase. As crianças atingidas apresentam retardamento de crescimento. Vomitam ou apresentam diarreia após consumirem leite, e são comuns hepatomegalia e icterícia, às vezes progredindo para cirrose. A formação de catarata é uma complicação, e também são comuns letargia e retardamento mental. O nível sanguíneo da galactose é muito elevado, e a galactose é encontrada na urina. A ausência da transferase nas hemácias é um critério definitivo de diagnóstico.

Tema 16 glicólise e gliconeogénese

A formação da catarata é mais bem entendida. A catarata consiste em opacificação do cristalino, normalmente transparente. Se a transferase não for ativa no cristalino, a aldose redutase fará com que o acúmulo de galactose seja reduzida a galactitol.



Tema 16 glicólise e gliconeogénese

O galactitol é osmoticamente ativo, e a água difundir-se-á para dentro do cristalino, provocando a formação da catarata. De fato, a incidência de formação de catarata com a idade é elevada nas populações que consomem muito leite na fase adulta.

A



B



Tema 16 glicólise e gliconeogénese

Há décadas sabe-se que os tumores exibem velocidades aumentadas de captação de glicose e de glicólise.

os tumores com uma alta captação de glicose são particularmente agressivos e, provavelmente, sinal de um mau prognóstico. Um análogo não metabolizável da glicose, o $2\text{-}^{18}\text{F-2-D-desoxiglicose}$, detectável por uma combinação de tomografia por emissão de pósitrons (PET) e tomografia auxiliada por computação (CAT), facilmente visualiza os tumores

Tema 16 glicólise e gliconeogénese

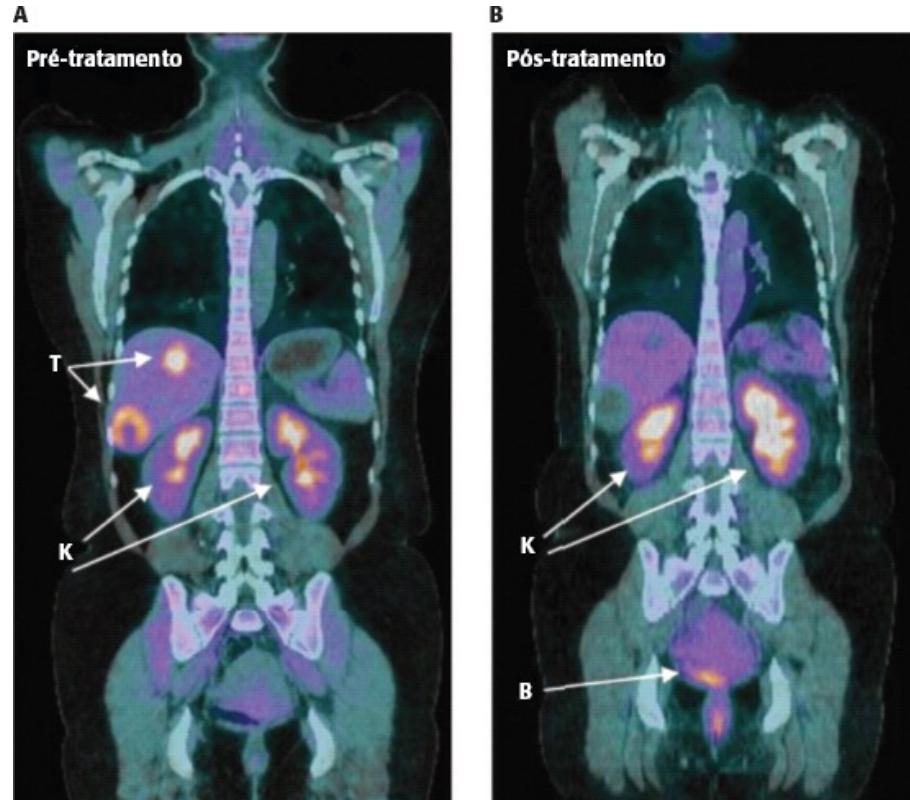
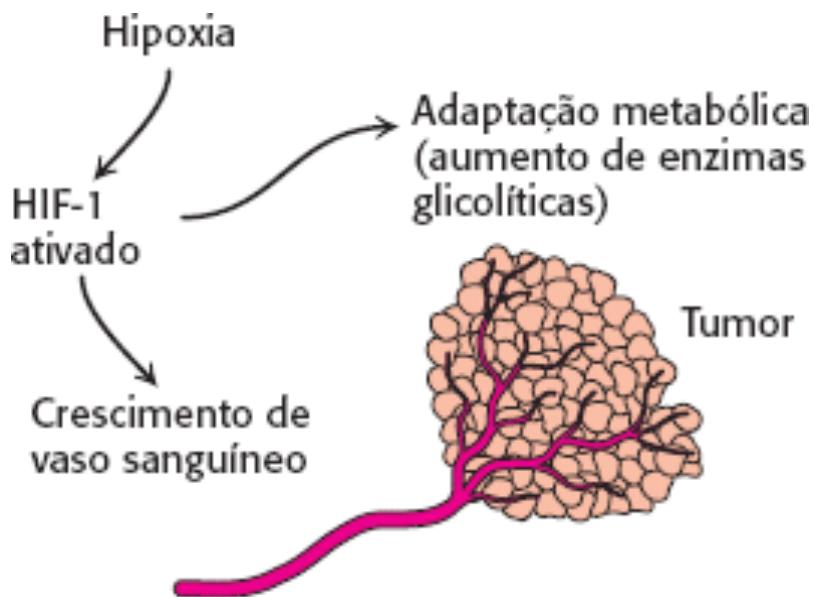


Figura 16.22 Tumores podem ser visualizados com $2\text{-}^{18}\text{F}\text{-2-D-desoxiglicose (FDG)}$ e tomografia por emissão de pósitrons. A. Um análogo não metabolizável da glicose infundido em um paciente e detectado por uma combinação de emissão de pósitrons e de tomografia auxiliada por computação revela um tumor maligno (T). B. Após 4 semanas de tratamento com um inibidor da tirosina quinase (Seção 14.5), o tumor não mostra captação de FDG, que indica metabolismo diminuído. O excesso de FDG, que é excretado na urina, também permite a visualização dos rins (K) e da bexiga (B).

Que vantagem seletiva tem a glicólise aeróbica do tumor sobre a fosforilação oxidativa mais eficiente energeticamente?



Alteração da expressão gênica em tumores devido à hipoxia. As condições de hipoxia intratumorais levam à ativação de um fator de transcrição induzido por hipoxia (HIF-1), que诱导 adaptação metabólica (aumento das enzimas glicolíticas) e ativa fatores angiogênicos que estimulam o crescimento de novos vasos sanguíneos.

25 Proteins and enzymes

Plasma proteins

The biochemistry laboratory routinely measures 'total protein' and 'albumin' concentrations, usually in a serum specimen, and reports the 'globulin' fraction as the difference between the first two results. Some proteins (e.g. immunoglobulins) are measured as classes, and immunochemical methods are available for measuring specific proteins and hormones. Enzymes are measured both by determining their activity and by immunochemical methods to assess their mass.

Total protein

Changes in total protein concentration are common. An elevated total protein concentration may mean the presence of a paraprotein. A decreased total protein usually means that the albumin concentration is low.

Albumin

Albumin is the major plasma protein and is synthesized and secreted by the liver. It has a biological half-life in plasma of about 20 days and it accounts for about 50% of the total hepatic protein production. Albumin makes the biggest contribution to the plasma oncotic pressure. If the albumin concentration falls very low, oedema is the result (Fig 25.1). There are four main reasons for the occurrence of a low plasma albumin concentration:

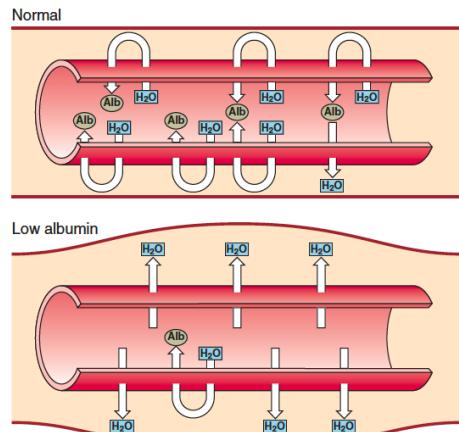


Fig 25.1 Pathogenesis of oedema in hypoalbuminaemia.

- **Abnormal distribution.** Albumin can move into the interstitial space as a result of increased capillary permeability in the acute phase response.

- **Decreased synthesis.** Due to malnutrition, malabsorption or advanced chronic liver disease.

- **Dilution.** Hypoalbuminaemia can be induced by overhydration.

- **Abnormal excretion or degradation.** The causes include the nephrotic syndrome, protein-losing enteropathies, burns, haemorrhage and catabolic states.

Although serum albumin measurements have previously been used to monitor a patient's response to long-term nutritional support, they are unreliable and insensitive.

Specific proteins

Measurement of a number of specific proteins gives useful information in the diagnosis and management of disease (Table 25.1). Characteristic changes in the concentration of certain plasma proteins are seen following surgery or trauma, or during infection or tumour growth. The proteins involved are called acute phase reactants (pp. 110–111). These acute phase proteins may be used

to monitor progress of the condition or its treatment.

Enzymes

Serum enzymes in disease

Enzymes may be classified in two groups. Some, such as the enzymes of the coagulation cascade, have a defined function in blood. Others appear in the blood incidentally and their measurement is of value in diagnosis. Damage to the tissues of origin, or proliferation of the cells from which these enzymes arise, will lead to an increase in the activity of these enzymes in plasma (Fig 25.2). It should be noted that increases in serum enzyme activity are only roughly proportional to the extent of tissue damage.

Enzymes that have been shown to have a diagnostic value are:

- **Alanine aminotransferase (ALT):** an indicator of hepatocellular damage.
- **Alkaline phosphatase:** increases in cholestatic liver disease and a marker of osteoblast activity in bone disease.
- **Amylase:** an indicator of cell damage in acute pancreatitis.
- **Aspartate aminotransferase (AST):** an indicator of hepatocellular damage, or a marker of muscle damage.

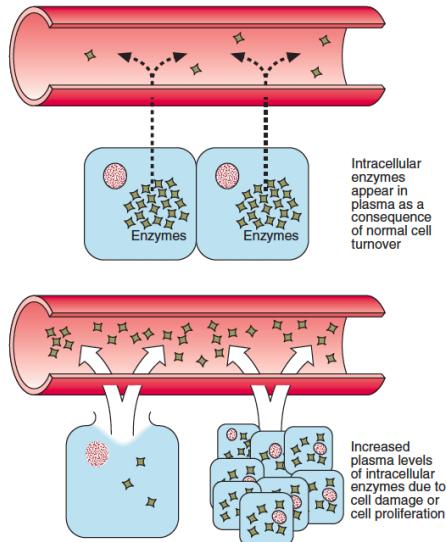


Fig 25.2 Plasma levels of intracellular enzymes.

62 Alcohol

Abuse of alcohol (ethanol) is a major contributor to morbidity and mortality, far outstripping other drugs in its effects on the individual and on society. Alcohol is a drug with no receptor. The mechanisms by which it exerts its detrimental effect on cells and organs are not well understood, but the effects are summarized in Table 62.1.

For clinical purposes alcohol consumption is estimated in arbitrary 'units' – one unit representing 200–300 mmol of ethanol. The ethanol content of some common drinks is shown in Figure 62.1. The legal limit for driving in the UK is a blood alcohol level of 17.4 mmol/L (80 mg/dL).

Table 62.1 Effects of ethanol on organ systems

System	Condition	Effect
CNS	Acute	Disorientation → coma
	Chronic	Memory loss, psychosis
	Withdrawal	Seizures, delirium tremens
Cardiovascular	Chronic	Cardiomyopathy
	Skeletal muscle	Myopathies
Gastric mucosa	Acute	Irritation, gastritis
	Chronic	Ulceration
Liver	Chronic	Fatty liver → cirrhosis, decreased tolerance to xenobiotics
	Acute	Diuresis
Kidney	Acute	Anaemia, thrombocytopenia
Blood	Chronic	Impotence
Testes	Chronic	



Fig 62.1 Alcohol content of common drinks.

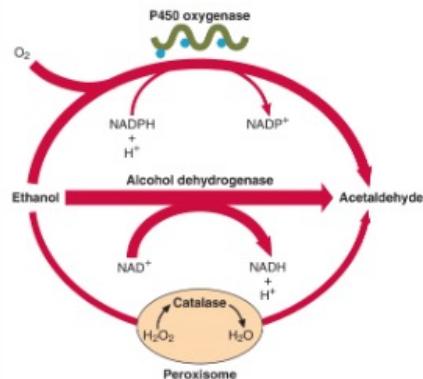


Fig 62.2 The metabolism of ethanol.

Metabolism of ethanol

Ethanol is metabolized to acetaldehyde by two main pathways (Fig 62.2). The alcohol dehydrogenase route is operational when the blood alcohol concentration is in the range 1–5 mmol/L. Above this most of the ethanol is metabolized via the microsomal P450 system. Although the end product in both cases is acetaldehyde, the side effects of induced P450 can be significant. Ethanol metabolism and excretion in a normal 70 kg man is summarized in Figure 62.3.

Acute alcohol poisoning

The effects of ethanol excess fall into two categories:

- those that are directly related to the blood alcohol concentration at the time, such as coma
- those that are caused by the metabolic effects of continued high ethanol concentrations.

The relative contribution of ethanol in cases of coma, especially where other drugs and/or head injury are present, may be difficult to distinguish. Blood ethanol determinations are the best guide. Where these are not available, plasma osmolality measurement and calculation of the osmolar gap may help.

Recovery from acute alcohol poisoning is usually rapid in the absence of renal or hepatic failure, and is speeded up if hepatic blood flow and oxygenation is maximized. The elimination rate of ethanol is dose-related; at a level of 100 mmol/L it is around 10–15 mmol/hour. Ethanol concentrations in a group of chronic alcoholics admitted in coma with acute alcohol poisoning are shown in Figure 62.4.

Alcohol inhibits gluconeogenesis and some patients are prone to develop hypoglycaemia 6–36 hours after alcohol ingestion, especially if they are malnourished or fasted. A small number of these malnourished patients develop alcoholic ketoacidosis.

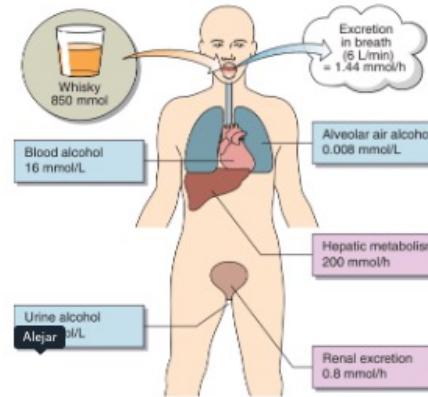


Fig 62.3 Metabolism and excretion of alcohol.

Chronic alcohol abuse

Many of the effects of chronic alcohol abuse are due either to the toxicity of acetaldehyde and/or the failure of one or more of the many homeostatic and synthetic mechanisms in the liver. One of the earliest signs of chronic alcohol abuse is hepatomegaly. This results from the accumulation of triglyceride due to increased synthesis from the carbohydrate load and reduced protein synthesis. Continued high ethanol intake may cause the following sequelae:

- impaired glucose tolerance and diabetes mellitus
- hypertriglyceridaemia
- cirrhosis of the liver with resultant decreased serum albumin concentration
- portal hypertension with resultant oesophageal varices
- coagulation defects
- cardiomyopathy
- peripheral neuropathy.

Diagnosis of chronic alcohol abuse

Chronic alcohol abuse can be very difficult to detect and is usually determined from the patient's history. In order to be more objective, there has been a continued search for markers of ethanol abuse. As yet there is no highly sensitive and specific marker. However, a number of blood components are altered and these can give an indication of chronic alcohol ingestion. The most commonly used are:

- Elevated γGT. This enzyme is increased in 80% of alcohol abusers. It is not a specific indicator as it is increased in all forms of liver disease and is induced by drugs such as phenytoin and phenobarbital.
- Elevated serum triglyceride.
- Hyperuricaemia.

There are a number of other potentially useful markers, notably isoforms of transferrin that are deficient in the carbohydrate linked to the protein. This carbohydrate-deficient transferrin is present in more than 90% of patients

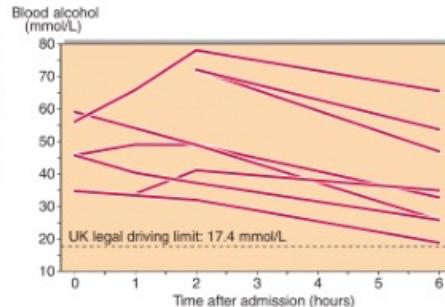


Fig 62.4 Alcohol concentrations in patients admitted in a coma

with chronic alcohol abuse. Such assays are not yet widely available.

Once the diagnosis of chronic alcohol abuse is made, these markers are of use in monitoring behaviour, since a single 'binge' will lead to their derangement. γGT is used regularly in this manner.

Chronic alcohol abuse exposes the individual to increased risk of damage from other substances. Chronic alcoholics have higher rates of smoking-related disease, and are more susceptible to poisoning with hepatotoxic substances. They also have different rates of metabolism of therapeutic drugs and care needs to be taken in treating them with drugs that are metabolized by the cytochrome P450 system.

Admission rates to hospital with alcohol-related diseases are high, and since the diagnosis is sometimes unsuspected, it should always be considered when carrying out an initial examination (Fig 62.5).

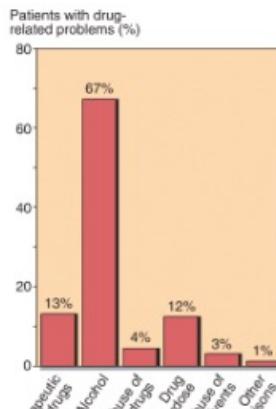


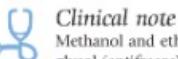
Fig 62.5 Admissions of drug-related problems to one UK hospital.

Case history 51

A 16-year-old boy whose epilepsy had recently become poorly controlled was found to have a raised γGT of 82 U/L. Because of his troublesome behaviour his parents suspected he was drinking.

- How might alcohol abuse be confirmed or excluded?
- His serum alkaline phosphatase was 520 U/L. Does this support a diagnosis of alcoholic liver disease?

Comment on page 169.



Clinical note

Methanol and ethylene glycol (antifreeze) are both metabolized by alcohol dehydrogenase to formic and oxalic acids, which are toxic. In order to prevent this metabolism, ethanol is infused to a concentration of 20 mmol/L until the alcohols, methanol and ethylene glycol, are excreted unchanged. Alcoholics who drink ethanol as well as **methanol** in fact protect themselves against the worst effects of methanol poisoning.

Alcohol

- Ethanol abuse is a common clinical problem.
- An elevated serum osmolality and an increased osmolar gap can be of diagnostic value in acute ethanol poisoning.
- Chronic ethanol abuse can be difficult to detect.
- Serum γGT is of limited value for diagnosis of ethanol abuse but good for monitoring abstinence.
- The effects of chronic alcohol abuse are not limited to the liver.

43 Growth disorders and acromegaly

Normal growth

Growth in children can be divided into three stages (Fig 43.1). Rapid growth occurs during the first 2 years of life; the rate is influenced by conditions in utero, as well as the adequacy of nutrition in the postnatal period. The next stage is relatively steady growth for around 9 years and is controlled mainly by growth hormone (GH). If the pituitary does not produce sufficient growth hormone, the yearly growth rate during this period may be halved and the child will be of short stature. The growth spurt at puberty is caused by the effect of the sex hormones in addition to continuing GH secretion. The regulation of GH secretion is outlined in Figure 43.2.

GH is only one of many hormones involved in growth. Insulin-like growth factors, thyroxine, cortisol, the sex steroids and insulin are also involved.

Growth hormone insufficiency

Any child whose height for age falls below the 3rd centile on a standard chart, or who exhibits a slow growth rate, requires further investigation. If GH deficiency is diagnosed, and treatment is required, then the earlier it is given the better the chance that the child will eventually reach normal size.

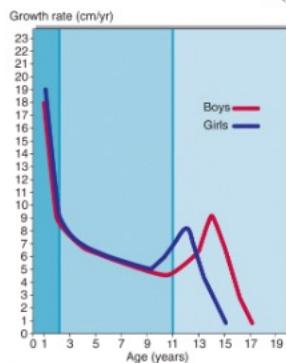


Fig 43.1 Median height velocity curve for boys and girls showing the three growth stages.

Growth hormone insufficiency is a rare cause of impaired physical growth. It is important to differentiate between children whose slow growth or growth failure is due to illness or disease and those whose short stature is a normal variant of the population. Causes of short stature are:

- having parents who are both short
- inherited diseases such as achondroplasia, the commonest cause of severe dwarfism
- poor nutrition
- systemic chronic illness, such as renal disease, gastrointestinal disorders or respiratory disease
- psychological factors such as emotional deprivation
- hormonal disorders.

Standard graphs relating age and height are available for the normal population. Accurate measurements of height should be made to establish whether a child is small for chronological age. These measurements are repeated after 6 and 12 months to assess the growth rate. The height of the parents should also be assessed. The bone age is the best predictor of final height in a child with short stature: this is determined by radiological examination of hand and wrist.

In most growth disorders bone age is delayed and by itself is of little diagnostic value, but taken together with height and chronological age, a prediction of final height may be obtained.

Tests of growth hormone insufficiency

Growth hormone deficiency may be present from birth or due to later pituitary failure. A variety of stimulation tests have been used to evaluate GH deficiency. Serum GH concentrations rise in response to exercise and this may be used as a preliminary screening test. They also rise during sleep, and high concentrations in a nocturnal sample may exclude GH deficiency. The lack of GH response to the stress of exercise or

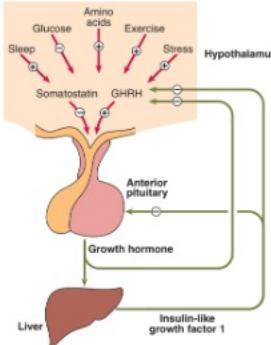


Fig 43.2 The normal regulation of GH secretion.



Clinical note

In the investigation of normal looking children with short stature, coeliac disease must always be considered. The diagnosis is frequently overlooked.

clonidine, a potent stimulant of GH secretion, is diagnostic. Some centres have now abandoned the use of insulin-induced hypoglycaemia as a diagnostic test in children because of its hazards, and instead use the arginine stimulation test.

The GH response to stimulation requires the presence of sex steroids. Thus prepubertal children, and hypogonadal adults, require 'priming' by the administration of either testosterone or oestrogen before GH reserve is assessed.

Increasingly, urinary growth hormone measurements are being used to assess possible GH lack in children. Random serum IGF-1 determinations may be of value. Levels within reference limits exclude GH deficiency.

Treatment

Genetically engineered GH is available and is used in the treatment of that small group of children with proven GH deficiency.



Fig 43.3 Clinical picture of an acromegalic patient.

Excessive growth

Growth hormone excess in children is characterized by extremely rapid linear growth (gigantism). The condition is uncommon and is most often due to a GH secreting pituitary tumour. Other causes of tall stature in children are rare and include:

- **Hyperthyroidism.** An increased growth rate with advanced bone age, is a feature of hyperthyroidism in children, or hypothyroid children over-replaced with thyroxine.
- **Inherited disorders** such as Klinefelter's syndrome (a 47 XXY karyotype). The relative deficiency of testosterone is associated with delayed epiphyseal closure.
- **Congenital adrenal hyperplasia.** (CAH) may cause rapid somatic growth in children, but usually leads to suboptimal adult height due to premature epiphyseal closure, as a result of androgen excess.

Acromegaly

Increased GH secretion later in life, after fusion of bony epiphyses, causes acromegaly (Fig 43.3). The most likely cause is a pituitary adenoma. Clinical features include:

- coarse facial features
- soft tissue thickening, e.g. the lips
- characteristic 'spade-like' hands
- protruding jaw (prognathism)
- sweating

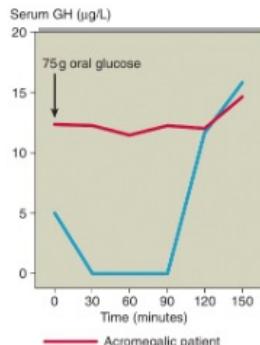


Fig 43.4 The response of GH in a glucose tolerance test in a normal and acromegalic patient.

biochemical information. It is now routinely measured in the diagnosis and especially monitoring of treated acromegaly, with an elevated level suggestive of active disease. Other measurements, e.g. IGF binding protein 3 (IGFBP3), have not yet attained widespread clinical use.

Treatment

- **Surgery.** Trans-sphenoidal hypophysectomy is the first-line treatment for most acromegalic patients. Its success depends on the size of the tumour.
- **Radiation.** This is usually reserved for patients whose disease remains active despite surgery. It may take years after pituitary irradiation before safe levels of GH are achieved. Medical treatment is required in the interim.
- **Medical.** Dopamine agonists like bromocriptine were widely used in the past, but response rates were low. The advent of long-acting synthetic analogues of somatostatin, such as octreotide, has transformed the medical management of acromegaly. These are expensive drugs with side effects, and it is sensible to screen patients for responsiveness by measuring GH after administering octreotide (octreotide suppression test).
- impaired glucose tolerance or diabetes mellitus.

Diagnosis

Formal diagnosis of acromegaly requires an oral glucose tolerance test with GH measurement (see pp. 82–83). Acromegalic patients do not suppress fully in response to hyperglycaemia (Fig 43.4), and indeed in some patients a paradoxical rise in GH may be observed.

IGF 1 is produced in response to GH and provides useful additional

Case history 33

James is 5 years old and is much smaller than his classmates at school. His growth rate has been monitored and has clearly dropped off markedly in the past year. He is an active child, and on examination has normal body proportions. His mother and father are of average height. His bone age is that of a 3-year-old child.

- What biochemical tests would be appropriate in the investigation of this boy?

Comment on page 167.

Growth disorders and acromegaly

- GH deficiency is a rare cause of short stature in children, and is investigated only after other causes of short stature have been eliminated.
- Diagnosis of GH deficiency is made on the failure of serum GH to rise in response to stimuli.
- Gigantism in children is caused by increased GH secretion, usually from a pituitary tumour. Acromegaly is the consequence of increased GH secretion in adults.
- Lack of suppression of serum GH levels in response to a glucose tolerance test is the diagnostic test for acromegaly.
- Serum IGF 1 concentrations are of value in the diagnosis of acromegaly and the monitoring of treatment.

50 Gonadal function

Sex steroid hormones

Testosterone is the principal androgen and is synthesized by the testes in the male. Oestradiol, which is secreted by the ovaries, varies widely in concentration in plasma throughout the female menstrual cycle. Steroids with oestriadiol-like action are called oestrogens. Progesterone is also a product of the ovary and is secreted when a corpus luteum forms after ovulation. Normal female plasma also contains a low concentration of testosterone, about half of which comes from the ovary and half from peripheral conversion of androstenedione and dehydroepiandrosterone (DHA) sulphate, which are secreted by the adrenal cortex. Some oestradiol is present in low concentration in normal male plasma.

Testosterone and oestradiol circulate in plasma mostly bound to plasma proteins, particularly sex hormone-binding globulin (SHBG). The plasma concentration of SHBG in females is twice that in males. In both sexes the effect of an increase in SHBG is to increase oestradiol-like effects, whereas a decrease in SHBG increases androgen effects.

In females, testosterone and SHBG concentrations are sometimes reported by the laboratory as a ratio (the free androgen index), which gives a clearer indication of androgen status than does serum testosterone alone. In males, calculated free testosterone (using equations) is a more reliable indicator than measured total testosterone; free androgen index is not useful.

Hypothalamic–pituitary–gonadal axis

The episodic secretion of the hypothalamic hormone, gonadotrophin-releasing hormone (GnRH), stimulates synthesis and release of the gonadotrophins. LH (luteinizing hormone) and FSH (follicle-stimulating hormone), from the anterior pituitary. Despite the names, both gonadotrophins act cooperatively on the ovaries in the woman and the testes in the man to stimulate sex hormone secretion and reproductive processes.

Male gonadal function

The testes secrete testosterone and manufacture spermatozoa. Before puberty, gonadotrophin and testosterone concentrations in plasma are very low. The development of the Leydig cells and their secretion of testosterone is influenced by LH, whereas Sertoli cell function is influenced by FSH (Fig 50.1). Testosterone is responsible for the development of the male secondary sex characteristics such as hair growth, deep voice and characteristic musculature.

Disorders of male sex hormones

Hypogonadism may result in deficient sperm production and decreased testosterone secretion. This may be due to a testicular deficiency (primary disorders or hypergonadotrophic hypogonadism) or to a defect in the hypothalamus or pituitary (secondary disorders or hypogonadotropic hypogonadism). In hypogonadotropic hypogonadism both gonadotrophins, or only LH, may be reduced. There may be a generalized failure of pituitary function.

Causes of primary hypogonadism include:

- congenital defects such as Klinefelter's syndrome or testicular agenesis
- acquired defects due to testicular infections (e.g. mumps), trauma, irradiation, or cytotoxic drugs.

Causes of secondary hypogonadism include:

- pituitary tumours
- hypothalamic disorders such as Kallmann's syndrome.

Dynamic tests such as stimulation with GnRH may help to establish the cause of the hypogonadism in some patients.

Disorders of male sexual differentiation

Disorders of male sexual differentiation are rare. Testosterone production may be impaired. In the testicular feminization syndrome, androgen receptors are inactive and target tissues cannot respond to stimulation by circulating

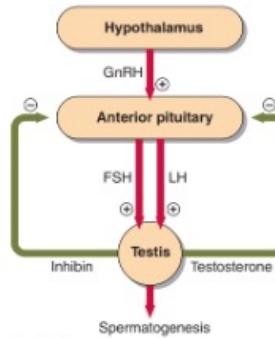


Fig 50.1 Control of testicular function by the gonadotrophins

testosterone, leading to a female phenotype.

Female gonadal function

Oestradiol is responsible for:

- female secondary sex characteristics
- stimulation of follicular growth
- development of the endometrium.

Concentrations are low before puberty, but then rise rapidly and fluctuate cyclically during reproductive life. After the menopause, plasma oestradiol concentrations fall despite high circulating concentrations of the gonadotrophins.

The normal hormonal control of the menstrual cycle is shown in Figure 50.2. At the beginning of the cycle, FSH is released and initiates follicular growth. At mid-cycle a surge of LH triggers ovulation. The ruptured follicle differentiates into the corpus luteum that secretes progesterone and oestradiol whose target is the endometrium, which they prepare for implantation.

Disorders of female sex hormones

Disorders of female sex hormones include:

- Subfertility, amenorrhoea and oligomenorrhoea (see p. 102).
- Hirsutism. This is an increase in body hair with male pattern

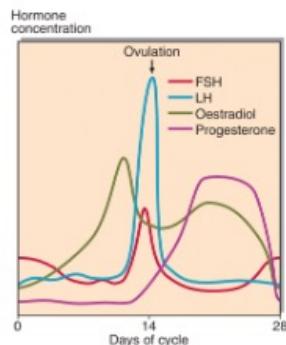


Fig 50.2 Plasma hormone concentrations throughout the female menstrual cycle.

distribution. It may be idiopathic but the commonest pathological cause is obesity (insulin resistance) often in association with polycystic ovarian disease. It is essential when investigating hirsute women that serious disease is excluded. A diagnostic decision chart for the investigation of hirsutism is shown in Figure 50.3.

■ Virilism. Although uncommon it is a sign of serious disease. Testosterone concentrations are markedly elevated in the virilized patient and there is evidence of excessive androgen action such as clitoral enlargement, hair growth in a male pattern, deepening of the voice and breast atrophy. Tumours of the ovary or of the adrenal are the likely cause.

The androgen screen in women

The observation of an elevated testosterone in a woman should always be investigated further. A decreased SHBG concentration is usually evidence of elevated androgen, as the synthesis of this protein in the liver is depressed by testosterone. By measuring the concentration of other androgens such as androstenedione and DHA sulphate (an 'androgen screen'), the source of the testosterone can be pinpointed (Fig 50.4). An elevated DHA sulphate suggests that the adrenal or an adrenal tumour, is overproducing androgens. If the ovary is the source then only androstenedione will be raised.

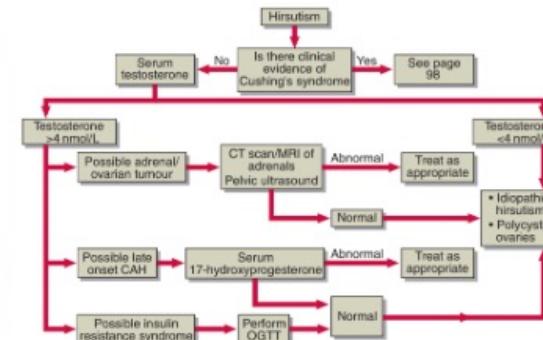


Fig 50.3 Diagnostic decision chart for the investigation of hirsutism.

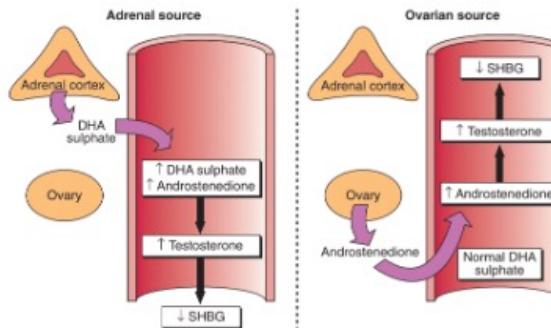


Fig 50.4 Investigation of an elevated testosterone concentration in a woman.

Case history 40

A 29-year-old woman complained of acne and irregular periods. On examination she was overweight and moderately hirsute.

Initial investigations showed a slightly elevated testosterone of 3.7 nmol/L, LH was 15 U/L and FSH 5.6 U/L.

- What other investigations should be undertaken to make a diagnosis in this patient?
Comment on page 768.

Gonadal function

- Testosterone is the main hormone secreted by the testes in the male and is regulated by pituitary LH. Testosterone is responsible for the male secondary sex characteristics.
- Oestradiol is the main product of the ovary and is responsible for the female secondary sex characteristics, development of the ovarian follicle and proliferation of the uterine epithelium.
- Hypogonadism in the male may be primary (where the cause is a failure of testosterone synthesis or of spermatogenesis in the testes) or secondary where the problem is in the hypothalamus or pituitary.
- Gonadal dysfunction in women may present as primary or secondary amenorrhoea, infertility, hirsutism or virilism.