9

Endocrine system

Endocrine control of physiological functions represents broadly targeted, slow acting but fundamental means of homeostatic control, as opposed to the rapidly reacting nervous system. In endocrine disease there is usually either an excess or a lack of a systemic hormonal mediator, but the cause may be at one of a number of stages in the endocrine pathway. Thyroid disease and diabetes mellitus represent contrasting extremes of endocrine disease and its management. Diabetes is one of the most serious and probably the most common of multisystem diseases. Optimal control of diabetes requires day-to-day monitoring, and small variations in medication dose or patient activity can destabilize the condition. Therapy requires regular review and possible modification. Furthermore, long-term complications of diabetes cause considerable morbidity and mortality.

Thyroid disease is a disorder of thyroid hormone production that has, compared to diabetes, equally profound overall effects on metabolic and physiological function. However, it causes few acute problems and has far fewer chronic complications. Moreover, management is much easier, requiring less intensive monitoring and few dose changes. Furthermore, control is rarely disturbed by short-term variations in patient behaviour.

Diabetes mellitus

Diabetes mellitus is primarily a disorder of carbohydrate metabolism yet the metabolic problems in properly treated diabetes are not usually troublesome and are relatively easy to control. It is the long-term complications of diabetes that are the main causes of morbidity and mortality. People with diabetes suffer far more from cardiovascular and renal disease than other people, and diabetes is the principal cause of acquired blindness in the West. Most people with diabetes do not die from metabolic crises such as ketoacidosis but from stroke, MI or chronic renal failure.

Diabetes is associated with obesity and lack of exercise, and the steady increase in prevalence in the West is being reproduced in large parts of the developing world as they adopt that life-style. Diabetes is in danger of becoming almost pandemic. Particularly worrying is the rise in the incidence of diabetes of both types in ever younger patients. This threatens to put an intolerable strain on health services, particularly in developing countries.

Physiological principles of glucose and insulin metabolism

Insulin action

Insulin is the body's principal **anabolic** hormone. It expands energy stores during times of adequate nutrition against times of food shortage. Opposing this action are several **catabolic** 'counter-regulatory' or 'stress' hormones that mobilize glucose for use when increased energy expenditure is necessary. The most important of these are adrenaline (epinephrine), corticosteroids, glucagon, growth hormone and growth factors. These two opposing systems work in harmony to maintain glucose homeostasis. Insulin also enhances amino acid utilization and protein synthesis, the latter action being shared with growth hormone.

Insulin action has three main components (Figure 9.1):

- **Rapid**: in certain tissues (e.g. muscle), insulin facilitates the active transport of glucose and amino acids across cell membranes, enhancing uptake from the blood.
- **Intermediate**: within all cells, insulin promotes the action of enzymes that convert glucose, fatty acids and amino acids into more complex, more stable storage forms.
- **Long-term**: because of increased protein synthesis, growth is promoted.

One important consequence is the prompt (though not complete) clearance of glucose from the blood after meals. Glucose would otherwise be lost in the urine because of the kidney's limited capacity for reabsorbing glucose filtered at the glomerulus.

Glucose transport

Glucose uptake into cells across the cell membrane is dependent on the concentration gradient between the extracellular medium (e.g. blood plasma, gastrointestinal contents) and the cell interior. However, because glucose is such an important metabolite, there exist a number of membrane transport pumps or facilitators in certain tissues. There are special insulin-
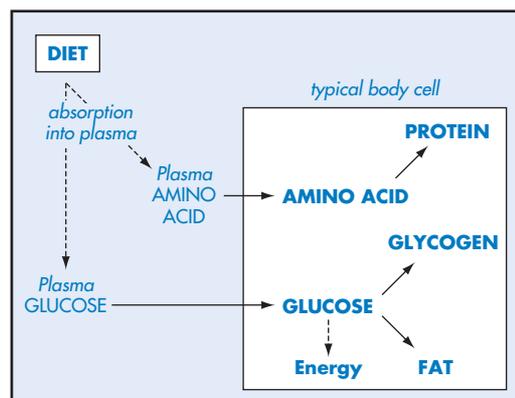

Figure 9.1 Simplified scheme showing the anabolic actions of insulin. Insulin aids the uptake of metabolites into body cells and enhances the action of enzymes that utilize them as precursors to synthesize more complex molecules. Note: not all actions shown occur in all body cells.

independent sodium-dependent transporters (SGLT) for uptake from the GIT into intestinal cells and a variety of insulin-dependent and insulin-independent glucose transporters (GLUT) for most other tissues or organs (Table 9.1).

In muscle and adipose tissue the transporter depends on an insulin-requiring active pump for glucose uptake, so insulin deficiency deprives them of glucose. Other cells, particularly in the liver, brain, kidney and GIT, do not absolutely require insulin for glucose uptake, but diffusion is nevertheless facilitated by it. In the liver, enhanced phosphorylation of glucose drives intracellular concentrations down, encouraging uptake. Insulin lack does not deprive tissues such as these of glucose; on the contrary, the hyperglycaemia associated with diabetes can produce intracellular glucose overload, and this may be responsible for some diabetic complications (p. 593). This is particularly relevant to tissues such as nerves, which are freely permeable to glucose.

Insulin also facilitates the uptake of amino acids into liver and muscle, and of potassium into most cells. This latter effect is exploited therapeutically for the rapid reduction of hyperkalaemia (see Chapter 14).

Metabolic effects

By facilitating certain enzymes and inhibiting others, insulin has wide-ranging effects on intermediary metabolism in most tissues (Table 9.2; Figure 9.1). The synthesis of the energy stores (glycogen in liver and skeletal muscle, fat in liver and adipose tissue) is facilitated, and their breakdown is inhibited. Tissue growth and cell division are also promoted by enhanced nucleic acid (DNA, RNA) synthesis, amino acid assimilation and protein synthesis.

Overall effect

Only a general appreciation of how insulin and the catabolic hormones control everyday metabolic variations is given here (see also References and further reading).

Anabolic actions of insulin

Following a meal, glucose is absorbed from the GIT into the blood and rapidly transported into the cells, to be converted into forms suitable for storage and later use.

In the liver some glucose is converted into glycogen and stored but most is converted into lipid (free fatty acid, FFA [or non-esterified fatty acid, NEFA], and triglyceride). Lipid is released into the blood as very-low-density lipoprotein (VLDL), to be taken up and stored in adipose tissue. However, the release of glucose into the blood is inhibited. Hepatic regulation of glucose output is an important mechanism for limiting the uptake of glucose into tissues where transport is independent of insulin.

In adipose tissue, fat breakdown is inhibited and glucose uptake promoted. The glucose provides glycerol for esterification with FFAs, and the resulting fat is stored. Adipose tissue also takes up the fat-containing chylomicrons obtained by digestion (see Chapter 3). In muscle, fat metabolism is inhibited and glycogen is

Table 9.1   Insulin requirement and transporters for glucose uptake into different tissues

Tissues not requiring insulin	Transporter	Tissues requiring insulin	Transporter
Gastrointestinal – uptake	SGLT	Adipose	
Gastrointestinal – release to blood	GLUT2	Muscle – skeletal, cardiac, smooth	GLUT4
Liver	GLUT7	Other tissues	
Nerves, brain	GLUT1,3		
Kidney tubules	GLUT2, SGLT		
Eye – retinal vessels, lens	SGLT		
Leucocytes	GLUT		
Blood vessel endothelium	GLUT		
Pancreatic beta cells	GLUT2		

SGLT, sodium-dependent glucose transporter; GLUT, glucose transporter.

Table 9.2   Metabolic effects of insulin

Metabolite	Process	Liver	Tissue Muscle	Adipose
Carbohydrate				
Increased	• Glycogen synthesis (glycogenesis)	✓	✓	↔
	• Glucose oxidation (glycolysis)	✓	✓	✓
Decreased	• Glycogen breakdown (glycogenolysis)	✓	✓	↔
	• Glucose synthesis (gluconeogenesis)	✓	↔	↔
Lipid				
Increased	• Fat synthesis (lipogenesis)	✓	↔	✓
	• Utilization of dietary fat	✓	↔	✓
Decreased	• Fat breakdown (lipolysis)	↔	↔	✓
	• Fatty acid oxidation (ketogenesis)	✓	✓	✓
Protein				
Increased	• Protein synthesis	✓	✓	✓
Decreased	• Protein breakdown (proteolysis)	✓	✓	↔
Nucleic acid				
Increased	• DNA and RNA synthesis	↔	✓	↔
	• Cell growth and division	↔	✓	↔

✓, insulin has important effect (increase or decrease) on process in this tissue; ↔, no effect.

synthesized, which increases glucose availability for immediate energy needs. Amino acid uptake is promoted so that growth can be continued.

Catabolic actions of counter-regulatory hormones

During stresses such as 'fight or flight', infection or any major trauma, catabolic hormones reverse these processes. Blood glucose is rapidly raised to supply energy for the muscles and if this is insufficient fats can also be mobilized. Peripheral oxidation of FFAs produces large amounts of energy, but in the liver excess acetyl-CoA is produced. This is condensed to produce high-energy ketoacids such as acetoacetate, which many tissues can utilize in small amounts. In insulin insufficiency these 'ketone bodies' may accumulate in the plasma, causing ketoacidosis.

Insulin deficiency

The consequences of insulin deficiency, and thus many of the clinical features of diabetes, can be deduced from these considerations (Figure 9.2).

It will be explained below that obese type 2 patients may not at first have an absolute deficiency of insulin; rather, there is a degree of insulin resistance. This may be described as a relative lack because the result is the same; moreover, eventually their insulin levels do fall. There are important differences between the physiological effects of partial (or relative) deficiency and total insulin deficiency.

Partial deficiency (type 2)

Even small amounts of insulin will prevent severe metabolic disruption, especially accelerated fat metabolism, i.e. ketosis. Thus, although fasting blood glucose levels may be raised, the main problems only arise after meals; these arise from impaired glucose transport and cellular uptake resulting in impaired clearance from the blood. Adipose and muscle tissue cannot take up glucose efficiently, causing it to remain in the blood, and glucose deficiency in muscle may cause weakness. Becuse other tissues cannot compensate sufficiently to assimilate the entire postprandial glucose load, the blood
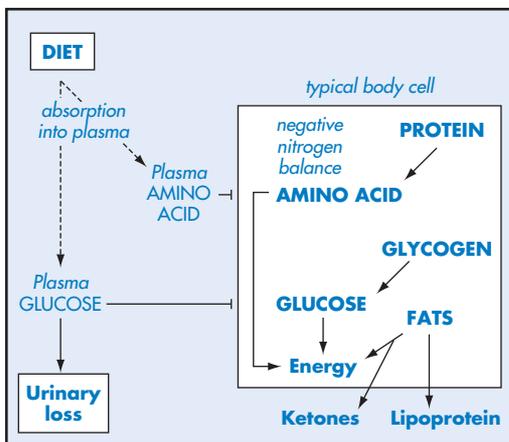
Figure 9.2 Metabolic consequences of insulin lack. Cellular uptake of glucose is prevented so that after exhausting their glycogen supplies, cells need to use fats and even protein for their energy needs. Compare with Figure 9.1. Note: not all actions occur in all body cells.

glucose level rises causing **hyperglycaemia** (>11 mmol/L).

When the blood glucose level increases so that the concentration in the glomerular filtrate exceeds the renal threshold (see Chapter 14, p. 876), glucose is lost in the urine (**glycosuria**). Urinary glucose acts as an osmotic diuretic carrying with it large volumes of water (**polyuria** and **urinary frequency**), resulting in excessive thirst and fluid intake (**polydipsia**). Because of reduced fat uptake by adipose tissue, plasma lipid levels rise, especially triglycerides (**dyslipidaemia**). LDL is relatively unaffected but HDL is reduced, increasing atherogenic risk (Chapter 4). Protein synthesis may be reduced but patients are often still relatively obese. However, they usually do lose weight in the weeks before first diagnosis, in part due to dehydration.

Total deficiency (type 1)

With no insulin at all there is severe hyperglycaemia at most times. This may raise the blood osmotic pressure sufficiently to cause neurological complications including coma; this is discussed on pp. 594–596. Cellular metabolism is profoundly disturbed. No glucose is available for energy metabolism, and the first result is a depletion of liver and muscle glycogen stores.

Subsequently fat is mobilized, mainly from adipose tissue, so that plasma triglyceride and FFA levels rise, as does lipoprotein. These supply energy needs for a little longer while the patient loses yet more weight. The brain cells switch to metabolizing the hepatically produced keto-acids. Fat stores are not replenished, and eventually may be exhausted. Finally, protein must be broken down into amino acids, which can be converted to glucose in the liver (**gluconeogenesis**), at the expense of lean muscle mass. Other than in uncontrolled diabetes, this process normally occurs only in times of prolonged starvation; it is a desperate remedy that is akin to burning the house down to keep warm. Further, without insulin, any glucose so produced cannot be utilized effectively anyway. This situation is inevitably fatal within months.

Thus many of the clinical problems in type 2 diabetes are a direct consequence of hyperglycaemia, while in type 1 diabetes there is also disrupted intracellular metabolism. In addition, chronic complications occur in both types, related to both hyperglycaemia and dyslipidaemia. These are discussed below.

Insulin physiology

Insulin (molecular weight about 5800 Da) is composed of 51 amino acids in two chains of 21 (A chain) and 30 (B chain) amino acids connected by two disulphide bridges. It is synthesized in the pancreatic islet beta-cells. Other cells in the islets are the alpha-cells (producing glucagon) and the delta-cells (producing somatostatin). Islet cells altogether comprise less than 3% of the pancreatic mass. Insulin is stored in granules in combination with **C-peptide** as proinsulin (molecular weight 9000 Da), which is split before release into the portal vein. Insulin has a plasma half-life of only about 5 min. Approximately 50% of insulin is extracted by the liver, which is its main site of action, and after utilization it is subsequently degraded. Eventually, kidney peptidase also metabolizes some insulin. C-peptide is less rapidly cleared and is thus a useful index of beta-cell function. The main control of insulin level is plasma glucose: a rise stimulates both the release and the synthesis

of insulin. Amino acids and possibly fats also promote insulin release (Figure 9.3).

A wide variety of other neuronal, endocrine, pharmacological and local influences on insulin release have been identified (Figure 9.3), but their physiological or pathological significance is not established. Adrenergic beta-receptors mediate release, so beta-blockers can theoretically inhibit this, though stimulation of inhibitory adrenergic alpha-receptors, magnified during the hyperglycaemic stress response, usually predominates.

Interestingly, glucose is a more powerful stimulant orally than parenterally, and various gut hormones have been implicated in this. Glucagon also promotes insulin release, possibly to facilitate cellular uptake of the glucose that it causes to be released into the plasma.

Pattern of secretion

It is important to note also that there is a continuous basal level of insulin secretion throughout the 24 h, independent of food intake, which contributes to the regulation of metabolism and promotes glucose uptake into cells. This amounts to about 1 unit/h. Following a meal there is an additional bolus secreted, which is biphasic. Within 1 min of blood glucose levels rising, preformed insulin is released from granules in beta-cells into the blood. This release is stimulated by certain antidiabetic agents (insulin secretagogues) and is the first component to be compromised in early diabetes. Should hyperglycaemia persist, further insulin synthesis is stimulated and there

is a delayed second phase of secretion after about 45 min. Appoximately 5–10 units are secreted with each meal.

Thus the plasma insulin concentration curve normally closely parallels the plasma glucose concentration curve throughout the day, reflecting every small change in nutrient supply or demand (Figure 9.4). Considering these subtle and sometimes rapid adaptations, it can be appreciated how far current therapeutic methods fall short of mimicking the physiological ideal.

In non-diabetics, the total daily secretion of insulin is probably rather less than the average daily requirement in type 1 diabetes of 50 units of exogenous insulin, mainly because of losses at the injection site.

Amylin

The 37-amino acid peptide amylin is co-secreted with insulin from beta-cells. It appears to contribute to glucose regulation by a local (paracrine) action on islet cells, which moderates intestinal glucose uptake, thereby reducing the load presented to the pancreas, or by suppressing glucagon secretion. In diabetes, amylin deficiency parallels that of insulin and it is believed that patients whose postprandial hyperglycaemia is not adequately controlled by conventional therapy may benefit from amylin agonists, although none is yet in clinical use.

Insulin receptors

These are present on the cell surfaces of all insulin-sensitive tissues and are normally down-
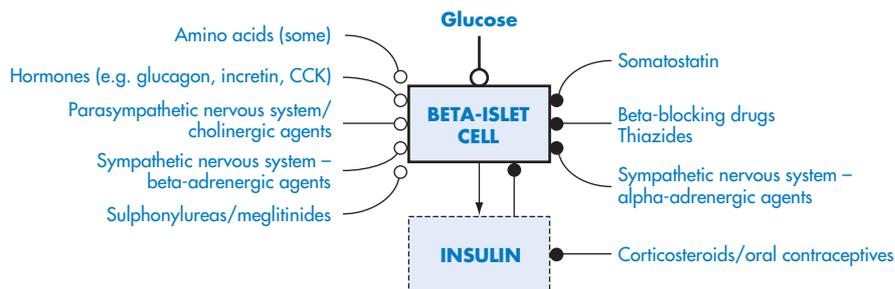

Figure 9.3 Factors affecting the release or action of insulin. CCK, cholecystokinin. ——● inhibition/antagonism; ——○ stimulation/potentiation.
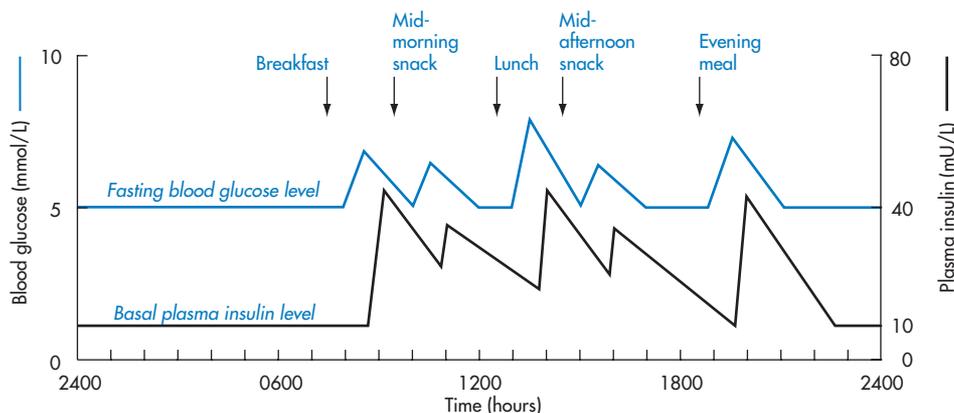
Figure 9.4   Schematic representation of normal diurnal variations in blood glucose and plasma insulin levels. As the blood glucose level rapidly rises after a meal, it is closely followed by an increase in insulin level to limit the rise. The insulin returns towards the basal level as blood glucose reaches the normal fasting level once more. Note how the two substances follow almost parallel curves, the insulin a little later than the glucose. The small but positive constant basal insulin level emphasizes that insulin has functions other than just dealing with dietary glucose. Note: this diagram does not differentiate the two phases of insulin release.

regulated by insulin, especially if it is present at continuously high levels, e.g. the hyperinsulinaemia of over-eating, obesity or obesity-related type 2 diabetes. This may account for the reduced insulin sensitivity (insulin resistance) found in some patients and the beneficial effect of weight reduction, especially of abdominal fat, on glucose tolerance: there is a vicious cycle whereby hyperglycaemia and reduced insulin action reinforce one another. Long-term insulin treatment also often gradually reduces the insulin requirement, perhaps owing to reduced glucose levels. However, there is still much to be learned about the interactions between insulin, insulin receptors and carbohydrate metabolism.

Epidemiology and classification

The hallmark of diabetes is hyperglycaemia, owing to abnormalities of insulin secretion or action. There are two primary forms of diabetes and a variety of minor secondary ones. In type 1 diabetes there is usually gross destruction of the insulin-secreting pancreatic beta-cells. In type 2 diabetes insulin is secreted but is either inadequate or insufficiently effective to meet metabolic needs.

The current WHO definition of diabetes is based on standardized measurements of plasma glucose concentrations. It defines three classes, diabetes, impaired glucose tolerance and impaired fasting blood glucose (Table 9.3). Patients in the second category are borderline and about half will progress to frank diabetes eventually (up to 5% per year). However, they need not be treated immediately, depending on age and the presence of other risk factors: older patients or those with no cardiovascular risk factors may just be monitored. More recently the category of impaired fasting glucose has been introduced in an attempt to identify at an even earlier stage those with latent or 'pre-diabetes' who should be monitored. It is a less reliable predictor but has the advantge that it does not require a glucose tolerance test (see below).

Often, a single random plasma glucose of >11.1 mmol/L (blood glucose 10 mmol/L) is sufficient for diagnosis in a patient with classic symptoms, although this should be confirmed with a fasting plasma glucose >7 mmol/L.

Table 9.3 WHO definitions of diabetes mellitus (based on plasma glucose levels, as measured in laboratory)

Class	Plasma glucose (mmol/L)		
	Fasting		**OGTT at 2 h**
Diabetes mellitus	>7	and/or	>11.1
Impaired glucose tolerance (IGT)	<7	and	7.8–11.1
Impaired fasting glucose (IFG)	6.1–7		
Normal fasting glucose	<6.1	and	<7.8

If whole blood is used (as obtained by finger prick) all figures would be approx. 10% lower (e.g. 6.1 and 10 mmol/L for diabetes mellitus).

The apparently non-uniform thresholds derive from conversion from old mg/100 mL units, as still used in North America.

OGTT, oral glucose tolerance test.

Laboratories may report plasma glucose levels, as specified by the American Diabetic Association diagnostic criteria, whereas finger prick tests measure blood levels; nevertheless, it is customary always to refer to blood glucose in discussing diabetes. In borderline cases the **oral glucose tolerance test (OGTT)** can be performed: the patient's blood glucose is measured before and at 2 h after a standardized 75-g glucose load, given orally following an overnight fast.

Epidemiology

Diabetes is known to affect more than 2% of the UK population, and probably as many again are likely to have impaired glucose tolerance or even frank diabetes if screened. The prevalence varies considerably between populations. For example, Europeans are prone to type 1, especially in northern Europe, whereas the incidence in Japan is less than 10% of that in Finland.

Type 2 seems to be related partly to the affluence of a population, possibly through the prevalence of obesity, inactivity or both, which are major risk factors. However, genetic factors are also important. In some ethnic groups the prevalence is very high, e.g. in some Pacific Islanders and the North American Pima Indians it reaches 50%. Among South Asian immigrants to the UK it is five times that in the host population, suggesting a possible genetic susceptibility to changed environmental factors, e.g. a diet richer in fats and sugar.

Classification

Primary diabetes – type 1 and type 2

In the vast majority of cases there is direct damage to the pancreatic islet cells. Different attempts to classify diabetes comprehensively have been confounded by the use of criteria that are not mutually exclusive (e.g. age at onset, patient build or need for insulin). For example, some older ('maturity onset' or type 2) patients eventually require insulin, some older patients need it from the start ('latent autoimmune diabetes in the adult', LADA) and a few younger patients may not ('maturity onset diabetes of the young', MODY). Whether the patient needs insulin may be the most practical distinction, but does not correspond consistently with other important parameters.

A classification based on the pathogenesis of the pancreatic damage is now accepted as the most meaningful. This distinguishes two broad types (Table 9.4), which correspond roughly with insulin dependency. The key criterion is the mode of pancreatic damage, but many other distinctions follow from this classification, including natural history, family history and patient type. These will be discussed in the following sections.

Secondary diabetes

A minority of cases with identifiable primary causes (e.g. severe pancreatitis, steroid-induced diabetes) do not fit readily into either of the conventional categories. They may or may not require insulin for treatment (p. 591).

Table 9.4   Comparison of the main types of primary diabetes mellitus

	Type 1	Type 2
Endogenous insulin	Absent	Present
Insulin deficiency	Absolute	Relative or partial
		Insulin receptor defect?
Insulin resistance	Usually absent	May be present
Pancreatic islet damage	Severe (destruction)	Slight/moderate
Immunology	Auto-immune; islet cell antibodies	No antibodies demonstrated
Usual age of onset	<30 years	>40 years
Build of patient	Thin	Obese (usually)
Therapeutic class	Insulin-dependent (IDDM)	Non-insulin-dependent (NIDDM; but may require insulin)
Genetics	Weak family history; HLA-linked	Strong family history
Ketoacidosis prone?	Yes	No

Aetiology and pathogenesis

Primary diabetes

Despite having similar clinical pictures and complications, types 1 and 2 primary diabetes have very different causes (Table 9.5).

Type 1 diabetes

In type 1 diabetes the islet beta-cells are almost completely destroyed by an autoimmune process. Antibodies against all islet cells, and beta-cells specifically, are found in 80% of patients. However, interestingly, it is not these anti-islet antibodies that mediate cell destruction but T-cells; the islets are invaded by inflammatory cells causing insulitis. Insulin autoantibodies may also be found but their significance is uncertain. As is usual with autoimmune disease, there is rarely a strong family history: siblings or children of people with type 1 diabetes have about a 5% chance of developing the disease. However, there is a correlation with the patient's HLA tissue type (see Chapter 2) and in a minority of patients an association with other autoimmune diseases, especially of endocrine tissues (e.g. thyroiditis, pernicious anaemia).

Table 9.5   Aetiology and pathology of primary diabetes

	Type 1	Type 2
Risk factors	HLA antigens (DR3, DR4)	Family history Over-eating; lack of exercise Toxin? Amyloid? Ethnic group
Trigger factors	Viral infection Metabolic stress/excessive demand Environmental toxin?	Obesity Metabolic stress/excessive demand
Pathogenesis	Rapid autoimmune destruction of islet cells	Gradual islet cell degeneration / depletion Peripheral insulin receptor defect?

Overt diabetes may follow many years of subclinical pancreatic damage, and when it occurs there is usually less than 10% of functional islet cell mass remaining. Clinical onset is usually abrupt, over a few weeks, and often associated with, or precipitated by, a metabolic stress such as an infection, which acutely increases insulin demand beyond capacity. This might account for the winter seasonal peak in incidence and also the brief temporary remission that frequently follows, as the infection remits and the marginal insulin levels once again just compensate. Subsequently, full-blown disease irreversibly takes hold. As with other autoimmune diseases, viral infection may be causing the expression of a normally suppressed HLA receptor, which subsequently activates lymphocytes (see Chapter 2). Other environmental triggers such as toxins or certain foods (including milk protein) may also be involved.

Autoantibodies may be found in some patients up to 15 years before the onset of acute disease. This could eventually provide a means of early identification of prediabetes, so that they may be treated prophylactically, possibly by immunotherapy. However, such markers are also often found in close relatives who never develop the disease, and the chance of the identical twin of a diabetic patient subsequently developing diabetes is less than 50%. The introduction of the category of 'impaired fasting glucose' was another attempt at early identification of potential sufferers.

Thus it seems that in type 1 diabetes there is a genetically determined HLA-dependent susceptibility that requires an environmental trigger for full expression. Following contact with this trigger, which may never be encountered, swift deterioration and complete insulin dependence are inevitable. There is still considerable ignorance of the relative contributions of genes and environment and of specific environmental factors.

Type 2 diabetes

These patients have one or more of the following fundamental abnormalities, and in established disease all three commonly coexist:

- Absolute insulin deficiency, i.e. reduced insulin secretion.
- Relative insulin deficiency: not enough insulin is secreted for metabolic increased needs (e.g. in obesity).
- Insulin resistance and hyperinsulinaemia: a peripheral insulin utilization defect.

In most cases type 2 diabetes is associated with obesity (particularly abdominal obesity) on first presentation, and in a quarter of all people with diabetes simple weight reduction reverses the hyperglycaemia. This is commonly associated with peripheral insulin resistance owing to receptor-binding or post-receptor defects. Obesity and reduced exercise also contribute to insulin resistance and are modifiable risk factors for type 2 diabetes. The resultant hyperglycaemia induces insulin hypersecretion, hyperinsulinaemia and insulin receptor down-regulation, i.e. further insulin resistance. Hyperglycaemia itself is known to damage beta-cells owing to the direct toxic effect of excessive intracellular glucose metabolism, which produces an excess of oxidative by-products; these cannot be destroyed by natural scavengers such as catalase and superoxide dismutase. The vicious cycle eventually depletes ('exhausts') the beta-cells, intrinsic insulin levels fall and some patients may eventually come to require exogenous insulin therapy. Thus, type 2 diabetes is usually a progressive disease, although the late onset usually means that some patients die before requiring insulin.

There is still debate as to the primary defect of type 2 diabetes. It has also been proposed that the amyloid deposits (insoluble protein) long known to be found in the pancreas of type 2 patients are related to abnormalities in amylin secretion (p. 586) and contribute to the pancreatic defect.

There is an association between abdominal obesity, hyperinsulinaemia, insulin resistance, hyperlipidaemia, type 2 diabetes and hypertension, and this combination of risk factors is termed **metabolic syndrome**. However, despite much research, as yet it is not known which of these factors (if any) is the prime cause, or if there is another underlying reason.

Genetics

The genetic component in type 2 diabetes is much greater than in type 1. A family history is very common, often involving several relatives. Identical twins almost always both develop the disease, and offspring with both parents having diabetes have a 50% chance of developing the disease. The 'thrifty gene' hypothesis proposes that the ability to store fat efficiently – and hence develop obesity – conferred a survival advantage in more primitive societies where famine was a regular phenomenon, hence its persistence in the genome. This may explain why some pre-industrial groups (e.g. Pacific Islanders) readily develop diabetes when exposed to the industrialized lifestyle.

Secondary diabetes

Most diabetes results from primary defects of the pancreatic islet cells. However, there are occasionally other causes of ineffective insulin action, impaired glucose tolerance and hyperglycaemia (Table 9.6).

Natural history

Onset

About 80–90% of diabetic patients have type 2 diabetes, which tends to occur late in life, hence the obsolete description 'maturity onset'. Onset is usually insidious and gradual, patients tolerating mild polyuric symptoms perhaps for many years.

The other 10–20% have type 1 diabetes and require insulin at the outset. Almost invariably they become ill at an early age: the peak onset of type 1 is around puberty, starting most commonly in the winter months. Although the disease may be present subclinically for some considerable time (months, or possibly years), clinical onset is invariably abrupt.

Presentation

Type 2 diabetes is usually first diagnosed following one of three common presentations (Table 9.7):

Table 9.6   Some causes of secondary diabetes

General mechanism	Aetiology	Example
Hepatic glucose metabolism defect	Liver failure	Viral hepatitis, drugs
Pancreatic destruction	Cirrhosis	Alcoholism
	Pancreatitis	
Anti-insulin hormones	Corticosteroids	Cushing's disease
		Steroid therapy
		Pregnancy ('gestational diabetes')
		Major trauma/stress
	Growth hormone	Acromegaly
	Adrenaline (epinephrine), etc.	Phaeochromocytoma
	Glucagon	Glucagonoma
	Thyroid hormones	Hyperthyroidism
		Major trauma/stress
		Adrenergic drugs
Hyperglycaemic/anti-insulin drugs		Thiazide diuretics, diazoxide
		Oral contraceptives
Insulin antibodies	Autoimmune disease	
Abnormal insulin receptors	Congenital lipodystrophy	

- About half of patients first complain of increasing polyuria and/or polydipsia.
- In about a third it is a chance finding of glycosuria or hyperglycaemia at a routine medical examination.
- In less than 20% of cases the patient complains of symptoms subsequently found to result from a complication secondary to diabetes.

Type 2 patients may be asymptomatic or may have been only mildly symptomatic for several years. Commonly, they ignore these symptoms or attribute them to ageing, and only present when classical symptoms such as polyuria, thirst, tiredness or recent weight loss (even though the patient may still be relatively obese) become unacceptable. In many other cases their diabetes is only detected when they undergo a medical examination, e.g. for insurance purposes or a new job. Alternatively, the complaint may be of an infective complication not obviously linked to diabetes, at least not in the patient's mind, such as recurrent candida infections or boils, a non-healing foot lesion or a persistent urinary-tract infection. Rarely, as the complications proceed insidiously even during this early period, the primary reason for consultation may result from vascular disease, nephropathy, neuropathy, retinopathy or impotence. In some cases IHD, even MI, is the first presentation.

A common manifestation of the complications is the 'diabetic foot'. The patient presents with a possibly gangrenous foot lesion, probably following a recent injury and subsequent infection.

Only very rarely will a type 2 patient first present with metabolically decompensated disease (ketoacidosis). These patients will probably have had impaired glucose tolerance for some time and then have undergone some major stress such as MI or serious infection. Another possible trigger factor could be starting a drug that impairs glucose tolerance, e.g. a thiazide diuretic or an atypical antipsychotic. Such stresses may also uncover latent disease in a less dramatic manner.

Unfortunately, a severe acute presentation is far more common at the onset of type 1 disease. This is usually associated with some metabolic stress (e.g. infection), and presents with rapid weight loss, weakness, extreme thirst, severe polyuria, urinary frequency and multiple nocturia. Some may even go on to acute metabolic decompensation (ketoacidosis) and even coma, being practically moribund on hospital admission. Following recovery with insulin therapy there may follow some months of apparent remission with a reduced or absent insulin requirement, the so-called 'honeymoon period', but these patients then deteriorate rapidly. Before the isolation and therapeutic use of insulin in the 1920s they inevitably died shortly thereafter.

Progression

Insulin secretion in type 2 diabetes declines relatively slowly, but up to one-third of patients may eventually need exogenous insulin, i.e. they are 'insulin-requiring' as opposed to insulin-dependent.

In most type 1 diabetes, pancreatic beta-cell destruction is already almost complete at diagnosis, and routine insulin requirements do not generally increase. However, in both types the multisystem complications progress throughout life at rates that vary considerably between patients and will very likely be the eventual cause of death. People with diabetes have a reduced life expectancy, although the prognosis has greatly improved with advances in treatment. Younger patients have mortality rates of up to five times that of the general population, while for older ones it is about twice normal. The precise prognosis for any given patient will depend on many factors, but particularly the overall consistency of control of blood glucose.

Table 9.7   Different presentations of type 2 diabetes

Typical diabetic symptoms (see text)	55%[a]
Chance finding	30%
Complication – infective	15%
– other	2%

[a] Approximate figures; after Watkins (2003) (See References and further reading).

Clinical features

Symptoms

The symptoms of diabetes as summarized in Table 9.8 are best understood in relation to their pathogenesis.

Symptoms due to hyperglycaemia

The classic symptoms, which give diabetes mellitus its name ('sweet fountain'), are easily explained by the osmotic effect of the elevated blood glucose levels that occur when glucose is denied entry to cells. They are more pronounced when the blood glucose level rises rapidly, e.g. in decompensation or acute onset. The osmotic effect of chronic hyperglycaemia will to some extent be compensated by compensatory hyponatraemia and an increased intracellular osmolarity (see Chapter 14).

When the blood glucose level exceeds the renal threshold (about 10 mmol/L), glucose appears in the urine in large quantities. The traditional method of distinguishing diabetes mellitus from diabetes insipidus – almost the only two idiopathic causes of chronic polyuria – was simply to taste the urine: in the former case it is sweet, and in the latter literally insipid (tasteless). Glycosuria predisposes to urinary-tract infection, partly because of the favourable growth medium presented to perineal organisms and partly because diabetic patients are generally more susceptible to infection (see below).

Diabetic urine dries to leave a white glucose deposit, a clue that sometimes leads to diagnosis: there may be underwear stains or white specks on the shoes of elderly males (from careless micturition). Severe plasma hyperosmolarity may reduce the intraocular pressure, causing eyeball and lens deformity, and glucose may alter lens refraction: both lead to blurred vision. This is sometimes a prodromal sign of hyperglycaemic crisis in type 1 diabetes.

Impaired metabolism and complications

The metabolic consequences of insulin lack were discussed in detail above. The pathophysiology of hyperglycaemia and ketoacidosis is now considered.

Complications

Most complications of diabetes are due to either acute metabolic disturbances or chronic tissue damage.

Acute complications

The most common acute complications are disturbances in glycaemic control. Optimal management of diabetes aims for a delicate balance, preventing excessive glucose levels but not forcing glucose levels too low. A variety of circumstances can drive the glucose level outside

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Table 9.8 Clinical features of diabetes

Direct consequences of high blood glucose levels
Polyuria, frequency, nocturia, polydipsia (osmotic diuresis)
Visual disturbance (osmotic changes to intra-ocular pressure)
Urethritis, pruritis vulvae, balanitis (urogenital infection)
Metabolic consequences of impaired glucose utilization
Lethargy, weakness, weight loss (intracellular glucose deficit)
Ketoacidosis (increased fat metabolism)
Long-term complications of hyperglycaemia and hyperlipidaemia
Vascular disease, heart disease, renal disease, neuropathy, eye disease, infections, arthropathy

these narrow limits, and if treatment is not adjusted accordingly, the result is either excess or insufficient glucose in the blood (Table 9.9).

Hyperglycaemia/ketoacidosis

Causes, pathogenesis and symptoms

Hyperglycaemia in treated diabetes usually arises because normal medication is somehow omitted or becomes insufficient to meet an increased insulin requirement. Drugs that raise blood glucose levels can also interfere with control. When diabetic control is lost, blood glucose rises and the symptoms develop gradually over a number of hours. Above a blood glucose level of approximately 15–20 mmol/L, both hyperosmolar and metabolic problems develop (Figure 9.5; Table 9.10).

Blood glucose levels can exceed 50 mmol/L and this high osmotic load (which is also in the extracellular fluid) cannot be matched within those cells from which glucose is excluded owing to the absence of insulin. Thus, water is drawn from the intracellular compartment and this causes tissue dehydration. This particularly affects the brain where the resultant reduced intracranial pressure leads to CNS depression. The skin is also dehydrated, and loses its elasticity; this reduced skin turgor can be detected by pinching a fold of skin and noting its delay in

Table 9.9   Causes of acute disturbances in diabetic control

Hypoglycaemia	Hyperglycaemia/ketoacidosis
Excess (mis-measured?) dose	Missed antidiabetic dose
Potentiation of oral hypoglycaemic (drug interaction)	Hyperglycaemic drugs, e.g. thiazides, steroids
Missed meal; dieting	Excess dietary intake
Unexpected physical activity	Metabolic stress, e.g. infection, surgery, pregnancy
Excessively tight blood glucose control	
Alcohol	

Figure 9.5   Pathogenesis and clinical features of acute hyperglycaemia and ketoacidosis.

Table 9.10   Clinical features of hyperglycaemia and ketoacidosis

Glycosuria, ketonuria
Polyuria, nocturia
Thirst, polydipsia

Hypotension
Rapid (bounding) pulse and respiration

Dry mouth, reduced skin turgor
Visual disturbance

Hyperkalaemia, acidosis, ketonaemia
Sweet smell of ketones on breath

Weakness, drowsiness, eventually coma

springing back, but this is less conclusive in the elderly, in whom skin elasticity is already reduced.

In the kidney the high load of glucose in the glomerular filtrate, not all of which can be reabsorbed, produces an osmotic diuresis. This results in a reduction in circulating fluid volume, leading to hypotension and reflex tachycardia. The high urine volumes also cause a loss of electrolytes, especially sodium and potassium. However, the plasma potassium level may be paradoxically high because acidosis inhibits the Na/K pump throughout the body, preventing intracellular potassium uptake (see below and Chapter 14, p. 891). Osmoreceptors and baroreceptors detect the electrolyte and fluid losses, causing thirst, but as CNS depression and confusion develop the patient often cannot respond by drinking.

In the absence of glucose, many cells start to metabolize fat instead. Adipose tissue releases fatty acids, and the liver converts some of these to acid ketones that can be readily utilized as an alternative energy source by many tissues. The resulting metabolic acidosis (diabetic ketoacidosis) is misinterpreted by the respiratory centre as carbon dioxide retention, resulting in an increased respiratory drive and hyperventilation. Acidosis impairs oxygen dissociation from Hb, exacerbating the gasping (overbreathing, 'air hunger'), and also causes peripheral vasodilatation, exacerbating the hypotension. Both respiratory rate and blood oxygen level fall as coma supervenes. Ketoacidosis is more likely to develop in type 1 patients, although fortunately it is uncommon.

People with type 2 diabetes usually secrete sufficient insulin to prevent them developing ketoacidosis (except during severe stress), but they may still suffer hyperosmolar non-ketotic hyperglycaemic states. This may result in coma and is associated with a higher mortality than ketoacidosis.

Management
Diabetic ketoacidosis is a medical emergency with about a 15% mortality rate. Close monitoring and very careful attention to the patient's fluid and electrolyte balance and blood biochemistry are essential (Table 9.11). Immediate attention is life-saving, but the patient may take several days to stabilize.

IV soluble insulin is essential. An initial bolus of about 6 units is followed by continuous infusion (6 units/h). Fluid replacement needs are estimated from measurements of the CVP and plasma sodium level. Hyponatraemia ('appropriate hyponatraemia', glucose having

Table 9.11   Principles of the management of ketoacidosis

Problem	Treatment
Underlying cause	Discover and treat
Hyperglycaemia and hyperosmolarity	Insulin (soluble): small bolus plus continuous infusion
Dehydration	IV infusion: saline/dextran/plasma
Acidosis	Bicarbonate?
Hyperkalaemia/potassium deficiency	Careful potassium repletion, after correction of acidosis
Hypoxaemia	Oxygen, up to 60% initially

osmotically displaced sodium in the plasma) and/or sodium depletion require 0.9% saline administration. However, if the dehydration has caused hypernatraemia, especially in the non-ketotic patient, hypotonic saline (e.g. 0.45%) may be indicated. Severe hypotension or shock require plasma replacement (see Chapter 14 p. 903). Potassium replacement is difficult to manage because the initial hyperkalaemia masks a total body potassium deficit. However, once insulin is started and potassium moves intracellularly, closely monitored IV potassium replacement is required. Acidosis will often resolve spontaneously with conservative therapy as ketone production falls and existing ketones are metabolized. Many clinicians would not use bicarbonate unless blood pH was below 7.00 for fear of overcompensating.

Hypoglycaemia

Causes

In all forms of diabetes, hypoglycaemia (blood glucose <3 mmol/L) is much more common than symptomatic hyperglycaemia, and it develops very rapidly, sometimes within minutes. Usually, either an excessive insulin dose is accidentally injected (many patients have eyesight problems) or else the normal dose of insulin or antidiabetic agent is not matched by an adequate dietary intake (Table 9.9). Insulin-induced hypoglycaemia is usually associated with injections of short-acting insulin. Deliberate overdosing is not unknown.

Hypoglycaemia induced by sulphonylurea antidiabetic drugs is rarer but more prolonged, more severe and more difficult to treat than insulin-induced hypoglycaemia. The elderly are especially prone, partly because the drugs are cleared more slowly and partly because of impaired homeostasis. Drug interactions that might potentiate oral antidiabetic drugs are considered on p. 615. Alcohol not only causes hypoglycaemia by inhibiting hepatic gluconeo-genesis but also impairs the patients' perception of it, reducing their ability to respond.

Pathogenesis and symptoms

Hypoglycaemic symptoms fall into two main groups (Table 9.12). At glucose levels below about 4 mmol/L insulin release is inhibited and the counter-regulatory hormones such as glucagon and adrenaline are released in an effort to raise blood glucose. At a glucose level below 3.5 mmol/L the body responds by activating the sympathetic nervous system and adrenal medulla (the 'fight or flight' response). The consequent **sympathetic/adrenal** symptoms (Table 9.12) should provide the patient with a preliminary warning (but see below).

As the glucose level falls below about 2.5 mmol/L, neurological signs develop owing to the deficiency of glucose in the brain. These **neuroglycopenic** features may be noticed more by others than by patients themselves, although many patients do report an awareness of subjective prodromes. Sometimes the signs are subtle changes in mood or visual disturbances, but eventually there is almost always erratic behaviour resembling drunkenness. This has sometimes led to police arrest and delayed treatment, occasionally with fatal results. Frequent hypoglycaemic attacks may have a cumulative deleterious effect on higher brain function (cognition), especially in the elderly. All people with diabetes should carry, in addition to a readily available sugar source such as dextrose tablets, a card or

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Table 9.12   Clinical features of hypoglycaemia

Adrenergic (autonomic) – enhanced sympathetic activity
- tremor, sweating
- shivering, palpitations
- anxiety, pallor

Neuroglycopenic – reduced CNS glucose delivery
- drowsiness, disorientation, confusion
- apparent drunkenness; aggression, inappropriate behaviour
- convulsions, coma, brain damage; death

Other effects – multiple or indirect pathogenesis
- hunger, salivation, weakness, blurred vision

bracelet stating that they have diabetes and should be given sugar if found acting strangely.

A patient's ability to recognize 'hypos' (their **hypoglycaemic awareness**) should be checked regularly because it tends to diminish. Long-term diabetes patients become less sensitive to the warning signs and thus more vulnerable. This may result partly from autonomic neuropathy and partly from reduced counter-regulatory hormone response. It is also possible that frequent attacks may reduce the patient's ability to recognize them. Awareness is progressively reduced by frequent hypoglycaemic episodes but may be at least partially restored by minimizing or eliminating episodes through relaxing control slightly, more careful monitoring and patient education.

Most of the adrenergic symptoms are mediated by beta-receptors, and so may be antagonized by concurrent beta-blocker therapy. Although this rarely presents a serious problem, such drugs should be avoided in people with diabetes if they already experience hypoglycaemic unawareness. Otherwise, there is no contra-indication but a cardioselective beta-blocker is preferred. Theoretically, beta-blockers might help by preventing beta-mediated insulin release (Figure 9.3), but this is swamped by the symptom-masking effect.

Management

Although both hypoglycaemia and hyperglycaemia can result in coma, there is rarely any problem distinguishing them, especially as rapid blood glucose test stick methods are readily available. A test dose of glucose would clinch matters because hypoglycaemia will be very rapidly reversed, whereas glucose would have no significant effect, either helpful or harmful, in hyperglycaemia. In contrast, insulin given blindly would severely exacerbate hypoglycaemia and should never be given where there is doubt.

The conscious patient must take glucose tablets, or sugar, chocolate, sweet tea, etc. Semi-conscious or comatose patients require IV glucose 20% or IM glucagon (1 mg). The response is usually satisfyingly prompt, occurring within minutes. Glucagon injection can usually be managed easily by patients' relatives, who should be fully informed on how to recognize and deal with hypoglycaemic episodes. Unless patients or their relatives are taught to recognize the early signs, the patient may become comatose before being able to correct it.

Persistent hypoglycaemic attacks require reassessment of therapy. Dietary modification may be required (e.g. increased carbohydrate), although this might compromise weight reduction efforts. Modern intensive insulin therapy regimens aimed at producing 'tight' glycaemic control have increased the likelihood of hypoglycaemia, and a judgement of risk and benefit has to be made when such regimens are considered (p. 626).

Unstable diabetes

A small proportion of people with type 1 diabetes prove exceptionally difficult to control, experiencing frequent episodes of hypoglycaemia, hyperglycaemia or both. They are variously termed **brittle**, **unstable** or **labile**. It is unlikely that this condition is inherent to their disease, and specific causes are always sought. Poor compliance through error, ignorance or disability, e.g. visual problems measuring insulin doses, unrecognized intercurrent illness and drug interaction must first be eliminated. In older patients with recurrent hypoglycaemia the possibility of reduced hypoglycaemic awareness must be investigated.

Recurrent hyperglycaemia/ketoacidosis is more common in young patients and may sometimes be associated with psychological or psychopathological factors such as teenage rebellion or illness denial, self-destructive impulses or other emotional instability. A particular subgroup has been identified of slightly obese females aged 15–25 years who may be covertly manipulating their therapy adversely. Supervised IV therapy in some of these patients seems to resolve the problem temporarily.

Chronic complications

In many patients, even before diagnosis, widespread damage occurs in the kidney, nerves, eyes or vascular tree (Figure 9.6). These long-term complications are to different degrees common to both types of diabetes, and their prevention or treatment are the real challenges for diabetes management and research.

Pathogenesis

It is important to determine whether or not these chronic problems are a direct consequence of hyperglycaemia. If so, then optimal control to achieve normoglycaemia would be expected to minimize them. Evidence has accumulated that this is broadly true for the so-called microvascular complications (mainly kidney, eye, nerves). The fact that similar complications arise in most types of diabetes, despite their different aetiologies, supports the hyperglycaemia hypothesis. The extensive Diabetes Control and Complications Trial (DCCT; 1992) confirmed that better control is associated with less severe complications in type 1 diabetes. The UK Prospective Diabetes Study (UKPDS; 1998) supported the same hypothesis in type 2 patients.

Other hypotheses have been proposed. It could be that an as yet unidentified primary lesion in diabetes is responsible independently for both the hyperglycaemia and the complications. If so, correcting one would not necessarily improve the other. Some complications could be secondary to the abnormal pattern or amount of insulin secretion, which is not completely rectified by conventional treatment. For example, the hyperinsulinaemia seen in many type 2 patients may contribute to blood vessel disease (macrovascular complications) or hypertension. Alternatively, the abnormally high levels of counter-regulatory hormones
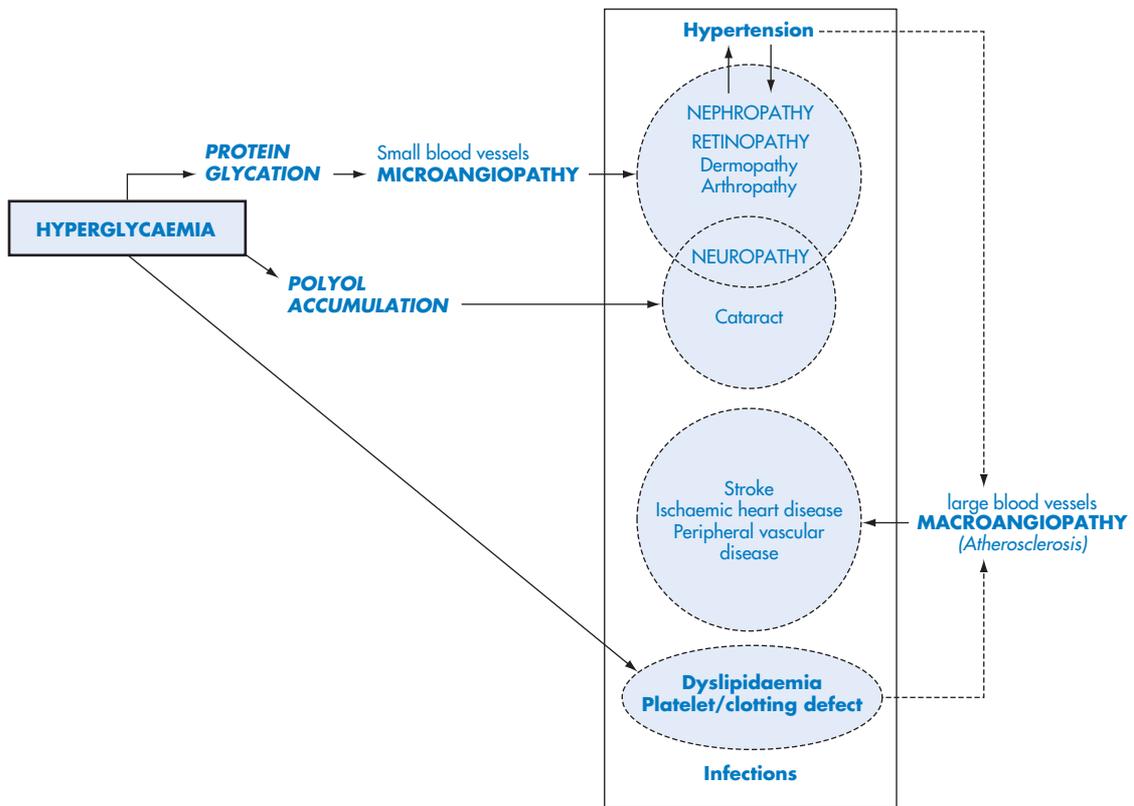

Figure 9.6 Possible pathogenetic mechanisms of chronic diabetic complications. The central box lists the clinical features. Also shown is possible interlinking of pathogenetic mechanisms.

usually found in diabetes may be deleterious. The involvement of growth hormone and insulin-like growth factor in angiopathy has also been investigated but no clear pattern detected. Finally, there seems to be a genetic variation in the susceptibility to different complications, regardless of the degree of glycaemic control.

Thus there is unlikely to be a simple answer, but the general strategy of normalizing blood glucose is well established as the best we currently have for minimizing complications.

Three general mechanisms are proposed for the pathological basis of the complications: **protein glycation** (glycosylation), abnormal **polyol** metabolism and accelerated **atheromatous** arterial changes.

Glycation

Normally, almost all body protein is to some extent glycated, i.e. glucose molecules from body fluids are covalently bound to free amine groups on protein side chains. The degree of glycation is directly proportional to the average blood glucose level. An accessible marker for this is Hb glycation, particularly the HbA1c fraction. Other proteins, and also lipids and nucleoprotein, throughout the body are similarly affected. In excess, one result is the formation of abnormal crosslinks between different regions of protein chains. Protein configuration is thus changed, disrupting secondary and tertiary structure and hence function. Basement membrane proteins seem particularly susceptible to glycation, the result being thickening and increased permeability (i.e. reduced selective barrier function). As basement membranes are present in most tissues, and especially in blood vessels, this could account for the widespread, multisystem distribution of diabetic complications. Chronic hyperglycaemia also results in oxidative stress through increases in mitochondrial superoxide formation, producing **advanced glycation end-products (AGPs)** that can cause a variety of damaging effects.

Basement membrane damage in capillaries and smaller arterioles can cause **microangiopathy** and subsequent ischaemia in almost any organ. **Retinopathy** is undoubtedly caused in part by this mechanism. **Neuropathy** may result from a combination of this and direct glycation of the sheaths of small nerve axons, e.g. sensory nerves. Similarly, glycation of the glomerular basement membrane probably causes the characteristic glomerular sclerosis of diabetic **nephropathy**, although renal arterial disease probably also contributes. Glycation of tendon sheaths and joint capsules may be responsible for the joint problems, particularly the stiffness in hands and feet, that some patients suffer; glycation of collagen in skin sometimes gives it a thickened, waxy appearance. The myocardium may also be affected, as may immune cells such as macrophages and leucocytes.

Polyol metabolism

Some tissues do not require insulin for glucose transport into their cells (Table 9.1), relying instead simply on diffusion down a concentration gradient. Thus, while other tissues are glucose-depleted in diabetes, these will accumulate excess glucose in the presence of hyperglycaemia. Being surplus to energy needs, some of the excess glucose is reduced to polyols such as sorbitol by the enzyme aldose reductase via an otherwise little used pathway (Figure 9.7).

The resulting polyols are not readily eliminated from the cells, possibly because they are more polar than glucose and of greater molecular weight. Furthermore, low dehydrogenase activity, particularly in the eye lens and nerve sheaths, means that they are not metabolized efficiently. The resultant accumulation of osmotically active molecules draws water into the cells, causing them to expand, severely disrupting their function and possibly killing them. Retinal blood vessels, the eye lens and the glomeruli may be damaged in this way, contributing to retinopathy, cataract and nephropathy, respectively. It has long been known that an analogous intracellular accumulation of galactitol in the lens is linked to the high prevalence of cataracts in the inherited metabolic disorder galactosaemia.

A further abnormality may also contribute. Myoinositol, an important intermediate in energy handling, may (although also a polyol) instead of accumulating become deficient. By a poorly understood series of steps this deficiency may impair nerve conduction (Figure 9.7).
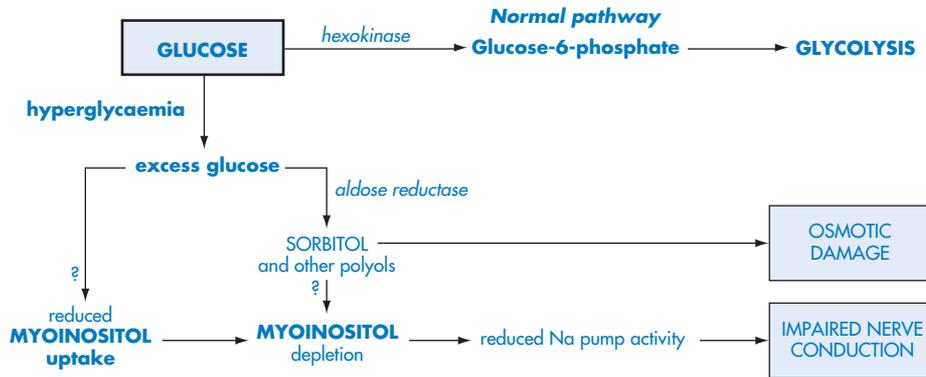
Figure 9.7   Polyol pathway and effects of polyol accumulation.

Macroangiopathy

Almost all people with diabetes suffer from increased obstructive vascular disease owing to a greatly increased predisposition to atherosclerosis. Several factors contribute to this. Because of their more active lipid metabolism, people with diabetes have raised plasma levels of triglycerides and lowered HDL, producing an unfavourable, atherogenic lipoprotein ratio (see Chapter 4, Figure 4.28). Furthermore, many type 2 patients are initially hyperinsulinaemic and insulin may itself be a growth factor for atheroma. Platelet aggregating ability is also usually raised, and hypertension is common. Thus major risk factors for atherosclerosis are intensified and cerebrovascular disease, stroke, IHD and peripheral vascular disease are common. Macroangiopathy also contributes to kidney disease.

Other mechanisms

As illustrated in Figure 9.6, other complications of diabetes occur, the pathogenesis of which remain obscure. Moreover, different complications may be inter-related or coexistent. Neuropathy may result partly from direct neuronal damage and partly from impaired blood supply to the nerve sheaths. Microangiopathy may result partly from glycation, partly from polyol accumulation and partly from hyperinsulinaemia. Once nephropathy is established, it promotes hypertension and vascular disease.

Diabetes and hypertension. There is an association between diabetes (especially type 2) and hypertension, as part of the metabolic syndrome. The precise cause and effect relationships have not yet been elucidated. Many hypertensives have insulin resistance, hyperinsulinaemia and impaired glucose tolerance, and insulin may have several hypertensive actions including promoting renal sodium retention, increasing sympathetic vasconstrictor activity and directly increasing vascular reactivity, via an effect on sodium handling. In some cases hypertension may be secondary to diabetic kidney disease, although the converse may also be true (see Chapter 4, p. 213). Alternatively, it may be that a third, as yet unknown, independent factor first causes insulin resistance, which then leads to both type 2 diabetes and hypertension. Hyperinsulinaemia could then be a common link in the vascular complications of both diabetes and hypertension.

The UKPDS (1998) found that rigorous control of blood pressure in diabetes reduced complications. However, prolonged therapy with two common antihypertensive agents, thiazide diuretics and beta-blockers, while effectively lowering blood pressure, can also lead to glucose intolerance or even overt diabetes. For this reason beta-blockers are not recommended as first-line treatment for hypertension in diabetes, and extra care is needed with both.

Clinical consequences

Almost any system in the body may be affected by diabetic complications, which is why diabetes is regarded as a multisystem disease (Table 9.13).

Eyes.   Diabetes is the most common cause of acquired blindness in developed countries. After 30 years of diabetes, about 50% of patients have some degree of retinopathy, and up to 10% become blind. The blindness is due to small-vessel damage in the retina, with dilatation, haemorrhage, infarction and ultimately excessive proliferation of new vessels that project into the vitreous humour (neovascularization). Retinopathy is frequently associated with nephropathy. People with diabetes also have an increased incidence of glaucoma and cataract.

Nervous system.   Diabetic neuropathy may affect any part of the peripheral nervous system, but most commonly starts with the peripheral sensory nerves, causing tingling and numbness (paraesthesias), loss of vibration sense or the sense of balance and limb position. It may interfere with the ability of blind people with diabetes in reading Braille. Autonomic neuropathy is potentially devastating because it can seriously disturb cardiovascular, gastrointestinal or genitourinary function, causing numerous symptoms; postural hypotension and impotence are common. Voluntary motor nerves are less commonly affected.

Renal.   Diabetic nephropathy is the cause of death in about 25% of type 1 diabetes. Predominantly a form of sclerosis of the glomerular basement membrane, it develops very slowly and so most commonly occurs in type 1 patients, up to 40% of whom may be affected. The increased glomerular filtration rate ('hyperfiltration') in early diabetes, which is due to hypertension and to the osmotic loading of hyperglycaemia, may overload renal capillaries. Nephropathy is heralded by microalbuminuria, with increasing proteinuria frequently progressing to end-stage renal failure, associated with worsening hypertension. Diabetic nephropathy is one of the most common causes of chronic renal failure, with people with diabetes comprising about 15% of the caseload of UK renal replacement therapy units. Renal decline is hastened by inadequate or tardy treatment of associated hypertension.

Cardiovascular.   About half of diabetic deaths are from the consequences of macroangiopathy. People with diabetes have a twofold greater risk of stroke and a fivefold greater risk of MI compared with matched non-diabetic subjects. Peripheral vascular disease is also common, with a 50-fold higher risk of peripheral gangrene. Some patients undergo progressively extensive amputation; usually the lower limbs (especially the feet; see below) are affected, but fingers are also at risk.

Hypertension is often associated with diabetes. Up to 50% of type 1 patients have it, and it is probably secondary to nephropathy. About a

Table 9.13   Clinical consequences of diabetic complications

System	Clinical features
Eyes	Retinopathy, glaucoma, cataract; blindness
Nerves	Sensory, autonomic and motor defects
Renal	Glomerulosclerosis; chronic renal failure
Cardiovascular	Ischaemic heart disease (angina, MI), peripheral vascular disease, stroke; cardiomyopathy; congestive heart failure
Locomotor	Slow-healing peripheral lesions; 'the diabetic foot'; amputations; joint stiffness
Immune	Increased susceptibility to infection

MI, myocardial infarction.

fifth of type 2 patients are hypertensive; the aetiology is uncertain but related to the metabolic syndrome, with obesity and hyperinsulinaemia contributing.

A rare complication is diffuse cardiac fibrosis (cardiomyopathy), which may lead to heart failure.

Locomotor.   The 'diabetic foot' is a common problem. In normal people minor foot injuries, such as a blister or a lesion from ill-fitting footware, usually heal before being noticed. In people with diabetes, however, these often develop into non-healing painless ulcers that become infected and irreversible damage sometimes occurs before medical attention is sought. In some cases this results in osteomyelitis or gangrene, both of which can lead to amputation. This results from a combination of poor peripheral sensation (neuropathy, so that the wound is not felt), poor peripheral circulation (angiopathy, so that healing is impaired) and reduced resistance to infection. All people with diabetes should see a chiropodist regularly. Correctly fitting footwear is essential. No pharmacist should attempt to treat any foot problem in a diabetic, or sell them 'corn plasters' or similar products. Any foot problem, however minor, should be referred to their chiropodist or doctor urgently.

Diabetes can also cause soft tissue damage resulting in limited joint mobility (stiffness), and a characteristic arthropathy, usually in the feet, where angiopathy and sensory neuropathy also contribute (Charcot joints; see Chapter 12).

Systemic.   People with diabetes are very prone to infections owing to an impaired immune response caused by defects in immune and inflammatory cells. Recurrent bladder infection is common, which can ascend to cause pyelonephritis: urinary retention and stasis due to autonomic neuropathy exacerbate this. Skin infections are also frequent, and contribute to foot problems.

Management of complications

General strategy
The overall approach to preventing diabetic complications, minimizing them or delaying their onset combines control of blood glucose, risk factor reduction and regular monitoring.

Optimal glycaemic control.   Although the aetiology and pathogenesis of the complications are still uncertain and likely to be multiple, the main clinical approach has been to aim for scrupulous control of blood glucose levels, keeping them within the normal range, in an attempt to mimic physiological normality. This is based on the assumption that complications are due to hyperglycaemia. This seems to be particularly likely for the microvascular, possibly polyol-related, complications in nerves, eyes and kidney. Evidence derives from clinical trials, including those using the more 'physiological' treatments such as continuous SC insulin infusion (p. 624) or other methods of achieving 'tight' glycaemic control. This means keeping fasting blood glucose levels below 7 mmol/L and not exceeding 11 mmol/L after meals, and may necessitate conversion to insulin therapy in poorly controlled type 2 patients.

Good control has been shown to reduce the incidence of complications. The most convincing evidence in type 1 diabetes was the DCCT trial, which reported significant slowing of deterioration in retinopathy, microalbuminuria and, to a lesser extent, neuropathy. The UKPDS trial found broadly similar benefits in type 2 patients and also strongly demonstrated the synergistic role of hypertension in exacerbating complications and the importance of achieving normotension as well as normoglycaemia. Unfortunately, this study failed to identify clearly the treatment mode that offered the best protection, although this had been one of its aims.

An unwanted side-effect of tight control is that by keeping the average blood glucose low the incidence of hypoglycaemia is increased, especially among elderly and unstable diabetics. In the DCCT trial there was a threefold increase in the incidence of hypoglycaemia when under tight control. This means that in some circumstances a compromise is necessary because of the acute and the long-term complications of frequent hypoglycaemic attacks. Thus, older patients in whom the diabetes onset occurred quite late, i.e. type 2, are usually allowed to run

higher average levels. The long delay in onset of complications will mean that life expectancy may be little reduced, whereas quality of life would be markedly reduced by frequent hypoglycaemia.

For the macrovascular complications (cardiovascular, cerebrovascular and peripheral atherosclerosis) this approach is less successful, perhaps because insulin and related endocrine abnormalities and hypertension may contribute directly, independently of glycaemia. It is still unknown whether the generally higher insulin levels associated with tight control regimens can actually exacerbate some macrovascular problems.

Minimize risk factors. It is important to control any additional risk factors that could exacerbate organ damage, especially via atherosclerosis. These include smoking, hypertension, obesity, hyperlipidaemia and hyperuricaemia.

Monitoring. This essential component in minimizing complications is discussed below (see also Table 9.22).

Reduce polyol accumulation. According to the polyol hypothesis for certain of the complications, it should be possible to impede this process by interfering with the metabolism of polyols. Unfortunately, aldose reductase inhibitors (e.g. sorbinil), although they do minimize sorbitol accumulation and prevent myoinositol depletion, have not proven clinically successful in reversing or even retarding neuropathy, cataract, nephropathy or retinopathy. Dietary myoinositol supplementation has also been unsuccessful.

Specific complications
Nephropathy. There are currently four methods that have been shown to slow the rate of deterioration in renal function:

- Careful glycaemic control.
- Control of hypertension.
- Use of ACEIs or ARAs.
- Moderate protein restriction (in more advanced nephropathy).

It is essential that people with diabetes are monitored annually for the onset of hypertension and microalbuminuria. In treating hypertension, ACEIs (and ARAs) seem to have an additional direct beneficial effect in diabetes, dilating intrarenal (efferent glomerular) vessels and thus minimizing glomerular hypertension. ACEIs are increasingly used early unless contra-indicated e.g. by bilateral renal artery stenosis, which is always a possibility in someone with diabetes. ACEIs are indicated when there is hypertension with proteinuria or microalbuminuria; in type 1 diabetes their use is recommended if there is microalbuminuria, even with normotensive patients. However, at present there is no evidence that ACEIs benefit normotensive diabetes with no evidence of nephropathy. Other antihypertensives may not offer similar extra benefits but another antihypertensive should be used if ACEIs are contra-indicated or inadequate at reducing pressure.

Once established, renal failure is managed as usual (see Chapter 14), although haemodialysis is more difficult because of vascular and thrombotic complications. Continuous ambulatory peritoneal dialysis is particularly suitable in diabetes because insulin may be administered intraperitoneally (thus directly entering the portal circulation, which is more physiological). However, there may be a problem with the glucose, which is usually added to dialysis fluid to promote water removal. People with diabetes are nowadays unlikely to be given low priority for renal transplantation, as they tended to be in the past, and this is sometimes combined with pancreatic transplantation (p. 605). There are however some problems: the poor general health of these patients and multiple organ damage increase the operative risk, and there is an increased likelihood of post-transplant infection owing to the immunosuppression required. Nevertheless, graft survival is only about 10–15% poorer than the average for renal transplants.

Macroangiopathy. The usual dietary constraints on saturated fat and cholesterol are important. Monounsaturated fats, especialy olive oil, are recommended. The HPS study supported the use of statins for all people with diabetes of either type at cardiovascular risk, whatever their lipid level, and this is now accepted. The CARDS study extended the recommendation in

type 2 diabetes to those patients with even normal or low lipids, regardless of CVS risk. However, such routine use is not yet officially recommended. In the PROactive trial type 2 patients with pre-existing macrovascular disease used pioglitazone in addition to their usual treatment. A small but significant reduction in all-cause mortality, MI and stroke was achieved but at the expense of weight gain and an increase in heart failure.

Other conventional atheroma risk factors such as smoking and hypertension must also be scrupulously addressed (see Chapter 4).

Neuropathy and neuropathic pain.   Little can be done for diffuse neuropathy, but neuropathic pain can be partially relieved and fortunately severe attacks, although prolonged, tend to remit. Drug therapy may be of help in the sometimes excruciating pain. Conventional analgesic or anti-inflammatory drugs are generally ineffective. A variety of other drugs have been tried and the first-generation tricyclic antidepressants (e.g. *amitriptyline*) are standard first-line therapy. Second-line agents include anticonvulsants such as *carbamazepine*, *gabapentin* or *topiramate* (see also Chapter 6).

Retinopathy.   Retinal disease is conventionally treated by laser photocoagulation.

Management

Aims and strategy

Preventative methods for diabetes are as yet poorly developed. More progress has been made with potentially curative surgery. However, at present the vast majority of people with diabetes require long-term management of established disease.

The cardinal aim of management in diabetes is to keep blood glucose levels within the normal range; this should produce patterns of glucose and insulin levels in the blood similar to those that follow normal changes in diet and activity (see Figure 9.4). Blood glucose levels should remain below the maxima in the WHO definition for impaired glucose tolerance (Table 9.1). Ideally, this would require a continuous basal level of insulin to maintain metabolism, supplemented by rapid pulses following meals and a reduced level during exercise.

Optimal management should attain three important interlinked aims:

- Prevent symptoms.
- Maintain biochemical stability.
- Prevent long-term complications.

At present, this ideal is not achievable. Even if pancreatic transplantation were to be perfected, insulin receptor defects might still remain. Current therapy is limited to artificially manipulating diet and insulin (endogenous or exogenous) in order to mimic normal patterns as closely as is practicable.

The older directive, paternalistic medical model for such manipulation is no longer acceptable, clinics preferring to negotiate a 'therapeutic contract' with the patient. The aim is to agree a desired level of control – optimal, prophylactic or perhaps merely symptomatic – based on the severity of the disease and the patient's age, understanding, likely compliance and normal way of life.

Sometimes it is inadvisable to strive too zealously to approach the ideal. For the elderly, where long-term complications are of less concern, keeping symptoms at a tolerable level without excessive disruptions to normal life patterns may be adequate. For this, the target need only be to achieve random blood glucose levels below 12 mmol/L. In some patients the incidence of hypoglycaemic attacks is unacceptably high if control is too tight. The advent of the insulin pen has enabled the flexibility to achieve these differing aims.

Prevention

Because type 1 disease involves immune destruction of the pancreas, immunotherapy has been attempted experimentally, as early as possible after initial diagnosis or even in the pre-symptomatic stage in at-risk individuals, e.g. where there is a strong family history or impaired glucose tolerance. In animal models anti-T cell antibodies, bone marrow transplantation,

thymectomy, *azathioprine* and *ciclosporin* have been tried. In the Diabetes Prevention Trial-1 early introduction of insulin therapy, to 'spare' the beta cells and perhaps to reduce their expression of autoantigens, was unsuccessful. Another trial using *nicotinamide* to inhibit macrophages has also failed to reduce progression.

However, considerable pancreatic damage has usually occurred by the time symptoms are noticed. Only about 10% of functional islet cells then remain, so no great improvement can be expected. Research is now concentrating on discovering reliable early prognostic markers, such as islet cell antibodies. Patients at risk could then be identified by screening.

No specific aetiological agents have been identified for type 2 diabetes, but risk factors are well known. These correspond with many of the well-established cardiovascular risk factors associated with the lifestyle of industrialized countries, i.e. diets high in sugar and fats and low in fibre and slowly absorbable complex carbohydrates, lack of exercise and obesity. Weight loss in particular has been shown to delay development of the disease in high-risk individuals and achieve remission in severely overweight people with diabetes. In the Diabetes Prevention Programme both intensive lifestyle intervention and *metformin* significantly reduced the risk of developing diabetes in people with impaired glucose tolerance. Another trial showed benefit with *acarbose*. In the Finnish Diabetes Prevention Study dietary modification and exercise was similarly beneficial. More recently the DREAM trial with *rosglitazone* over 3 years showed significant reduction in progression from impaired glucose tolerance/impaired fasting glycaemia to overt type 2 diabetes.

Cure: organ replacement

Pancreatic transplants are now a realistic option. Dual renal plus pancreatic transplantation is especially considered for people with diabetes with advanced nephropathy, because such patients are going to have to undergo immunosuppression anyway. One-year patient survival exceeds 90% and 5-year graft survival exceeds 50%. Transplantation substantially increases the quality of life, although of course is still limited by the risks of surgery and the penalty of lifelong immunosuppression (Chapter 14).

The implantation of donated **beta-islet cells** is still experimental but looks promising. Stem cells may offer even more fundamental a solution for the future. A number of **artificial pancreas** devices have been devised, although none is yet available for routine use (p. 624).

Therapeutic strategy

Using conventional methods, the only way for a diabetic to enjoy relatively normal eating and activity (i.e. unpredictable, unplanned and uncontrolled) would be to have frequent, precisely calculated injections of soluble insulin (or appropriate doses of a rapidly acting oral hypoglycaemic [insulin secretagogue] drug). The dose would be based on blood glucose measurement or guided by experience and recent diet and activity level: thus insulin is supplied on demand in a manner emulating normal physiology (see Figure 9.4). With the introduction of insulin pens, such an 'insulin demand-driven' strategy is becoming practicable, although dosage adjustment is still imprecise. The artificial pancreas, if perfected, may prove a better option.

'Insulin supply drive'

The alternative (and original) approach, still used for many older patients, is to turn physiology on its head and to accept a model driven by insulin supply. Instead of matching insulin supply to instantaneous changes in demand, demand in the form of diet and activity is adjusted and controlled to conform to available insulin (whether endogenous or administered exogenously). Because both drugs and insulin must be given prospectively this is in effect 'feeding the insulin', as opposed to the normal situation where insulin follows feeding. Meals and activity must be regular and of predictable composition: explicit adjustments in drug or insulin dose must be made to allow for deviations (Figure 9.8).

This places considerable constraints on patients, particularly children. Education and counselling are extremely important and Diabetes UK performs a valuable role here.
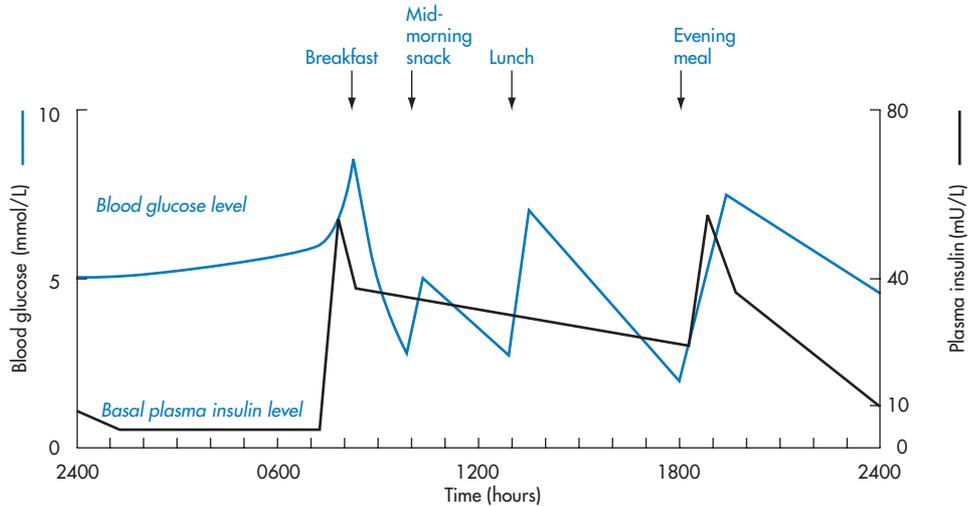
Figure 9.8 Matching food intake to available insulin – schematic representation. In the insulin supply-driven model, insulin levels are maintained artificially either by direct injection or by augmentation using oral hypoglycaemic agents. To prevent hypoglycaemia, sufficient glucose must be provided by the diet at regular intervals. Note what would be the effect of missing the mid-afternoon snack: blood glucose would start to fall dangerously low just before the evening meal. Unusual activity, by causing increased glucose demand, would complicate this picture.

People with type 1 diabetes are inevitably reasonable compliers in the strictest sense, in that the severe metabolic upset precipitated by drug defaulting is a powerful motivator. Nevertheless, excellent compliance with diet, and the very tight control of blood glucose demanded for avoidance of long-term complications, is less common, especially in type 2.

Treatment modes

Dietary management is the bedrock of treatment. All people with diabetes, irrespective of other treatments, require some control of their eating and exercise patterns, both in terms of total calorific intake, types of nutrients and eating schedule. Indeed, about half of patients will need no more than this, especially those who lose weight. A further 25% will need to augment their natural insulin with drugs. The remainder will need insulin.

The initial choice is usually related to how the patient first presents (Figure 9.9). Younger patients, who are frequently non-obese, usually present unambiguously with type 1 insulin-dependent diabetes, although a variable insulin-independent ('honeymoon') period may occur following diagnosis.

Older patients, who are often obese, will almost always be type 2 and must be tried first on diet alone. Should this fail, drug therapy will be added. All drugs used in diabetes are classed in the BNF as **antidiabetic**, and this term will be used generically here (although NICE refers to these drugs as 'glucose-lowering drugs'). The older term 'oral hypoglycaemic' is obsolescent, owing to the development of classes of drugs that do not directly lower blood glucose. Those that do, i.e. sulphonylureas and meglitinides, are more accurately described as insulin **secretagogues**.

Type 2 patients are usually to some extent overweight on presentation, and a biguanide is the first choice. Otherwise a sulphonylurea is selected. Sometimes a synergistic combination of the two types will be required. For those for whom these measures are ineffective a glitazone may be added. For some patients even this is
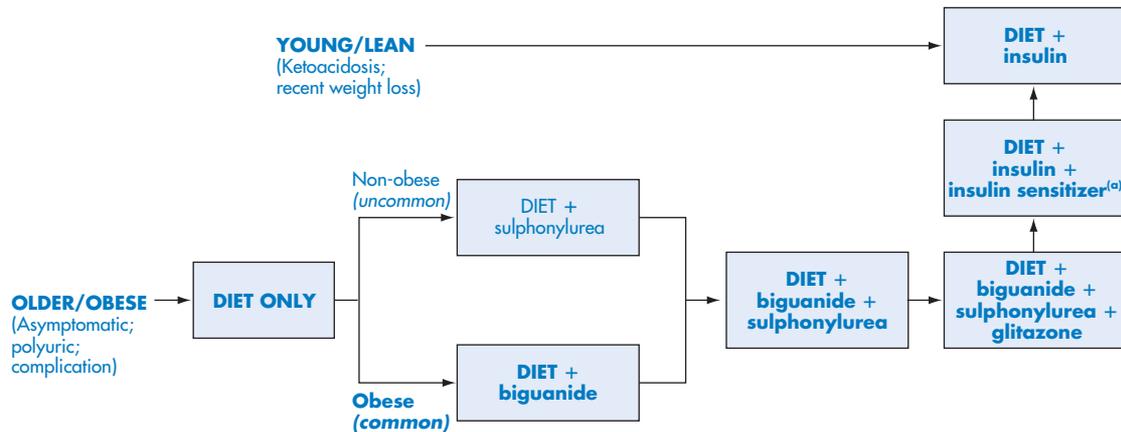
Figure 9.9   Treatment strategy for diabetes related to presenting symptoms. Meglitinides may be substituted for sulphonylureas. A glitazone or glucosidase inhibitor can be added or substituted at any stage to attempt to improve control before moving to next stage (but avoid meglitinide + sulphonylurea). See text. [a]Insulin sensitizer = metformin or glitazone.

unsatisfactory and, especially if ketoacidosis occurs, insulin treatment is needed, as it will be eventually in those whose disease progresses faster. Type 2 patients may also need insulin temporarily during periods of increased requirement such as major infection, surgery or pregnancy. Combining antidiabetic drugs with insulin therapy is being used increasingly (see below).

At any point in this sequence, an adjunctive drug that reduces intestinal glucose absorption or reduces insulin resistance may be added.

Initiation of treatment

On first diagnosis, all patients will be fully examined and investigated to establish baseline measures for monitoring development and progression of any complications. This will include ophthalmological, renal, cardiovascular, neurological, lipid and foot assessment.

Some patients will need to be treated first in hospital, especially type 1 patients first presenting with ketoacidosis. Blood glucose levels will be measured 3-hourly during this period, to establish the diet and possibly the drug or insulin dosage necessary to achieve the agreed level of control. After discharge some will continue to attend as outpatients. Others will be managed by general practice clinics, which often include specialist diabetic nurse practitioners. However, regular diabetic clinic visits are desirable if they have developed complications or management becomes difficult. Some type 1 and most type 2 patients without acute complications may be treated by their GP from the outset.

Diet

Most type 2 patients must first be encouraged to try to control their disease on diet alone, and no patient taking antidiabetic drugs or insulin should believe that these obviate the necessity to control their diet. Recommendations about diet have evolved in several important ways. Fats are now discouraged, while complex carbohydrate and fibre are encouraged, and the overall approach is now far less restrictive. The recommended diabetic diet, save in a few respects, now closely resembles the normal healthy diet that everyone should eat: regular meals low in fats, simple sugars and sodium and high in complex carbohydrate (starch) and fibre.

Formerly, inflexible, unrealistic or impractical prescriptions and restrictions (diet sheets, 'exchanges') took little or no account of the psychological importance of individual dietary habits, dietary preferences and ethnic variations.

The result was poor compliance complicated by guilt and anxiety. The modern approach recognizes that:

- Dietary records or recall are an imprecise basis for future modification.
- Nutrient uptake varies even from precisely regulated and measured portions, owing to the interactions between foodstuffs, variations in temperature, physical form and degree of chewing, etc.
- Compromise is needed to devise a regimen with which the patient can be concordant.

Thus a perfect diabetic diet is difficult to achieve in practice, and although the pursuit of it is worthwhile, this could be counter-productive in some patients. Rather, efforts are made to ensure that patients understand, in their own fashion, what the aims are. Counselling and education are then used to maximize motivation. Advice from a dietician with experience in modifying diabetic diets to suit individual lifestyles can help achieve good compliance.

Four aspects of diet need to be considered (Figure 9.10):

- Total energy intake.
- Constituents.
- Timing.
- Variation.

Energy intake

All patients need to adjust their calorific intake to achieve and maintain the desired bodyweight for their size, aiming for a body mass index of about 22 kg/m^2. For most people with type 2 diabetes, who are frequently obese, this implies a weight-reducing diet. Reliable tables are now available to predict the required energy intake according to age, gender, activity level and lifestyle.

Constituents

Macronutrients
The unselective restriction on carbohydrate that used to characterize diabetic diets is now considered misconceived. Carbohydrate is not harmful if taken mainly as slowly absorbed complex polysaccharides, e.g. starch. Such carbohydrates allow people with type 2 diabetes to make best use of their limited endogenous insulin secretory capacity by not raising postprandial blood glucose too rapidly. Foods can be classified
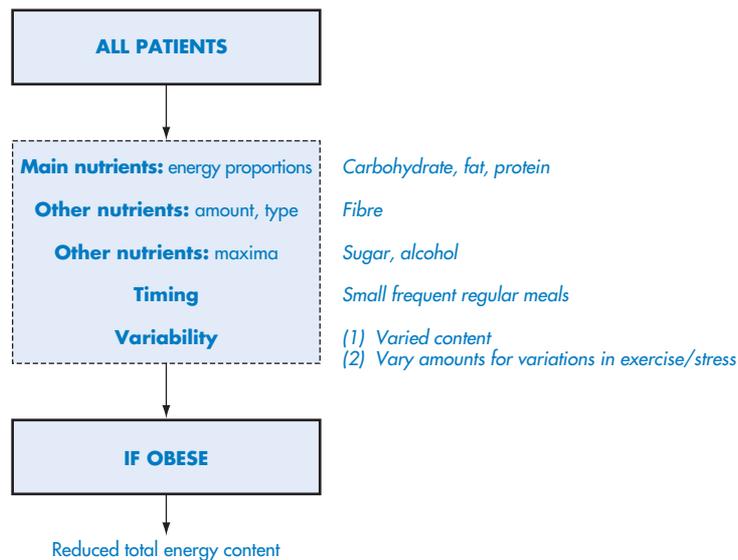

Figure 9.10   Dietary considerations in diabetes (see also Table 9.14).

according to their **glycaemic index**, which represents the ratio of the total glucose absorption they produce compared with that from a standard test meal of wholemeal bread and cottage cheese. The lower the index the better, and representative values are rice 80%, potatoes 77%, pasta 60% and lentils 45%. Foods acceptable to various ethnic minorities, such as chappatis, kidney beans, chickpeas, etc. are also now encouraged where appropriate.

The relatively high fat content of early diabetic diets, which was needed in a carbohydrate-reduced diet to provide calories more cheaply than with protein, is now seen to be dangerously atherogenic. A reduced fat intake, low in saturated fats and comprising about one-third polyunsaturated and one-third monounsaturated fat (e.g. nuts, fish, olive oil) is now encouraged. Cholesterol itself is usually reduced inherently along with saturated fats. There are no particular constraints on protein except for patients with suspected nephropathy, when restriction is indicated.

Other nutrients
A small amount of simple sugar (sucrose) is now considered acceptable, if the calorific content is accounted for. This is usually consumed as a constituent, e.g. of baked products. Artificial non-nutritive sweeteners are still preferred and patients must be advised to monitor their intake of 'hidden' sugar in processed foods. So-called 'diabetic foods' often contain sorbitol or fructose and, while they may not raise blood glucose as much as sucrose, have a high energy content and cause diarrhoea in excess. They are also expensive, offer nothing that a well-balanced diabetic diet cannot offer, and are not recommended by Diabetes UK.

Alcohol is not prohibited if its high calorific content is accounted for and its hypoglycaemic effect is appreciated, i.e. it should be taken with some carbohydrate. Recent evidence of its protective effect against heart disease suggests that once again similar recommendations should apply to the diabetic population as to the population as a whole. There should be little added salt, to minimize rises in blood pressure.

Fibre is extremely important. Although fibre is primarily carbohydrate, the terminology is somewhat inconsistent; however, the distinctions are relevant (Figure 9.11). Starch, in staple foods like bread, potatoes and rice, is the main digestible carbohydrate energy source. Older classifications grouped all other indigestible matter together as 'dietary fibre', but there are important and distinct components. The non-starch polysaccharides (NSP) are now known to be particularly important in diabetes. They provide no energy but further delay absorption of glucose from starch digestion (see above), and by forming intestinal bulk promote a feeling of satiety that may reduce appetite and therefore help weight control.

The (semi)soluble or viscous fibres and gums found in fruit, vegetables and pulses (Figure 9.11) produce in addition a modest reduction in blood cholesterol, possibly by binding bile salts and thereby preventing their enterohepatic recirculation. The insoluble NSP fibres, as in bran and unmilled cereals and grains, have little effect on cholesterol, but contribute to stool bulk along with other fibrous residues, e.g. lignin. Although undigested in the ileum, some of this material is hydrolysed by colonic flora to release absorbable and metabolizable carboxylic acids.

Proportions
The recommended proportions of macronutrient energy intake are approximately 60:30:10 (carbohydrate:fat:protein; Table 9.14); traditional diabetic diets used to be nearer 25:65:10. Within the fats, only a third should be saturated fats. How the patient implements this has also changed. Clinics no longer issue rigid menus, kitchen scales and detailed tables of what can be exchanged for what. More generalized recommendations with much wider variability are found to be more successful.

One such approach simply visualizes a meal plate divided into segments (Figure 9.12). About two-thirds contains polysaccharide: equal parts staple carbohydrate sources such as rice, pasta or potatoes starch and fibre such as fruit or vegetables. The remainder is mostly composed of fats and protein sources such as meat, fish and dairy products. A small amount of sugar is allowed. The patient is advised to construct each meal in these proportions. This roughly conforms to the recommended proportions, allowing for some
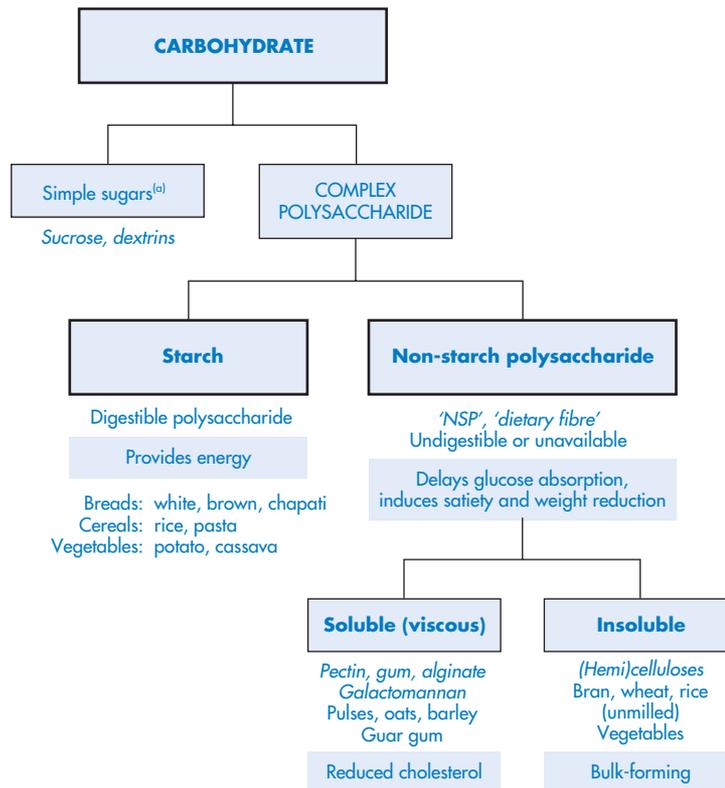
Figure 9.11   Different forms of dietary carbohydrate, including fibre; with functions and examples of foodstuffs. [a]Avoid as far as possible.

fat and protein being included along with the carbohydrate.

Timing

Small, regular, frequent meals are important. This means similar calorific intake at all main meals and regular snacks in between. For type 2 patients this minimizes the load put on the pancreas at any one time. For both types it helps to keep blood glucose levels within closer limits, minimizing the risk of hypoglycaemia between drug or insulin doses and the risk of postprandial hyperglycaemia. There is some evidence that this too is a pattern that might benefit the general population. Nibbling or 'grazing' appears to produce lower average plasma lipid and blood glucose levels and less obesity compared with a similar calorific intake obtained from intermittent, larger meals.

Variation

People with diabetes need to understand that these constraints do not prevent them having a varied, appetizing and nutritious diet. They should also understand how to augment their diet to match any unplanned or unusual exercise or stress so as to avoid hypoglycaemia. Temporary changes in a patient's metabolic requirements (as in serious illness) or oral absorptive capacity (e.g. gastroenteritis) require appropriate adjustment, which may involve temporary insulin therapy in a type 2 patient, and regular blood glucose monitoring is then essential.

Type 1 patients using the 'insulin pen' will generally be even more flexible (see below). In mildly diabetic elderly patients the diet will also be far less rigid, for reasons already discussed. On the other hand, the diets of growing children need constant reassessment. The availability of

Table 9.14   Nutrients in diets recommended for diabetic and general population[a]

	Nutrition Subcommittee of the Diabetes Care Advisory Committee of Diabetes UK [b]	National recommendations for optimal UK diet[c]
Carbohydrate	50–60%	50–60%
Total fat	30–35% *[saturated fat 10%]*	30–35%
Protein	1 g/kg body weight	10%
Simple sugars	≤10%	60 g
Cholesterol[d]	Not specified	Not specified
Soluble fibre[e]	Not specified	18 g
Alcohol	2 units (female)	2 units (female)
	3 units (male)	3 units (male)

[a] Percentages are rounded and given as maximum proportion of total energy intake. Amounts are per day.

[b] Diabetes UK, *Diabetic Medicine* 2003; **20**: 786–807.

[c] Based on reports from National Advisory Committee on Nutrition Education (NACNE, UK DoH) and Committee on Medical Aspects Of Food Policy (COMA, UK DoH).

[d] Cholesterol intake usually automatically reduced sufficiently if saturated fat intake less than 10%.

[e] 15 g soluble fibre equivalent to 18 g non-starch polysaccharides (NSP) or 30 g total dietary fibre.
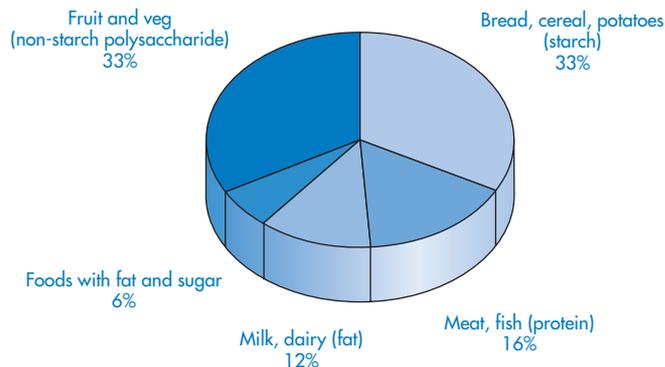

Figure 9.12   The 'plate model' of meal planning recommended by Diabetes UK. Each meal should be constructed roughly of the types of foods and in the proportions shown, visualizing them as making up the complete plate of food. (Adapted from www.diabetes.org.uk/eatwell/food_diabetes/index.html).

nutrients and the habits and constraints of different ethnic groups also need to be taken into account. Dieticians are an essential part of the diabetic team.

Diet as sole management may fail in up to two-thirds of type 2 patients. Primary failure is usually due to poor compliance, poor motivation or inadequate counselling. Secondary failure usually results from disease progression, with falling insulin production. The next stage is to introduce oral antidiabetic drugs.

Oral antidiabetic drugs

Aim and role

Oral antidiabetic drugs (OADs) are used as the next step for type 2 patients in whom diet has failed to control their condition adequately. The majority may then be controlled by a combination of diet and oral drugs for a number of years, but some type 2 patients may eventually require insulin treatment.

There are four main therapeutic targets for OADs (Table 9.15). Doubts over the safety of some of these drugs have now been resolved. The results of the University Group Diabetes Programme (UGDP) trial in the 1970s, which suggested significant toxicity in the sulphonylureas, are now discredited. *Phenformin*, an early biguanide, caused numerous deaths from lactic acidosis and was withdrawn. Newer biguanides are much safer: only *metformin* is currently available in the UK; elsewhere *buformin* is used.

Novel incretin analogues are undergoing trials. Incretin is a newly discovered peptide hormone, secreted in the small intestines following food intake, which enhances insulin secretion and suppresses glucagon, slows gastric emptying and reduces food intake. It was isolated from a lizard that eats only four times a year. *Exenatide* has been shown to lower glycated Hb levels and weight. Sitagliptin inhibits incretin inactivation.

All OAD strategies depend on endogenous insulin secretion and are therefore effective only in patients with type 2 disease who retain appreciable beta-cell function. Ketosis-prone patients, patients with brittle disease or those whose fasting blood glucose exceeds 15–20 mmol/L, almost invariably need exogenous insulin, in both type 1 and type 2 patients.

Action

These drugs have different, albeit complementary and sometimes overlapping, actions on the underlying abnormalities in type 2 diabetes, so combination therapy is indicated if monotherapy fails.

Alpha-glucosidase inhibitors (*acarbose*) inhibit the final stage of the digestion of starch within the intestine by blocking the enzyme disaccharidase. This reduces the rate of glucose absorption and thus the postprandial glucose load presented to the islet cells. Thus, a pancreas with a limited insulin secretory rate might be better able to handle this load with less hyperglycaemia. It can be regarded as anti-hyperglycaemic rather than a hypoglycaemic agent. It has a relatively small effect on glycaemia and is used only as an adjunct to other therapy, but may be added at any stage to improve control.

Sulphonylureas enhance the release of preformed insulin in response to circulating glucose, partly by increasing beta-cell sensitivity to blood glucose. This mimics the acute phase of the normal response to hyperglycaemia. However, sulphonylureas do not directly stimulate subsequent insulin synthesis. Inhibition of

Table 9.15   Oral antidiabetic drugs

Therapeutic target	Site of action	Group	Examples
Reduce or retard glucose uptake	Intestine	Alpha-glycosidase inhibitors	Acarbose
Enhance insulin secretion[a]	Pancreas	Sulphonylureas	Tolbutamide, glibenclamide, glipizide, glimepiride, gliquidone
		Meglitinides	Repaglinide, nateglinide
Enhance insulin action	Peripheral receptors	Biguanides	Metformin, buformin[b]
Reduce gluconeogenesis	Liver		
Reduce insulin resistance	Peripheral receptors (esp. adipose tissue)	Thiazolidinediones (Glitazones)	Rosiglitazone, pioglitazone

[a] Insulin secretagogues.

[b] Buformin not licensed in UK.

glucagon has also been suggested. Pharmacodynamically, they differ only in relative potency but there are important pharmacokinetic differences between them. Sulphonylureas can be combined with most other OADs except the meglitinides. Although some doubt was cast over the safety of the long-established combination with *metformin* by the UKPDS, this has not been confirmed and the combination is still widely used.

Meglitinides (prandial glucose regulators) also stimulate insulin release but not at the sulphonylurea receptor. They are claimed to do so more specifically in response to the blood glucose level and thus to mealtime glucose load, making them more glucose-sensitive. They have two main advantages over sulphonylureas. A more rapid onset means they can be given 15 min or less before a meal, giving patients more flexibility and control; and their shorter duration of action reduces the likelihood of postprandial hyperinsulinaemia and between-meals hypoglycaemia. In addition, if a meal is missed they can easily be omitted. *Nateglinide* has a prompter and shorter action than *repaglinide*. Currently *nateglinide* is only licensed for use with *metformin*, whereas *repaglinide* can be substituted for sulphonylureas at any stage. The combination of a meglitinide with a sulphonylurea is irrational.

Biguanides do not stimulate or mimic insulin but are insulin sensitizers. They have two main actions: they increase peripheral glucose uptake and utilization and they inhibit hepatic gluconeogenesis and release of glucose from the liver into the blood. The underlying effect is probably via a general inhibitory action on membrane transport. Intracellularly, this would prevent glucose entering mitochondria, thus promoting anaerobic glycolysis in the cytosol. Because this is less efficient than aerobic glycolysis, cellular glucose uptake and utilization are increased. This may also account for a tendency to cause lactic acidosis. In the intestine, reduced membrane transport may be useful in slowing and reducing glucose absorption. There may also be intestinal lactate production. They may also have an anti-obesity action. Only *metformin* is licensed in the UK.

Biguanides can be combined with most other OADs.

Glitazones (thiazolidinediones: *rosiglitazone* and *pioglitazone*) are also insulin sensitizers. They activate a nuclear transcription regulator for an insulin-responsive gene (peroxisome proliferators-activated receptor-gamma, PPARγ), which has numerous complex effects on lipid and glucose metabolism. An important component is to promote triglyceride uptake and peripheral adipose growth. The effect of this is to reduce triglyceride availability, increase glucose utilization, reduce insulin resistance and thus reduce insulin levels. They also shift fat from visceral, muscle and hepatic sites to peripheral adipose tissue, which although resulting in an increase in weight, produces a more favourable cardiovascular risk. This is partly because they alter blood lipids favourably, lowering triglyceride and raising HDL levels.

The PROactive study suggested this group may reduce complications, both macrovascular (by reducing insulin and lipid levels) and microvascular (by reducing hyperglycaemia) complications, but this has not yet been confirmed. The prototype, *troglitazone*, was withdrawn soon after release owing to liver toxicity but *rosiglitazone* and *pioglitazone* are safe and effective either alone or in combination if other OADs fail to achieve control, although their precise role has not yet been determined. Currently NICE recommends that they should not be added as second-line drugs to either *metformin* or a sulphonylurea, except when these latter two drugs cannot be used in combination owing to contra-indications or intolerance.

Biopharmacy and pharmacokinetics

Sulphonylureas are generally well absorbed although potential bioavailability differences mean that patients should avoid changing formulation or brand. Most sulphonylureas are more than 90% protein-bound (except *tolazamide*, 75%), and so are liable to competitive displacement interactions.

There are important differences in clearance, half-life and duration of action, which determine frequency of administration, precautions and contra-indications. Clearance is usually hepatic with subsequent excretion of inactive or less active metabolites (Table 9.16; Figure 9.13),

usually renally. The older *chlorpropamide* is partially cleared renally and also has active metabolite, which accounts for its long half-life. Those with inactive metabolites (e.g. *tolbutamide*) generally have the shortest half-lives. Some sulphonylureas have metabolites that are chiefly excreted in the bile, which makes them more reliant on hepatic function.

The duration of action, or biological half-life, is related to the plasma half-life but is often longer, owing partly to the activity of metabolites. *Chlorpropamide* has too long a duration of action and frequently produces between-meals hypoglycaemia; it has little if any role now and is contra-indicated in the elderly. The other popular first-generation sulphonylurea, *tolbutamide*, fell from favour because its action was felt to be too short, requiring frequent dosing. However, for this reason it may be useful in the elderly, to minimize hypoglycaemia. Most newer second-generation drugs avoid these problems, but there are wide interpatient variations in the handling of all sulphonylureas and dose regimens must be individualized. *Glibenclamide* is a special case because it is concentrated within beta-cells so its biological half-life is considerably longer than its plasma half-life. For this reason, it too is avoided in the elderly.

Biguanides differ substantially from the sulphonylureas, being poorly absorbed, little protein-bound and cleared predominantly by renal excretion (with about 30% cleared by hepatic metabolism). *Metformin* has a short half-life and may require thrice daily dosing at higher doses. However, modified-release preparations are available for dosages up to 1 g twice daily; higher doses need standard-release therapy. *Buformin* is longer-acting.

Renal clearance of biguanides may exceed glomerular filtration rate, implying some tubular

Table 9.16   Relative duration of action of sulphonylureas

Relative duration of action[a]	Very short	Short	Medium	Long	Very long
Daily dose frequency	2–3	2–3	1(–2)	1	1
Examples	Gliquidone	Tolbutamide	Glimepride, glipizide, gliclazide	Glibenclamide	Chlorpropamide[b]

[a] Approximate descriptive indication of relative durations: precise time will vary from patient to patient.
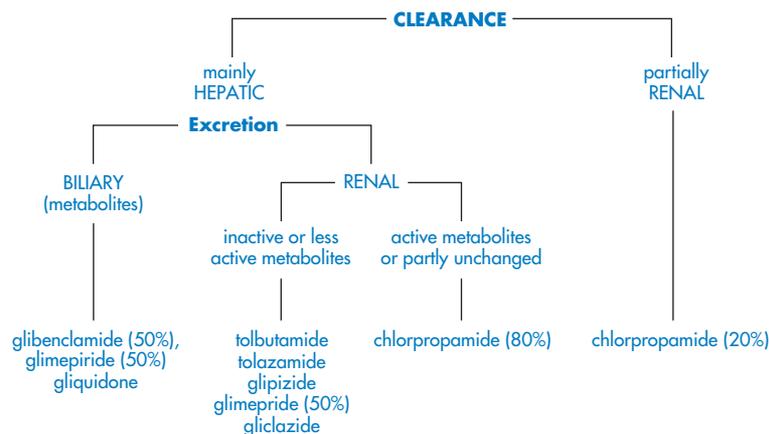
[b] No longer recommended.

Figure 9.13   Clearance and excretion of the sulphonylureas.

secretion. Thus minor renal impairment, un-noticed because of a normal serum creatinine level, might still permit significant accumula-tion, and renal function monitoring is essential with their use.

Meglitinides are rapidly absorbed, reaching a peak within 1 h and have a very short half-life, being cleared and eliminated hepatically. This means they may be useful in controlling blood glucose in close association with meals.

Glitazones (thiazolidinediones) are rapidly absorbed and hepatically metabolized. Although the half-life is less than 24 h, and once or twice daily dosing is adequate, full effect takes at least a week, owing to the slow speed of fat redistribution.

Alpha-glucosidase inhibitors are not absorbed, acting slowly within the gut.

Adverse reactions

Sulphonylureas are well tolerated and free from serious long-term adverse effects. The principal problem is hypoglycaemia, which may be protracted and even fatal. A related drawback is the tendency to produce or maintain obesity. Both effects can be linked to increased insulin levels, which also are giving concern over a possible exacerbation of macrovascular compli-cations, insulin being a possible growth factor in arterial walls.

Hypoglycaemia may be caused by an overdose, an interaction, a missed meal or unexpected activity and occurs more commonly with the longer-acting drugs (*glibenclamide* and *chlor-propamide*), especially in the elderly, who must avoid them. (The possible compliance advantage is far outweighed by the likelihood that a meal will be forgotten while plasma drug levels are still significant.) With the newer, shorter-acting drugs any hypoglycaemia that does occur is brief and more easily rectified.

Chlorpropamide can occasionally cause a mild disulfiram-like flush with alcohol (due to acetaldehyde dehydrogenase inhibition), and occasionally hyponatraemia and a syndrome of inappropriate secretion of ADH. These effects, as well as minor idiosyncratic reac-tions, are uncommon with second-generation sulphonylureas.

Meglitinides do not present such risks of hypo-glycaemia and weight gain as the sulphonyl-ureas. No serious class effects have become apparent so far.

Biguanides (with the exception of *phenformin*) cause minor adverse effects, being somewhat less well tolerated than sulphonylureas. The nausea, diarrhoea, muscle discomfort and occasional malabsorption experienced may be due to the membrane effects inherent in their mode of action. Malabsorption of vitamin B_{12} can occur. Biguanides are best taken with food, the dose being increased gradually to improve tolerance. Iatrogenic lactic acidosis, which has a high mortality, occurs rarely with *metformin* and the risk can be further reduced by careful monitoring of renal and hepatic function and ensuring that it is avoided in patients with renal impairment and hypoxic/hypoxaemic condi-tions such as cardiopulmonary insufficiency. Because biguanides do not release insulin, they cannot cause hypoglycaemia and they do not cause weight gain.

Alpha-glucosidase inhibitors frequently cause uncomfortable and sometimes unaccept-able or intolerable gastrointestinal problems owing to the increased carbohydrate load deliv-ered to the large bowel. Subsequent bacterial fermentation causes distension, pain, flatulence and diarrhoea.

Glitazones can cause a number of problems. Fluid retention results in oedema, and heart failure in up to 3% of patients: this is potentiated in combination with insulin. There may also be a mild dilutional anaemia. Hypoglycaemia is rare but weight gain is common. In view of the hepatotoxicity of the withdrawn troglitazone, monitoring of hepatic function and avoidance in hepatic impairment is needed, but they are safe in renal impairment if allowance is made for the fluid retention.

Interactions

Interactions with OADs are potentially serious because the patient's delicate biochemical balance is maintained by a specific dose. Potenti-ation can rapidly cause hypoglycaemia, whereas antagonism could lead, more slowly, to a loss of glycaemic control and a return of polyuric

symptoms. Pharmacokinetic interference with absorption, binding or clearance occurs almost exclusively with the sulphonylureas, when the temporary introduction of an interacting drug can alter the free OAD plasma level, with potentially dangerous consequences. A number of drugs cause a pharmacodynamic interaction by a direct effect on glucose tolerance (Table 9.17). Fortunately, clinically significant problems are relatively rare, and certainly far fewer than the theoretical possibilities. Moreover, different drugs, especially among the sulphonylureas, have different tendencies to show a given interaction.

Pharmacokinetic potentiation

Drugs that increase gastric pH may enhance absorption of sulphonylureas. Highly plasma protein-bound drugs can theoretically displace sulphonylureas. However, following redistribution and alterations in clearance there may be little overall change in free drug levels. Moreover, the newer sulphonylureas bind to different plasma protein sites and are less prone to this effect. The hepatic clearance of sulphonylureas can be reduced by severe liver disease and by enzyme-inhibiting drugs and enhanced by enzyme inducers; similar considerations apply to

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Table 9.17   Important interactions and precautions with antidiabetic therapy

Potentiation → hypoglycaemia	Antagonism → hyperglycaemia
Interference with antidiabetic therapy generally[a]	
Beta-blockers – mask/may cause hypoglycaemia	(Beta-blockers, calcium-channel blockers)[b]
ACEIs – increase glucose uptake	Corticosteroids
Alcohol – potentiates hypoglycaemia	Thiazide (and loop) diuretics
Fibrates	(Antipsychotics)
MAOIs	
Interactions with sulphonylureas[c][d]	
Absorption	
(Antacids, H$_2$-RAs)	
Binding displacement	
Salicylates (high doses)	
Hepatic clearance	
Sulphonamides ⎫	Chloramphenicol ⎫
Warfarin ⎬ enzyme inhibition	Rifampicin ⎬ enzyme induction
Antifungals: imidazoles ⎭	Anticonvulsants ⎭
Liver failure	Excess alcohol
Renal clearance	
NSAIDs	
Sulfinpyrazone	
Renal impairment	
Interactions with biguanides	
Renal/hepatic impairment	
Alcohol (potentiates lactic acidosis)	

[a] Problems possible with either oral or insulin therapy.

[b] Entries in parentheses are known to be rare or minor.

[c] There are wide variations in the significance of specific interactions with individual oral antidiabetic drugs, and not all possible interactions are indicated. This table is merely to show possible effects and mechanisms. A detailed text is recommended to ascertain clinical significance of an interaction.

[d] Meglitinides have similar pharmacokinetic properties to the sulphonylureas.

ACEIs, angiotensin-converting enzyme inhibitors; H$_2$-RAs, H$_2$-receptor antagonists; MAOI, monoamine oxidase inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs.

the meglitinides. The glitazones have not been reported to cause any hepatic enzyme interactions. The renal clearance of unchanged drug or active metabolites of any of these drugs can be reduced by renal impairment and by certain drugs that cause fluid retention (e.g. NSAIDs).

Pharmacodynamic potentiation

Alcohol is directly hypoglycaemic in fasting conditions, and it may also potentiate biguanide-induced lactic acidosis. Both MOAIs and beta-blockers tend to cause hypoglycaemia; the former may inhibit glucagon secretion and the latter inhibit hepatic glycogenolysis. Beta-blockers can 'mask' the effects of hypoglycaemia as perceived by the patient. Beta-blocker interactions are seen mainly with non-cardioselective agents if at all, but aside from those with *propranolol* they are rare and usually insignificant. ACEIs enhance glucose uptake and utilization by cells, although the effect may diminish with continued therapy and is of uncertain significance.

Antagonism

Drugs that induce liver enzymes can increase the clearance of hepatically metabolized sulphonylureas. Various drugs tend to raise blood glucose, either directly or via the suppression of insulin release. Paradoxically, given the masking effect referred to above, beta-blockers can block insulin release.

As a consequence of the inhibited disaccharide digestion, oral treatment of hypoglycaemia in patients taking glucosidase inhibitors should preferably be with glucose/dextrose rather than sucrose preparations.

Contra-indications and cautions

The main precautions may be summarized thus:

- People with diabetes need to take particular care when changing dose, brand or type of antidiabetic medication.
- Medication records should be monitored to identify the introduction of potentially interacting drugs.
- The elderly are particularly prone to hypoglycaemia with the longer-acting OADs; these patients may be forgetful about meals, less able to recognize hypoglycaemia, and less tolerant of it homeostatically and neurologically.
- Alcohol use must be carefully controlled: although initially it may cause hyperglycaemia (owing to its caloric content), it enhances hypoglycaemia and may impair the ability to respond to it.
- Alcohol also dangerously enhances the possibility of lactic acidosis with biguanides and it causes unwelcome flushing with sulphonylureas, particularly *chlorpropamide*.
- Some clinicians manage all patients with significant renal impairment (common in people with diabetes) or hepatic impairment (less common) with insulin.

Selection

Combinations

Most type 2 patients are overweight and a biguanide is the preferred first choice. It is also satisfactory for others but a sulphonylurea might be started in the non-obese. Patients who fail to achieve blood glucose control on either regimen use a biguanide in combination with a sulphonylurea. Meglitinides, with their faster, shorter action may be substituted for the sulphonylurea at any stage if the patient prefers it, especially if they are tending to suffer hypoglycaemia or weight gain. A glitazone can be added as a third agent when dual therapy fails, especially if the patient has persistent postprandial or between-meals hyperglycaemia, both of which imply insulin resistance. However, if *metformin* plus a sulphonylurea combined fail to control the patient, it is likely that they have very little beta-cell capacity left and the introduction of insulin should be considered rather than adding a third drug (see below).

Acarbose could be added at any of these stages to improve control but has a limited benefit and is often poorly tolerated. *Sitagliptin* and *exenatide* (p. 612) are available as third-line agents.

Constraints

In addition to these pharmacodynamic considerations, the choice of any OAD must take account of:

- duration of action;
- mode of clearance;
- age;
- renal and hepatic function;
- tolerance of adverse effects;
- patient preference for number of daily doses.

The elderly must avoid the longer-acting drugs, while other patients may have particular reasons for preferring more or less frequent dosing. By analogy with insulin regimens, a combination of a single daily dose of a long-acting drug, combined with regular top-up doses of a short-acting one, has been recommended, but is little used. In general there is little to choose between the sulphonylureas, but patients with renal impairment might do better with *gliquidone* (Figure 9.13).

Some patients cannot be controlled on maximal tolerated doses of combined OADs. This may occur after many years of therapy as the beta-cell function inexorably declines (i.e. secondary failure), occurring in up to one-third of type 2 patients within 5 years of diagnosis. Alternatively some patients present late, when there has already been considerable degeneration (primary failure). In either case the situation signifies that there remains insufficient residual beta-cell function, and exogenous insulin supplement becomes mandatory.

At that stage small doses of insulin may be added to OAD therapy to provide a basal level. This may delay the onset of full insulin therapy, and may be preferred by patients anxious about full insulin dependence. When type 2 patients eventually need to be controlled with insulin they do not of course become type 1, and they may more accurately be referred to as having **insulin-requiring type 2 diabetes**. Insulin-augmented OAD therapy will be considered below after insulin has been discussed (see p. 627).

Insulin

About two-thirds of people with diabetes are treated with insulin, about half of whom are truly insulin-dependent type 1 and others are type 2 in secondary failure of OAD therapy.

Patients using insulin require much finer control of all aspects of management, including diet, activity and dose measurement, than other people with diabetes. There is less margin for error because patients rely totally on the injected dose. In contrast to type 2 patients, they lack the small basal insulin secretion that, although insufficient to prevent hyperglycaemia, keeps the type 2 patient free from metabolic complications like weight loss and ketosis.

Aims and constraints

In theory, it should be possible to attain glycaemic control with insulin that closely mimics the natural physiological variations in response to food intake, exercise and metabolic requirement. However, until recently it was not possible even to approach that.

Recall that natural insulin secretion from the pancreas into the portal vein is finely and continuously tuned to variations in blood glucose level (p. 586; see Figure 9.3): this is very different from the usual exogenous insulin therapy. An approximation might be attained with a continuous basal injection plus regular IV boluses of a rapidly acting insulin preparation to coincide with meals and, ideally, continuously titrated against the blood glucose level. This would resemble the natural pattern except for the portal delivery to the liver. However, such a regimen is impractical for most patients.

Absorption from the usual SC injection sites, whether as depot injections or by continuous delivery, can vary in any one patient from time to time and from site to site, particularly with the otherwise more convenient longer-acting preparations. Moreover, whereas exercise inhibits normal insulin secretion, it tends to speed absorption from an injection site by promoting peripheral circulation; thus when less insulin is required, more is delivered exogenously. It is also likely that SC injections administered by some patients are effectively IM now that perpendicular injection is recommended, changing absorption characteristics. Alternatively, some patients retard absorption by injecting into fat, which is less painful. Furthermore, the clearance of most forms of injected

insulin is generally slower than endogenous insulin, the half-life of soluble insulin after SC injection being about 1 h.

Until recently the most common compromise was to give a mixture of a fast-acting and a moderately long-acting preparation before breakfast (e.g. *soluble* plus *lente*), perhaps with a booster dose of soluble in the evening. With appropriate 'feeding the insulin' throughout the day (p. 605) acceptable control can be achieved. However, it results in relative hyperinsulinaemia, a tendency to hypoglycaemia during the day and after midnight (especially if a meal or snack is missed or there is unanticipated exertion), and hyperglycaemia before breakfast (Figure 9.8).

Three recent advances have brought treatment closer to the ideal for many patients. Ultra-short-acting analogues such as *lispro* allow closer matching to meals; long-acting analogues such as *glargine* provide more consistent basal levels; and 'insulin pen' systems permit easier and more accurate injection.

Insulin types

Developments in insulin technology have produced a range of chemically pure, immunologically neutral preparations of standard strength (100 units/mL in the UK and North America) with a wide range of pharmacokinetic parameters.

Pharmacokinetic differences
Formulations of insulin can be divided into four broad groups depending on their duration of action; their times of onset and periods of peak activity also vary considerably (Table 9.18). The fastest action is provided by solutions of insulin. In solution, insulin molecules normally associate non-covalently into hexamers, which are progressively dissociated by dilution in body fluids to the active monomer. This process, which delays onset and prolongs duration, can be accelerated by small rearrangements of molecular structure that affect association characteristics but not pharmacodynamic activity. Increased duration may also be provided by forming stable suspensions of carefully controlled particle size that gradually dissolve in a uniform manner. Alternatively, solubility char-

acteristics can be manipulated. Other chemical manipulation produces ultra-long-acting (basal) formulations. A number of premixed formulations provide combinations of these properties.

Ultra-short (rapid) action. By substituting different amino acids at key positions, insulin analogues have been produced that exist in monomeric form with little tendency to associate but retain full activity at insulin receptors. In *insulin lispro* lysine and proline are placed at positions B28 and B29 near the end of the B chain; *insulin aspart* has aspartic acid at B28. These agents have an onset of less than 15 min, reach a higher peak within about half the time of conventional soluble insulin (1 h as opposed to 1.5–2.5 h) and a duration of action little greater than 5 h (as opposed to 6–10 h). Thus, they can be injected less than 15 min before a planned meal, or even just after one has been started; the optimal time will need to be determined for each patient. The advantages include:
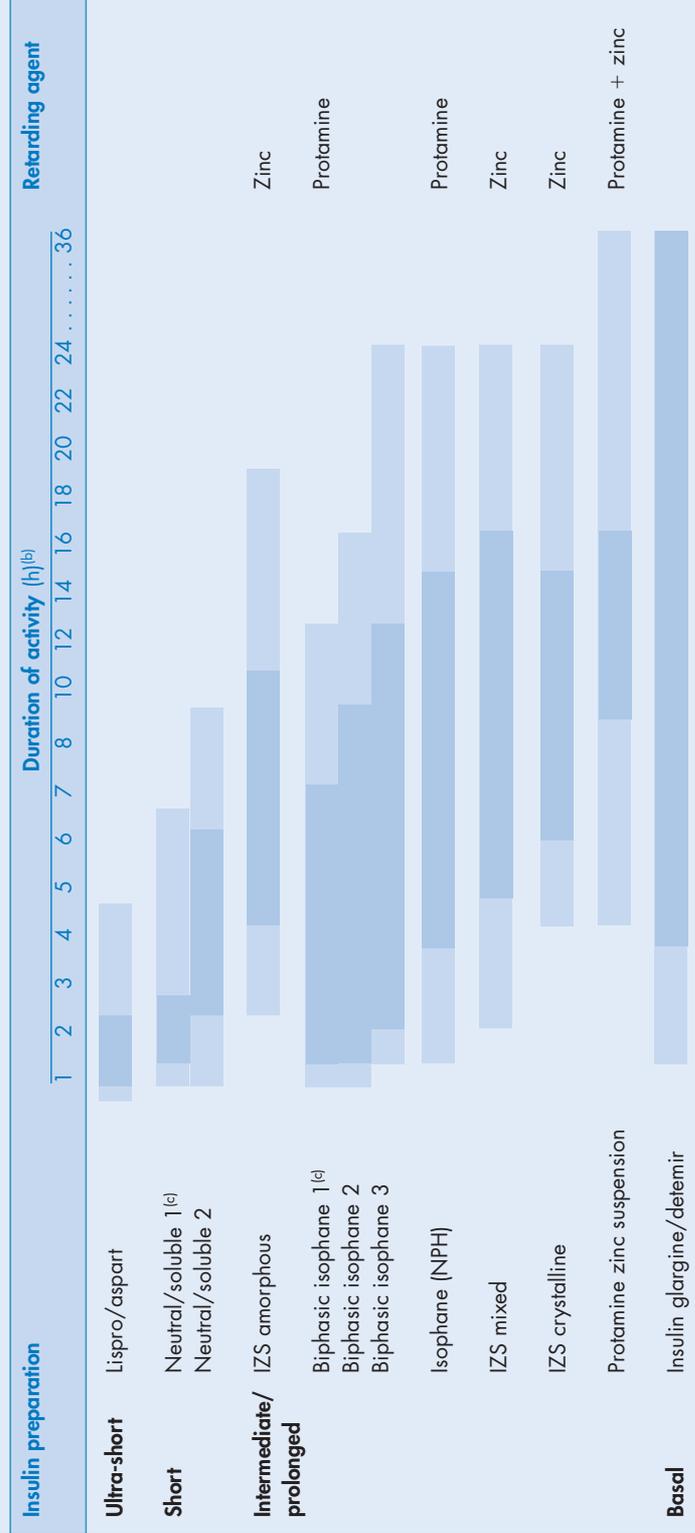
- Less imposed delay between injection and food intake (especially breakfast), and/or reduction of postprandial hyperglycaemia if delay not observed.
- Convenient pre-meal bolus doses, as part of basal-bolus regimen (below).
- Easier adjustment for unexpected food intake or missed meal.
- Reduction of between-meals hypoglycaemia, caused in some patients by excessive duration of action on regular short-acting preparations.
- Less reliance on foods with a low glycaemic index.

However, there is no advantage in using these intravenously instead of soluble insulin in emergencies or as part of a 'sliding scale' regimen (see below). Patients who switch need careful re-education about the relative timing of injection and food intake.

Short action. Clear solutions of soluble (neutral) insulin act less rapidly than ultra-short analogues and are cleared within 6–10 h. They are useful:

- when IV use is required, e.g. for ketoacidosis;
- when titrating a newly diagnosed patient's requirement;

Table 9.18 Approximate pharmacokinetic parameters of insulin preparations[a]

Insulin preparation		Duration of activity (h)[b] 1 2 3 4 5 6 7 8 10 12 14 16 18 20 22 24 36	Retarding agent
Ultra-short	Lispro/aspart		
Short	Neutral/soluble 1[c] Neutral/soluble 2		
Intermediate/ prolonged	IZS amorphous		Zinc
	Biphasic isophane 1[c] Biphasic isophane 2 Biphasic isophane 3		Protamine
	Isophane (NPH)		Protamine
	IZS mixed		Zinc
	IZS crystalline		Zinc
	Protamine zinc suspension		Protamine + zinc
Basal	Insulin glargine/detemir		

Duration of biological activity

Peak activity

[a] Data given are only approximate comparative indications. Activity in patients varies with manufacturer, dose, site and technique of injection, etc. (see Table 9.20).

[b]

[c] Numbers indicate representative different preparations available in UK.

IZS, insulin zinc suspension; NPH, neutral protamine Hagedorn; Biphasic, generic name for range of mixtures of short- and medium-acting preparations.

- in a continuous SC infusion system;
- for the temporary insulin therapy of type 2 patients during pregnancy, surgery or severe illness.

Soluble insulin is being replaced by ultra-short-acting preparations when a booster dose is needed rapidly, or when frequent injections are needed for patients with brittle diabetes.

Soluble insulin to cover a particular meal should be injected 15–30 min, or occasionally 45 min, beforehand. When newly diagnosed type 1 patients are being assessed they are usually put on an **insulin sliding scale** regimen, with 4-hourly soluble insulin doses adjusted according to the current blood glucose level.

Intermediate and prolonged action. Many patients still receive part of their daily insulin dose as a depot injection. This is intended to provide a continuous basal level of insulin for metabolic activity, with little effect on postprandial glucose disposal. The particular regimen is dictated partly by life pattern and patient preference, but ultimately by trial and error. Depot preparations are formulated by complexing insulin with either zinc or protamine, a non-allergenic fish protein. This produces a fine suspension that is assimilated at a rate that is dependent on particle size and injection site perfusion. Being a suspension, it cannot be given intravenously. Available products span a wide spectrum of times of onset, peak activity and duration, allowing flexibility in tailoring regimens (Table 9.18).

The *insulin zinc suspension* (IZS) range contains an insulin–zinc complex in either crystalline or amorphous form, the latter being more readily absorbed. *Insulin zinc suspension mixed* is 30% crystalline and 70% amorphous, and *insulin zinc suspension crystalline* is 100% crystalline, with proportionate increases in duration of activity. (Insulin zinc suspension amorphous, which is no longer available, was purely amorphous and combined prompt onset with quite prolonged, but rather variable, action). *Isophane insulin* containing protamine as the retarding agent also has an intermediate activity.

Protamine zinc insulin and *insulin zinc suspension crystalline* are the longest-acting prepara-

tions available. If an excessive dose of this type is injected, the hypoglycaemic effect is correspondingly prolonged and glucose or glucagon injection may be needed to reverse it. Because the variability in response between different preparations increases with the duration of action (even in the same patient), these very long-acting forms are little used unless patients of long standing are stabilized on them.

A variety of premixed *biphasic* preparations (compatible combinations, usually of soluble and isophane forms) are available to provide further flexibility. Some patients mix specific combinations immediately before injection.

Basal. A more physiological approach to insulin provision has recently evolved. The **basal-bolus regimen** is designed to provide a continuous backgound level of insulin supplemented by bolus doses at mealtimes. Existing prolonged action formulations, while lasting 24 h or more, did not provide the required consistency of release: they all tended to give a peak at 6–12 h (Table 9.18). Two different strategies have been devised to solve this problem. In *insulin glargine*, amino acid substitutions have changed the isoelectric point of the molecule from below pH 7 to neutral. As a result it is soluble when administered in a slightly acid solution but precipitates out as microcrystals at body pH after injection. Subsequent dissolution and absorption from the depot provides a predictable, consistently sustained action with an essentially flat activity profile for up to 24 h (Table 9.18). In *insulin detemir*, attaching a C14 fatty acid chain to the insulin molecule substantially increases reversible binding to albumin in body tissue, with a similar result.

Purity and antigenicity
There are two significant factors here: chemical, and therefore immunological, similarity to human insulin; and contamination with extraneous antigenic material. Originally, all insulin was extracted from ox or pig pancreases supplied by slaughterhouses. (Approval for insulin treatment from these sources has been obtained from most major religions, but strict vegans may present a problem.) Beef insulin differs from the human insulin polypeptide sequence by three

amino acids, and porcine by just one. These differences affect antigenicity but not hypoglycaemic potency. As may be expected, porcine is the better tolerated, but neither causes great problems.

Contaminants derived from the extraction process (e.g. pro-insulin), insulin breakdown products and other unrelated proteins, can stimulate the production of insulin antibodies, and allergic reactions used to be quite common. Consequently, chromatographic purification is now used giving highly purified or mono-component animal insulins that cause far fewer problems.

Human insulin is made either semi-synthetically, by chemically modifying the single variant amino acid in purified porcine insulin (emp, enzyme-modified porcine), or biosynthetically (crb, chain recombinant-DNA bacterial; prb, proinsulin recombinant-DNA bacterial; pyr, precursor yeast recombinant). Biosynthesis is becoming the preferred process and human insulin now costs less than animal forms.

Unfortunately, the expectation that human insulin would be vastly superior has not been realized. Anti-insulin antibodies are not significantly less common with human insulin than with the highly purified porcine form, and allergic phenomena still occur, probably due to breakdown products occurring during manufacture, storage, etc. Nevertheless, almost all new patients are started on human insulin, and use of animal-derived insulin is now rare.

Human insulin is slightly more hydrophilic than animal forms. Thus, although it has an identical biological action to pork insulin when given intravenously, it is assimilated more rapidly from SC sites and acts more quickly in otherwise identical formulations. It is also cleared more rapidly, possibly by binding more avidly to those hepatic and renal enzymes that destroy it. These differences are slight and only relevant to patients transferring from one form to the other.

Adverse reactions

The chief adverse effects of insulin are hypoglycaemia, injection site problems, immunological phenomena and resistance. These may be partially inter-related.

Hypoglycaemia
This is the most common complication of insulin therapy and potentially the most harmful; the clinical aspects were discussed on pp. 596–598. Insulin can cause hypoglycaemia either through an excessive (e.g. mis-measured) dose or through an unexpectedly reduced insulin requirement (most commonly, a missed meal).

Human insulin has been associated with an apparent increase in the incidence of hypoglycaemic attacks, including some deaths. This was initially attributed to a reduced hypoglycaemic awareness, i.e. hypoglycaemia is not more common but is permitted to progress more frequently. The autonomic warning symptoms of hypoglycaemia (see Table 9.12) seemed to be experienced less intensely or at a later stage when using human insulin, perhaps owing to autonomic (sympathetic) neuropathy.

There is no pharmacodynamic rationale for this phenomenon and it has been suggested that it is only incidentally related to human insulin use. The change to human insulin came at a time when the need for tighter control became apparent and aids to this, e.g. injector pens and home blood glucose monitoring, were developed. Improved control produces lower mean glucose levels and therefore an increased risk of hypoglycaemia. Thus it is not now regarded as a serious problem of human insulin, although it is stressed that great care is necessary in transferring a patient to human insulin. Close monitoring is essential and the daily dose may need to be reduced, particularly when changing from beef insulin or for patients with a higher than average daily insulin requirement.

Injection site lipodystrophy
Some patients develop unsightly lumps (**lipohypertrophy**) or hollows (**lipoatrophy**) at frequently used injection sites if they fail to rotate the sites regularly. These are not due to scar tissue but are caused by local disturbances of lipid metabolism. Lipoatrophy seems to be an immunological phenomenon; immune complex deposition may possibly stimulate lipolysis in SC

adipose tissue. It responds to changing to a purer form of insulin, initially injected around the depression. Lipohypertrophy is more common with the newer insulins and may result from enhanced local lipogenesis, a known insulin action. It is reversed when the site is no longer used. Although patients may prefer to inject at these easily penetrated, relatively painless sites, such an approach results in delayed and erratic absorption.

Insulin antibodies and insulin resistance

Insulin antibodies (insulin-binding globulins) occur in up to 50% of insulin-treated patients. It might be expected that they would speed the clearance of insulin by forming immune complexes that would be eliminated in the usual way by the monocyte–macrophage system. However, on the contrary, insulin antibodies delay assimilation and prolong the action and so are potentially beneficial. They are otherwise usually harmless, although they may sometimes be responsible for insulin resistance (see below).

Insulin allergy ranges from minor local irritation to, very rarely, full-blown anaphylaxis. The less serious reactions commonly remit on prolonged use and are minimized by using the highly purified modern insulin formulations as first choice. The size of the insulin molecule is borderline for antigenicity. Hyposensitization has been used to treat insulin allergy, by injecting extremely dilute insulin solutions at progressively higher concentrations to induce tolerance. Very occasionally, local steroid injections need to be given with the insulin.

The term insulin resistance tends to be used in an ambiguous manner (Table 9.19). In pathogenetic terms, it refers to one of the common underlying problems of type 2 diabetes, namely reduced receptor sensitivity. As an adverse effect of insulin treatment, it refers to the requirement in some insulin-dependent diabetes for doses of insulin far above the physiological norm.

In the latter sense, insulin resistance occurs only rarely and may be defined as an insulin requirement >1.5 units/kg/day (about 100 units daily in an average patient). There are many possible causes; probably the most common is simply obesity, but poor injection technique may be an unsuspected problem. Insulin resistance is less common now with the use of the monocomponent and human formulations. Treatment involves eliminating any obvious cause and then gradually switching to highly purified or human insulin. As a final resort, systemic steroids, which are themselves diabetogenic, may be needed.

Administration

Delivery systems

Pen injectors. Multidose insulin reservoir injector pens are now the most popular delivery system. Each pen has a replaceable cartridge

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Table 9.19   Possible causes of insulin resistance

Metabolic	Obesity
	Increased catabolic hormones
	Interacting diabetogenic drugs (e.g. steroids)
Immunological	Anti-insulin antibodies
	Anti-insulin-receptor antibodies
Pharmacokinetic or biopharmaceutic	Poor injection technique
	Increased insulinase activity
	Reduced assimilation from injection site
	• local enzymic degradation
	• scar tissue
	• lipohypertrophy
Genetic	Receptor defect

loaded with up to 300 units (3 mL), representing up to 1 week's supply for some patients. There are various forms of metered-dose injectors. One automatically delivers a 2-unit dose for each depression of a trigger, i.e. 2 units per 'click', a situation that is particularly beneficial to visually impaired people with diabetes; another form permits full doses to be preset visually on a digital scale, which may be palpable or audible. Most have a maximum deliverable single dose to minimize the risk of overdose. Each type of pen should only be used with the appropriate cartridge. The main advantages are correct dose measurement, and hence less error, and the facilitation of multiple daily dosing as part of a basal-bolus regimen.

Standard syringe.   The use of disposable plastic syringes with fixed needles is no longer the norm in the UK. If stored in a fridge, these syringes may be re-used for up to 1 week, without significant contamination of the vial contents (which contain a bacteriostat) and no increase in skin reactions. Patients change the syringe when the needle is blunted or the barrel graduations become unclear. Injection through clothing, long practised by some people with diabetes, has also been reported to not cause significant problems. Patients must use a safe method of contaminated waste and 'sharps' disposal.

Artificial pancreas.   The ideal replacement pancreas has not yet been constructed. One experimental approach involves a feedback-controlled, blood-glucose driven 'closed loop' system. A sensor in an IV catheter monitors blood glucose continuously and the results are fed to a microprocessor that calculates the instantaneous insulin requirement. This drives a portable pump, strapped to or implanted in the patient, delivering the appropriate dose. The main problem is in designing a suitably sensitive indwelling blood glucose sensor. In another experimental system, an implanted insulin reservoir enclosed in a glucose-sensitive gel membrane permits insulin diffusion in proportion to external glucose concentration. The reservoir is replenished percutaneously.

Continuous SC insulin infusion is a more practicable but still relatively expensive 'open

loop' option, without the automatic dosage control. An external reservoir/pump strapped to the body delivers a continuous basal level of insulin via an indwelling catheter, with meal-time boosts being activated manually. Modifications include an implanted pump, contolled by radio, and the use of an intraperitoneal catheter, which has the theoretical advantage of more closely mimicking the natural insulin secretion. Clearly this method would only suit patients who are able to manage the technology and understand the relationship between blood glucose, diet, activity and insulin dose. However, current prototypes are as yet too bulky, expensive and demanding of patients' motivation for general use.

Other forms.   Simple oral administration of insulin is impossible owing to intragastric enzymic destruction. Systems are being developed that avoid this but do not require the complications of injection. One approach is to incorporate insulin into liposomes that would be taken orally. The lipid coat would act as an enteric coating and the liposomes would be absorbed unchanged from the gut, as are chylomicrons. Percutaneous **jet injection** has also been tried. **Intranasal administration** is being explored, using a liposomal or polymer vehicle. People with diabetes with advanced nephropathy on peritoneal dialysis find it convenient to add insulin to their **dialysis fluid**.

A *metered dose inhaler* (inhaled human insulin, Exubera) for pulmonary absorption is now available in the UK. It seems to offer an activity profile similar to injection with the rapidly acting insulin analogues but may be more acceptable to some patients in combination with a single basal insulin dose by injection. Concerns remain over cost and possible lung damage, especially in smokers, who should not use it. Moreover, bioequivalence is an issue for patients switching to inhaler, not least because the dose is expressed in milligrams, 1 mg being equivalent to 3 units.

Storage
Insulin should always be kept cool, but is stable at room temperatures for up to 28 days. Formulations incorporating polyethylene-

polypropylene glycol, specially developed for prolonged reservoir use, are stable for even longer. Thus, insulin may safely be used in pens and continuous SC infusion, etc. and while travelling. Pharmacy stocks and patients' reserve supplies are refrigerated (but not frozen). Before withdrawing a dose, the vial should be warmed to body temperature and gently mixed by inversion or rotation (but not shaken).

Mixing

If a combination of two preparations of different durations is required, specially formulated proprietary mixtures should be used whenever possible, and extemporaneous mixing avoided. The *insulin zinc suspension* formulations are intended to be stable after intermixing but others are not, and mixtures of these must be injected within 5 min. One problem is the adsorption of the soluble form onto the retardant from the longer-acting one, which may seriously interfere with the expected rapid action of the former. The order of mixing is important: the soluble form is drawn up first, then the depot form. This avoids contamination of the whole vial of soluble insulin with zinc or protamine.

Injection

Now shorter needles have become available, deep SC injection perpendicular to the skin is universally recommended. Most patients cope well, but instruction and counselling when treatment is started are clearly important, especially with children. Diabetes UK and a number of interested manufacturers produce helpful literature on this and all other aspects of diabetes care.

Equally important is the need to rotate the site of injection regularly so that any one site is only used once in 10–20 injections. Seven general areas are recommended by Diabetes UK (upper arms, thighs, buttocks, abdomen), but within these areas the precise injection site used on one occasion can be avoided on the next; they provide a template to assist such variation. This minimizes skin reactions, especially lipohypertrophy. Patients can also use the slower assimilation sites, e.g. thighs, for the overnight dose. Sites usually covered by clothing are preferred. Factors that may alter absorption from the injection site, possibly upsetting control, are summarized in Table 9.20.

Dosage regimens

An initial dose titration period on first starting insulin will indicate the total daily dose required, but decisions on how this is to be distributed throughout the day require discussion with the patient. With fewer, medium-acting injections overall control is poorer and

Factor	Example	Effect on absorption	
		Slower/reduced	Faster/increased
Pharmaceutical	Incorrect mixing of delayed and rapid forms (especially if injection delayed)	+	
	Depth of injection	+	+
Local inactivation	Proteolytic enzymes	+	
	Insulin antibodies	+	
Local perfusion	Regional differences (abdomen > arm > thigh)	+	+
	Exercise (in limb sites); massage		+
	Skin temperature	+	+
	Angiopathy	+	
	Scar tissue	+	
	Lipohypertrophy	+	

Table 9.20   Factors affecting insulin absorption from injection site

there is the added risk of hypoglycaemia, with the threat of coma if a meal is missed. However, when multiple injections are linked with close blood glucose monitoring, aimed at achieving lower glucose levels (so-called 'tight glycaemic control') there is the risk of more frequent episodes of hypoglycaemia. On the other hand, use of multiple short-acting regimens can lead to hyperglycaemia between injections and poorer control. For each patient a balance must be struck that imposes no more restriction on their life than they are prepared to tolerate, which as closely as possible meets their treatment objectives. Achieving this is not easy. Factors to consider are:

- the patient's pattern of glycaemia (e.g. nocturnal hypoglycaemia, morning hyperglycaemia);
- age;
- severity of complications;
- occupation, social habits and routine;
- compliance;
- physical disabilities;
- comprehension of disease, prescribed regimen and associated equipment;
- patient preference;
- ethnic and religious constraints.

The blood glucose targets are usually:

- never below 4 mmol/L;
- fasting (preprandial) 4–7 mmol/L;
- postprandial and bedtime <9 mmol/L.

Specialized units can organize test periods of 24-h blood glucose monitoring via temporary indwelling sensors to plot the patient's pattern of glycaemia. However, the interpretation of these data is complex and it is an uncommon technique. Somewhat easier is for the patient to perform a short period of self-monitoring and recording, the results of which can be discussed with their diabetologist.

There are also more general considerations, especially when first starting insulin. Many people have a distaste for injections or fear them, and the psychological stress of accepting reliance on injections for life can be substantial. This is more of an issue with type 2 patients as they approach secondary failure on OADs, which is considered below.

The choice ranges from multiple daily injections of short-acting insulin closely co-ordinated with eating and activity pattern, to a convenient but very unphysiological single daily dose of a longer-acting preparation (Table 9.21).

Whatever the regimen, the total daily dose required is usually 0.5–1.0 unit/kg (about 50 units). This is usually divided as ⅔ during the day and ⅓ at night for minimum frequency regimens and 50/50 for basal-bolus regimens.

Minimum dose frequency regimen
Because of the potential compliance benefits of fewer daily injections, this method used to be favoured. However it is no longer preferred because it imposes inflexibility on activity patterns and mealtimes, and risks both poor control and episodes of hypoglycaemia. The regimen usually consists of morning and evening doses of a combination of short- and medium-acting preparations, the relative doses being determined by trial and error.

There are numerous possible variations. For example, the morning dose could be a mix of about one-third soluble and two-thirds intermediate-acting forms, which covers breakfast and provides a sustained level throughout the day. This may be repeated in the evening, or later in those patients who get serious pre-breakfast hyperglycaemia. Alternatively there may simply be a booster dose of soluble before the evening meal. If one of the commercially available premixed combinations can be used it is certainly convenient, especially with a pen. More flexibility is provided by individually determined combinations, but a pen cannot then be used.

Some patients can be controlled satisfactorily with just a single dose of a long-acting form. This includes type 2 patients with significant residual endogenous insulin production in whom OADs have failed, and some elderly patients requiring only symptomatic relief and for whom the threat of long-term complications is less critical.

Multiple injections
These are now preferred for all patients who can manage to self-inject frequent doses of short-acting insulin throughout the day, before each food intake. In addition, an evening dose of

Table 9.21   Examples of insulin regimens

Regimen	Before breakfast	Before lunch	Before evening meal	Bedtime	Examples of patient groups suited to the regimen
1a	Long[a] ± short	–	–	–	Insulin-requiring type 2 (with metformin)
1b	–	–	–	Intermediate	Some elderly patients
2	Intermediate + short	–	Intermediate + short	–	Some type 1
3	Intermediate + short	–	Short	Intermediate	Some type 1
4	Short	Short	Short	Intermediate	Well-motivated type 1 Unstable Morning hyperglycaemia and/or nocturnal hypoglycaemia
5 (Basal-bolus)	Ultra-short-acting analogue[b]	Ultra-short	Ultra-short	Long-acting analogue[c]	Well-motivated type 1 Many newly diagnosed type 1

[a] Duration of action.

[b] E.g. Insulin aspart or lispro.

[c] E.g. Insulin glargine or detemir.

long-acting insulin is given for basal needs. The most recent variation of this basal-bolus regimen utilizes ultra-short-acting and long-acting analogues, e.g. Table 9.21, regimen 5.

A multiple injection regimen is especially useful for brittle patients requiring close control, or for temporary transfer of patients to insulin, e.g. type 2 patients during pregnancy or with serious infections. However, many clinics are starting most new patients on such a regimen, for which injector pens are ideal. Existing patients are also being converted. Many patients can, with experience, finely judge the dose required according to their food intake and exercise. Others, more committed, will measure their blood glucose level immediately before the next scheduled dose and adjust the insulin dose accordingly.

The improved, more physiological control provided by this type of regimen reduces the development or progression of complications; in some trials they have even remitted. Such regimens can also, if used properly, minimize the risk of hypoglycaemia between meals and of overnight hyperglycaemia.

Insulin for type 2 patients

Most type 2 patients will eventually need insulin as their beta-cell capacity become exhausted (secondary failure). Owing to the insulin resistance common in type 2, their insulin requirement when they become completely insulin dependent will often exceed that of a type 1 patient. However, it may be preferable not to wait until insulin is absolutely necessary to initiate treatment. It may be psychologically preferable to start patients on a combination of oral agents and small insulin doses. They will invariably note an improvement in their well-being and can adjust to insulin injections before becoming completely reliant on them. The combination can also be helpful in difficult to control type 2 patients with high insulin resistance, or those with persistent morning hyperglycaemia. Another situation where the combination is useful is with patients who are already using insulin but are showing resistance: adding *metformin* may reduce their insulin requirement.

The most logical combination is insulin plus an insulin sensitizer. *Metformin* is the usual

choice. Combining insulin with a secretagogue such as a sulphonylurea or a meglitinide is irrational. One regimen is to add a small dose of about 15 units of medium-acting insulin each evening. When switching to this regimen, OAD doses are reduced.

Summary

Diabetes therapy must be individualized following regular close consultation between patients and their clinicians. To a certain extent the optimal result is found by trial and error, but this must be supported by diligent monitoring of blood glucose and reporting of all hypoglycaemic episodes and other disturbances of control.

Monitoring

People with diabetes require self-monitoring of their biochemical control, and regular assessment by a clinician of the development or progress of long-term complications. The former has recently been much simplified and improved. Type 1 patients need much closer monitoring than type 2.

Biochemical control

While even moderate control relieves symptoms and prevents serious biochemical abnormalities, tight control is believed to be essential if complications are to be minimized. In general, diligent monitoring is more important for type 1 diabetes, but all patients should record all test results.

Glucose

Urine glucose

This has been the traditional way of assessing control. A few elderly patients still use the colour reaction based on Benedict's test for reducing substances. It is imprecise, non-specific and cumbersome, even with the ingeniously formulated Clinitest reagent tablets.

Urine glucose estimations can never provide precise information about current blood glucose levels, particularly low, potentially hypoglycaemic ones. Urinary concentrations will vary according to urine volume independently of blood glucose. Furthermore, aglycosuria does not necessarily guarantee normoglycaemia, owing to differences in renal threshold between patients and in the same patient at different times.

Nevertheless, urine testing remains useful as a simple initial screen and for type 2 patients not prone to hypoglycaemia when tight control is not essential, e.g. the elderly and patients averse to repeated skin puncturing. A few patients may be monitored adequately by regular urinalysis and occasional blood glucose measurements, once the relationship between the two has been established.

Urinary glucose measurement also has the advantage that timing is less important than with blood testing because urine concentration reflects control over the previous several hours. Thus, newer glucose oxidase-based urine dipsticks have been developed that are more specific for glucose and far more convenient because they can simply be passed through the urine stream.

Blood glucose

There are three main uses for blood glucose monitoring: to detect hyperglycaemia or incipient hyoglycaemia; to monitor closely in times of changing glucose/insulin need (e.g. intercurrent illness); and to determine a new patient's diurnal glucose profile so as to construct an appropriate insulin regimen.

Most patients, especially with type 1 disease, measure their blood glucose directly using a drop of blood from a finger prick on a glucose oxidase stick. This provides an immediate measure of glycaemia that is reasonably accurate and reliable, not overly prone to error from poor technique, and easy to read. Sticks for unaided visual reading are being replaced by ones to be inserted into automated meters that display the result digitally and may give audible warnings. Some meters can store the most recent results, for reporting at clinics.

Various spring-operated skin puncture devices may be used to help obtain the blood drop easily and safely, and percutaneous techniques of measurement are being developed.

A few type 1 patients regularly test four times daily, including at the lowest points, before meals and in the morning, and at the high point after meals. This is necessary only in the more erratic, brittle patients, in intensive multiple-dose regimens in younger patients, or when previously well-controlled patients start to experience problems. Others, once stabilized, will test randomly a few times weekly and some may perhaps use urine dipsticks daily. The main guideline is to identify a patient's risk times (e.g. between-meal hypoglycaemia or postprandial hyperglycaemia) and subject those to special scrutiny.

Once type 2 patients have become stabilized, weekly or even monthly fasting blood glucose measurement is usually sufficient.

Dose modification falls into two basic strategies. Well-motivated patients on the basal-bolus regimen who are suitably trained by the diabetic team will be able to modify their *next* insulin dose, based on the results of their preprandial glucose level and the glycaemic content of their next meal. This is termed 'dosage adjustment for normal eating (DAFNE)'.

For patients who prefer regular dosing, frequent changes following this apparently logical DAFNE strategy is both inconvenient and inappropriate. More systematic is to note pre-meal blood glucose over several days. If it is consistently unsatisfactory, they must alter the *previous* scheduled dose on future days, because the current pre-meal level is a reflection of the previous dose.

Glycated (glycosylated) haemoglobin

The abnormal, quantitative glycation of systemic protein as a consequence of excess blood glucose (p. 599) applies also to blood proteins, including Hb and albumin, as well as to plasma fructosamine. Because these substances remain in the blood for long periods (120 days for Hb, 7–14 days for the others), their glycation gives a long-term, integrated picture of blood glucose levels over those periods. This can be measured at diabetic clinics and is useful in tracing any problems with control that might not be revealed by patients' tendency to be extra meticulous on the few days before each clinic visit.

Care must be taken to ensure adequate time between successive measurements, especially after a treatment change. This allows the level to restabilize, bearing in mind the normal 120-day red cell lifespan. A reading taken too soon will give a falsely high reading because the glycosylated red cells originally measured will not have died. One the other hand, when there is a reduced red cell number or increased cell turnover, e.g. in haemolysis or blood loss, a falsely low reading may be given.

The glycated Hb level gives the best index of the control needed to minimize complications and is now regarded as the 'gold standard'. Non-diabetics have about 5% of glycated Hb (HbA_{1c}) and the target level for optimal diabetes control is currently <7.5%, or <6.5% in patients at increased arterial risk, e.g with hypertension.

Ketones

Regular ketonuria monitoring is unnecessary for type 2 and most type 1 patients, but is essential in brittle ketosis-prone people with diabetes, and in all patients during periods of metabolic stress such as infection, surgery or pregnancy. Great accuracy is not required and urine dipsticks are adequate because any ketonuria at all in the presence of glycosuria indicates a dangerous loss of control. Combined glucose/ketone sticks are preferred, especially as heavy ketonuria may interfere with some standard glucose sticks.

Clinical monitoring

In addition to biochemical monitoring, regular medical examination is important in the long-term care of people with diabetes. This will identify as early as possible the development of any of the many possible systemic complications. Table 9.22 lists the factors that need to be monitored at intervals that will vary from patient to patient.

Table 9.22   Regular assessment in diabetic clinic

System	Test or examination
Biochemical	Glycated haemoglobin
	Blood lipids, body weight
Feet	Chiropody; pulses
Eye	Fundoscopy, acuity, cataract
Renal	Proteinuria, creatinine (clearance)
Neurological	Detailed sensory, motor and autonomic neurological examination
Cardiovascular	Blood pressure, ECG, peripheral perfusion (pulses, etc.)
	Symptoms of ischaemia

Thyroid disease

Thyroxine is a simple catechol-based hormone but it has multiple crucial subcellular actions essential to life. It is involved with oxygen utilization within all cells, and thyroid abnormalities have profound effects on most organ systems in the body. Thyroid disease is one of the most common endocrine disorders, yet fortunately it is relatively straightforward to treat and to monitor. This is partly because the thyroid axis is largely independent of other endocrine systems and partly because the long half-life of thyroid hormone means that dosing is not as critical as for insulin replacement. Thus frequent variations in thyroid hormone levels do not normally occur and the acute disturbances of control seen with abnormal insulin and glucose levels are rare. Furthermore, long-term complications are few and uncommon.

Physiological principles

Synthesis

Thyroid hormone is synthesized from the aromatic amino acid tyrosine (closely related to phenylalanine and catecholamine) in the thyroid gland, which sits across the trachea in the front of the neck. Iodine is an essential ingredient, and the conversion from dietary inorganic iodide to iodinated thyroid hormone is termed the organification of iodine. Ionic iodide in the blood is taken up by the thyroid gland by an active **sodium/iodide symporter** (Figure 9.14) then, catalysed by **thyroid peroxidase**, oxidized to give I_2, which is then bound to the aromatic ring of the tyrosine residues.

Mono- and di-iodotyrosine are covalently attached to thyroglobulin within the colloid-filled thyroid follicles, dimerized with another tyrosine ring, then further iodinated to either **tri-iodothyronine (T_3)** or **thyroid hormone (T_4)**. T_3 is five times more potent than T_4, but 75% of thyroid hormone is synthesized and transported as T_4. This is largely converted in target tissues to T_3. Several weeks' supply is stored in the gland in the bound form, but it is released into the blood as free hormone.

In this chapter the term **thyroid hormone(s)** will be used when referring to the natural physiological hormone. Thyroxine (T_4) when used as a drug is officially termed *levothyroxine*, and tri-iodothyronine (T_3) when used as a drug as *liothyronine*.

Control and release

Control of thyroid function is an example of a classic endocrine negative feedback loop, which enables fine control of many body systems according to need. A relatively simple peripherally active hormone (**thyroid hormone**) is
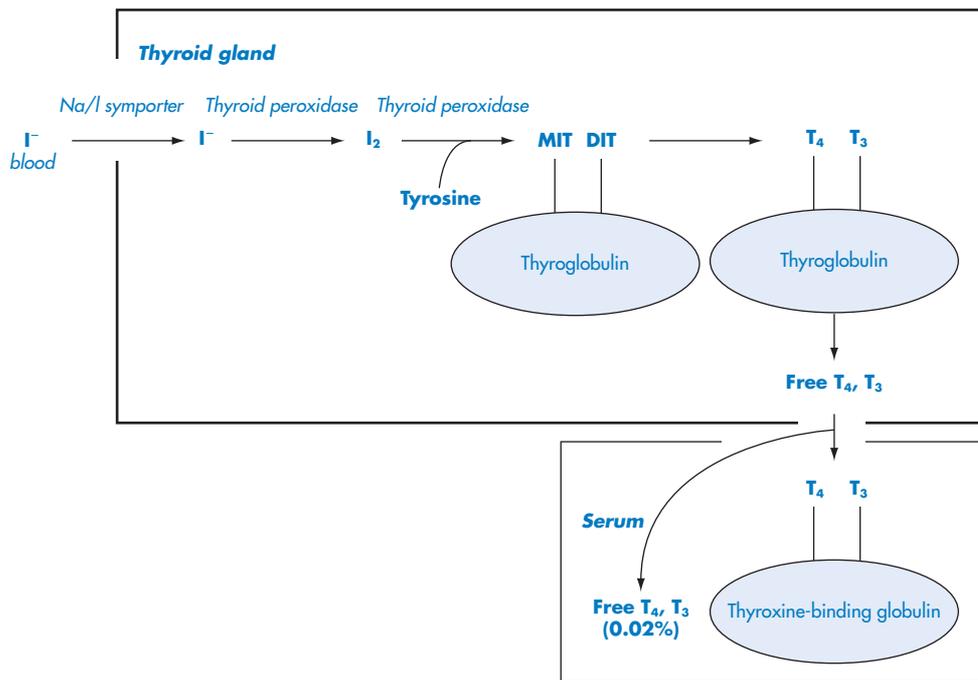
Figure 9.14   Thyroxine synthesis. I, iodine; MIT, mono-iodotyrosine; DIT, di-iodotyrosine; T_3 tri-iodothyronine; T_4, thyroxine; Na/I symporter, see text.

released from an endocrine gland that is its site of synthesis, stimulated by a peptide trophic hormone (**thyroid-stimulating hormone**, thyrotropin, TSH) from the pituitary and also under CNS influence via a releasing hormone (**thyrotropin-releasing hormone**, TRH) from the hypothalamus (Figure 9.15). Both the synthesis and the release of trophic and releasing hormones are inhibited by the active hormone.

TSH is a 221-amino acid glycoprotein with receptors on the thyroid that mediate both the synthesis and the release of thyroid hormones. It is the main physiological control on thyroid function, an important clinical indicator of thyroid malfunction and a component in the aetiology of some thyroid diseases. Hypothalamic control via the tripeptide TRH is less important because low thyroid hormone levels can stimulate TSH release directly, but it enables the CNS to exert an influence on thyroid function; it is particularly concerned with temperature control. Disease of this arm of the thyroid axis is rare.

Distribution and metabolism

Approximately 80 µg of thyroid hormones are released daily, peaking overnight when TSH levels are highest. It has a biological half-life of about 7 days, being cleared by de-iodination in the liver and kidneys. It is carried in the blood almost entirely bound, mostly to **thyroid-binding globulin**; only 0.02% is carried as free T_3 and free T_4 (FT_3, FT_4). However, only the free hormones are biologically active.

Actions of thyroid hormone

Thyroid hormone enters target cells and after conversion to T_3 interacts with nuclear receptors to influence the expression of genes coding for proteins invoved in energy metabolim, oxygen consumption and general tissue growth; thus it has far-reaching effects on metabolism, growth and development (Table 9.23). In some ways the action resembles that of catecholamines (e.g
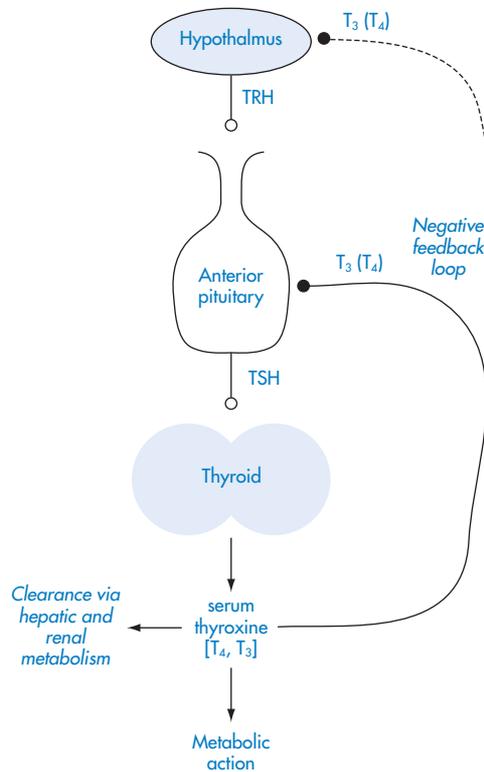
Figure 9.15   Control and release of thyroxine (hypothalamic-pituitary-thyroid axis). ——● inhibit; ——○ stimulate; T_3, tri-iodothyronine; T_4, thyroxine TSH, thyroid-stimulating hormone; TRH, thyrotropin-releasing hormone.

adrenaline), to which it bears a structural resemblance, but the effect is far more prolonged and more fundamental, whereas the catecholamines have a very brief action.

Metabolism and growth.   Thyroid hormone has a generally catabolic effect, stimulating metabolism and increasing oxygen consumption, basal metabolic rate and body temperature. However, in children there are anabolic effects leading to protein synthesis and growth. Carbohydrate absorption is increased and plasma lipid levels fall.

Cardiovascular and renal.   There are inotropic and chronotropic effects mediated via up-regulation of numerous systems, including beta-receptors. In addition the calorigenesis promotes peripheral vasodilatation and secondary

fluid retention to maintain cardiac output and blood pressure.

CNS.   The action on the CNS is known mostly through the consequences of thyroid malfunction, considered below. There are important effects on mentation and CNS development. However, little is known of the precise mechanisms.

Investigation

The three key parameters of thyroid function are serum levels of FT_3, FT_4 and TSH. Older tests measured protein-bound iodine and total thyroid hormone, but now the precise radio-immunoassay of free hormones and TSH gives a far better correlation with physiological and

Table 9.23   Actions of thyroid hormone

System	Effect
Metabolism	
Calorigenesis	↑ oxygen consumption and oxygen dissociation
	↑ basal metabolic rate, ↑ temperature
Lipid	↓ total cholesterol (↑ hepatic LDL receptors)
Carbohydrate	↑ absorption from GIT
Cardiovascular	Inotropic: beta-receptors up-regulated
	↑ heart rate, ↑ cardiac output
	Peripheral vasodilatation
Renal	Fluid retention
Neurological	Essential for nervous system development
	(No calorigenic effect in brain)
Growth	Essential for normal growth, including bone

clinical status. It is possible to measure the binding proteins, and several factors can change binding, but the feedback control is sensitive and precise, so FT_4 levels tend to be very stable. It is not usually necessary to measure TRH. The measurement of FT_4, FT_3 and TSH together is know as a **thyroid function test (TFT)**. It has become clear that TSH levels are the most important index of thyroid status, and management now stresses normal TSH levels.

In the initial investigation of thyroid disease an autoantibody screen should be done for anti-thyroid antibodies, and also for anti-intrinsic factor and anti-gastric parietal cell antibodies, because there is an association with other autoimmune diseases including pernicious anaemia. Liver function, lipid profile, blood glucose and full blood count are also necessary.

The possibility of primary hypothalamic or pituitary disease should always be borne in mind when thyroid dysfunction is detected, particularly hypothyroidism. In this case both thyroid hormone and TSH levels will be low.

Thyroid disease

Normal thyroid function is described as **euthyroidism**. **Hypothyroidism** (underactivity) and **hyperthyroidism** (overactivity) are about equally common and together constitute the most prevalent endocrine abnormalities. Usually the cause is idiopathic, often involving autoimmuity, although iatrogenic causes occur. Detection and diagnosis are usually straightforward, and management of hypothyroidism is also simple. Hyperthyroidism is more complex to manage and may develop complications.

There are several potentially confusing aspects to thyroid disease. Firstly, certain aetiological factors, such as autoantibodies, amiodarone and iodine, are common to both hypo- and hyperthyroidism; similarly, an enlarged thyroid gland (goitre) can occur in both. The action of iodine/iodide can seem paradoxical, causing either stimulation or inhibition in different circumstances. Long-term hyperthyroidism can eventually evolve into hypothyroidism, and some forms of hypothyroidism can have a hyperthyroid phase.

Hypothyroidism

Aetiology and epidemiology

Hypothyroidism is far more common in women than in men (prevalence 1.5% vs 0.1%) and more common in the elderly, although it can affect the very young and is then far more serious. It is usually due to intrinsic thyroid gland disease although rarely it may occur

secondary to hypothalamic or pituitary disease, or to drugs (Table 9.24).

Simple **atrophy** is the commonest cause, mainly affecting elderly women. There may be an autoimmune component as it is sometimes associated with other autoimmune disease, but no antibodies are found. Autoimmune destruction is the main cause of **Hashimoto's thyroiditis**, which can affect the middle-aged and elderly. Also common is hypothyroidism secondary to the treatment of hyperthyroidism (see below).

In the developed world dietary **iodine deficiency** is now almost unknown, partly owing to iodination of salt, but it is far more common in developing countries. Congenital hypothyroidism secondary to maternal iodine deficiency affects the developing nervous system of the fetus to produce **cretinism**.

The term **myxoedema** is sometimes used as a synonym for hypothyroidism but more precisely describes one characteristic dermatological sign.

Pathology

Low levels of thyroid hormone compromise many crucial metabolic processes, as can be inferred from Table 9.23. There is a general slowing of basal metabolic rate, a fall in temperature, and slowing of physical and mental processes. More detail is given on p. 635.

Investigation and diagnosis

The standard thyroid function test is definitive. When thyroid hormone levels fall there is almost invariably a compensatory rise in TSH. However, a small rise in TSH may precede both clinical signs and a fall in thyroid hormone level by many months; this is known as **subclinical hypothyroidism** (see below).

In rare hypothalamic-pituitary causes the combination of low FT_4 and low TSH levels is diagnostic.

Screening for autoantibodies to thyroid peroxidase or thyroglobulin is not necessary for diagnosis but can indicate a possible cause, and can act as an alert for possible autoimmune complications in Hashimoto's thyroiditis. Occasionally there may be anti-TSH receptor antibodies with a blocking effect, although such antibodies are usually stimulant, causing hyperthyroidism (Graves' disease, see p. 637).

Hypothyroidism is often diagnosed following vague generalized complaints of tiredness and lack of energy. However, these common symptoms can of course have many other causes, which sometimes makes diagnosis of mild

Table 9.24   Causes of hypothyroidism

Aetiology	Example
Common (90% of cases in developed countries)	
Atrophy (idiopathic)	Commonest form; no goitre
Autoimmune destruction	Hashimoto's thyroiditis
Iatrogenic	Secondary to treatment of hyperthyroidism (antithyroid drugs, surgery, radiotherapy)
Less common	
Dietary	Iodine deficiency where natural level low; goitre present
Congenital	Cause of cretinism (1/4000 in UK)
Iatrogenic	Lithium, amiodarone
Secondary	Hypothalamic or pituitary disease

disease problematic. Thyroid disease should always be borne in mind as a differential diagnosis of depression in the elderly.

Clinical features

Most of the features of hypothyroidism can be understood from a knowledge of the physiological action of thyroid hormone (Table 9.25). The overall clinical impression is of slowness and dullnes of intellect combined with an unprepossessing appearance. Therefore a history from a relative might be helpful, to identify recent or specific changes, which may be less apparent to the patient because onset is usually insidious. The two most common erroneous diagnoses in mild disease would be simple ageing, owing to the slowness, stiffness and general aches and pains, or depression.

The most characteristic symptoms are the general physical and mental sluggishness,

Table 9.25   Principal clinical features of hypothyroidism

	Common feature	Less common
Systemic/metabolic	Tiredness Weight gain Cold intolerance Goitre Hyperlipidaemia	Hypothermia, cold periphery
Haematological		Anaemia – iron deficiency – pernicious/macrocytic – normochromic normocytic
Cardiovascular	Bradycardia	Pericardial/pleural effusion Hypertension Heart failure
Dermatological	Dry, thick skin	Dry, thin hair; alopecia Myxoedema (non-pitting oedema) Periorbital oedema Vitiligo
Musculoskeletal	Delayed relaxing reflexes Slow movement Myalgia, arthralgia, stiffness	Peripheral myopathy Carpal tunnel syndrome Ataxia (unsteadiness) Deafness Hoarseness
Neuropsychiatric	Depression Slow thought Poor memory	Dementia Psychosis
Gastrointestinal	Constipation	Anorexia
Reproductive	Menorrhagia/oligomenorrhoea	Infertility Delayed puberty
Developmental		Growth retardation Mental retardation; cretinism

lethargy, intolerance of cold, weight gain and coarsening of the skin. The voice is hoarse and hair is dry, brittle and falling. There may be a characteristic swollen thyroid, visible in the neck as a **goitre**.

The classic dermatological feature is **myxoedema**, which is an accumulation of mucopolysaccharide in the dermis that causes widespread skin thickening and puffiness. This form of oedema is non-pitting because it is not caused by excess fluid accumulation (contrast with the pitting oedema of heart failure; see Chapter 4, p. 184).

The heart rate is slowed and this may cause heart failure. The periphery is cold.

Thought processes and memory are impaired and mild depression is common. There is usually weight gain and constipation, despite anorexia.

Biochemically, in addition to abnormal thyroid functions tests (low FT_3 and FT_4, raised TSH), there is usually hyperlipidaemia and possibly abnormal liver enzymes. Haematology (see Chapter 11) may show a mixed picture of iron deficiency (hypochromic, microcytic anaemia), folate and/or B_{12} deficiency (macrocytic anaemia) or simply a normochromic, normocytic pattern.

Subclinical hypothyroidism

In some patients there are few if any symptoms and FT_4/FT_3 levels are within normal limits but TSH is elevated; this might be identified as a chance finding. The pathogenesis is probably an early stage of thyroid insufficiency being compensated by slightly elevated TSH level, initally keeping thyroid hormone levels adequate. Eventually the slowly progressive nature of idiopathic hypothyroidism will lead to frank insufficiency that does not respond to increasing levels of TSH: thyroid hormone levels then fall and symptoms develop. Regular monitoring is all that is required during the asymptomatic phase.

Complications

If thyroid hormone levels are corrected there is no reduction in life expectancy and there are no long-term problems.

Heart failure or 'myxoedemic' coma can be precipitated by severe metabolic stress, such as trauma, infection or hypothermia, which may acutely increase thyroid hormone requirement. Psychosis can also occur ('myxoedemic madness'). If the fetus is exposed to inadequate thyroid hormone *in utero*, irreversible neurological damage leads to cretinism. Hypothyroidism in children results in retardation of mental and physical development that is partially reversible on thyroid hormone treatment. Newborn are routinely screened.

Management

The management of hypothyroidism is relatively straightforward, simply requiring oral thyroxine for life. The general aim is to restore T_4, T_3 and TSH levels to within the normal ranges. TSH should not be suppressed too much in an attempt to maintain T_4/T_3 at high–normal levels: this represents overtreatment and can lead to long-term cardiovascular complications. Thus a mid-range TSH level is usually regarded as the primary objective, ensuring of course that T_4/T_3 are also within range. However, low-end TSH levels are regarded by some as preferable.

Levothyroxine

This is the synthetic replacement drug used for maintenance therapy, which is identical to natural thyroxine (T_4). (This has completely replaced the original dried thyroid gland, a natural product derived from animal sources, with all the quality control risks these entail.) *Levothyroxine* is well absorbed on an empty stomach, but absorption is delayed and possibly reduced by food. Dosing is not nearly as critical for *levothyroxine* in hypothyroidism as it is for

insulin in diabetes, because *levothyroxine* has a half-life of about 7 days and a gentle dose–response curve. Moreover, day-to-day requirements do not change even with intercurrent illness, nor do they tend to alter over the long term. Owing to the natural diurnal variation of TSH secretion, which peaks overnight, a single dose is usually taken each morning before breakfast.

Levothyroxine is initialized at 50 μg daily and increased by 50 μg daily every 2–4 weeks depending on response. Clinical improvement is usually evident within the first month of therapy. Thyroid function testing is required 6 weeks after each dose change. Most patients are stabilized on 100–200 μg daily; subsequently only annual TFTs will be needed.

More care is needed when initializing treatment in the elderly or those with known IHD, using a lower starting dose, e.g. 25 μg on alternate days, and smaller increments, because the cardiac over-stimulation could precipitate ischaemic symptoms or even an MI. Sometimes *liothyronine* (T_3) is used for its shorter half-life, permitting a more rapid correction of overdosing. Regular ECGs are advisable and beta-blocker cover may be needed to limit the heart rate.

Side-effects

The adverse effects of excess *levothyroxine* (thyrotoxicosis) are exactly what would be predicted from the physiological action of excess thyroxine and are described below (p. 640). With overdosage, as with untreated hyperthyroidism, there is the possibility of osteopenia or osteoporosis in women, which should be monitored.

Cautions and interactions

The dose may require increasing in pregnancy. Hepatic enzyme inducers (e.g. *rifampicin*, *phenytoin*) increase clearance. Some drugs reduce absorption, so *levothyroxine* should be taken at a different time from *sucralfate*, *aluminium hydroxide* and iron salts (Table 9.26). Other factors that affect the control of hypothyroidism are also shown in this table.

Liothyronine

Liothyronine (tri-iodothyronine, T_3) has a swifter onset and shorter half-life than *levothyroxine* and it is about five times more potent. It is mainly used for emergency treatment of severely hypothyroid states such as coma, or for initiating treatment in those with CVD. It is available in injectable and oral forms.

Hyperthyroidism

For several reasons, hyperthyroidism is not simply the opposite of hypothyroidism. The causes are more diverse, there are more potential complications and there are more treatment options with worse side-effects. Note that the term **thyrotoxicosis** is used to describe the syndrome resulting from excess thyroid hormone levels, but **hyperthyroidism** refers specifically to when the syndrome is due to excessive secretion from the thyroid gland.

Aetiology and epidemiology

Hyperthyroidism is about 10 times more common in women, in whom the point prevalence is about 1%. However, the lifetime incidence in women is over 2%, some forms being acute or reversible.

Graves' disease, caused by IgG autoantibodies that stimulate the TSH receptor, is the commonest form, representing some 75% of all cases (Table 9.27). It typically follows a fluctating but progressive course, eventually leading to hypothyroidism, either naturally or as a result ot treatment.

Autonomous growth of multiple, hypersecreting 'toxic' nodules in the thryoid gland is the second most common form and this is more often seen in elderly females, but isolated 'toxic' adenomas (benign tumours) can also occur. These are usually associated with goitre. Occasionally

Table 9.26 Cautions and interactions of levothyroxine therapy

(a) Factors affecting thyroid function or levothyroxine treatment	Increased thyroid hormone action or thyroid function	Reduced thyroid hormone action or thyroid function
Interfere with thyroid hormone action	–	Enzyme inducers (e.g. rifampicin) $\downarrow$ absorption (e.g. aluminium hydroxide, iron, etc.) $\downarrow$ TSH secretion (corticosteroids, dopamine)
Interfere with thyroid status	Amiodarone (inhibit peroxidase) Lithium (unknown effect)	Amiodarone (excess iodine) Lithium (blocks iodine uptake and thyroid hormone release) Iodide/iodine excess, e.g. older 'expectorants' Iodine deficiency Monovalent anions e.g. pertechnetate (TcO_4^-), perchlorate (ClO_4^-), thiocyanate (SCN^-): compete for iodine uptake. Pregnancy ($\uparrow$ thyroid hormone requirement)

(b) Drugs affected by levothyroxine treatment	Drugs with action enhanced	Drugs with action diminished
Drug interaction	Sympathomimetic (mimic action) Warfarin (potentially $\uparrow$ action – monitor)	Propranolol, digoxin ($\downarrow$ serum level) Insulin/oral hypoglycaemic ($\downarrow$ glucose tolerance)

Table 9.27 Causes of hyperthyroidism	
Aetiology	**Examples**
Most common (75%)	
Autoimmune stimulation	Graves' disease (stimulatory anti-TSH receptor antibody)
Less common	
Multinodal goitre	
Adenoma	
Thyroiditis	Post partum, viral, autoimmune
Iatrogenic	Amiodarone, excessive levothyroxine dose
Dietary	Excess iodine
Rare	
Secondary	Pituitary – excessive TSH secretion
	Other endocrine abnormalities

general thyroid inflammation (**thyroiditis**) occurs following radiation, childbirth or viral illness; there may be an underlying autoimmune aetiology to this. It usually remits without recurrence. **Thyroid cancer** is one of the most common radiation-induced tumours, via ingestion of radioiodine (^{131}I), e.g. after radiological accidents such as at Chernobyl.

Amiodarone, which has a high iodine content, frequently causes mild hyperthyroidism, possibly leading to thyrotoxicosis on prolonged therapy. It can also cause hypothyroidism (Table 9.24). Very rarely hyperthyroidism can be secondary to pituitary hyperactivity (Table 9.27).

Pathology

High levels of thyroid hormone cause a general acceleration of metabolic processes with increased metabolic rate and energy utilization, hyperthermia and increased cardiovascular activity (see below). There is a compensatory fall in TSH, often to undetectable levels.

Investigation and diagnosis

Owing to the several possible aetiologies, more extensive investigation is required than for hypothyroidism. Typical clinical features will invariably be borne out by a TFT, which will usually show raised FT_4 and FT_3 and barely detectable TSH.

Further investigation will depend upon the degree of suspicion of different aetiologies, but could include:

- Autoantibody scan; thyroid peroxidase and thyroglobulin antibodies are usually found, but there is a 10–20% false-negative rate because they may also occur in unaffected individuals. TSH-stimulating receptor antibodies are difficult to assay and are not routinely sought.
- Imaging is best done with radiolabelled sodium pertechnetate (^{99m}Tc), which is preferentially taken up into the thyroid by the symporter but not organified. This will show the overall size of the organ, with concentration in any nodules, showing their number and size. It is a prerequisite if ablation therapy is planned. Ultrasound is less invasive. MRI or CT scanning is used if ophthalmopathy (see below) is suspected.
- Biopsy: if a tumour is suspected.

Clinical features

The clinical features of hyperthyroidism (Table 9.28) should be contrasted with those of hypothyroidism (Table 9.25): the picture is strikingly different. The range of features varies slightly according to aetiology but is broadly

consistent. Typically the patient is thin, nervous, agitated, hyperactive, hot, thirsty and sweaty.

Examination will show a raised heart rate, possibly even atrial fibrillation; in severe cases there may be signs of heart failure. The neck will usually be swollen and auscultation of the goitre will reveal bruits (the sound of rapid, excessive blood flow). There are also usually diarrhoea and anxiety.

In Graves' disease the common complication of ophthalmopathy (see below) will cause bulging eyes and an unblinking stare, known as **exophthalmos** – the classic sign of thyrotoxicosis. Another characteristic Graves' feature is **pretibial myxoedema**, where the deposition of fibrous material causes painless dermal nodules on the shin.

Course

Graves' disease may follow a relapsing and remitting course, with remissions facilitated by therapy. However, remissions become increasingly likely following each successive relapse. Paradoxically, the end-stage for some patients may be autoimmune hypothyroidism. There is an increased risk of osteoporosis and heart disease in untreated disease.

Table 9.28   Principal clinical features of hyperthyroidism

	Common feature	Less common
Systemic/metabolic	Fatigue, weakness Hyperactivity, restlessness Weight loss Heat intolerance, sweating Polydipsia Goitre	Hyperthermia, warm periphery Polyuria Bruit over gland (excess perfusion)
Cardiovascular	Tachycardia, atrial fibrillation Palpitations	Heart failure (high output) Hypertension
Musculoskeletal	Hyper-reflexia Tremor	Myopathy Lid retraction, lid lag
Neuropsychiatric	Irritability, anxiety, dysphoria Insomnia	Depression Psychosis
Gastrointestinal	Increased appetite	Diarrhoea
Reproductive		Oligomenorrhoea Loss of libido
Dermatological		Pruritis Pretibial myxoedema[a]
Ophthalmopathy[a]	Grittiness Periorbital, conjunctival oedema Scleral injection ('red eye') Proptosis (exophthalmos)	Diplopia Impaired acuity
Family history	Autoimmune disease e.g. Graves' disease, pernicious anaemia, vitiligo, type 1 diabetes mellitus	

(a) Only in Graves' disease.

Complications

Ophthalmopathy (thyroid eye disease)

A characteristic eye disease affects about half of Graves' disease patients. It is potentially serious and for unkown reasons it is associated with smoking. The cause is autoimmune inflammation of the oculomotor muscles, with fibrous overgrowth. This pushes the eyes forward and impairs eye movement. The overexposed corneas can become dry and painful, and there may be diplopia (double vision). In the most severe form (<10% cases) the retro-orbital swelling can compress the optic nerve and threaten sight.

It can be detected by examination of eye movement and testing for double vision at the extremes of lateral eye rotation, but MRI scanning is needed for precise assessment. Its severity is not related to thyroid hormone levels nor is it relieved if euthyroidism is achieved by medical or surgical means, probably because it is due to antithyroid antibodies rather than excessive thyroid hormone itself. For most patients it is an unsightly inconvenience rather than a threat to sight.

Thyroid crisis ('storm')

This rare condition, which occurs when there are very high levels of thyroid hormone, is potentially fatal. There is excessive cardiovascular stimulation, high fever and extreme agitation. It can be triggered in hyperthyroid patients by extra metabolic stress, such as infection, by mental stress, or by radioiodine therapy.

Autoimmune disorder

Other autoimune diseases including pernicious anaemia, myasthenia gravis, type 1 diabetes and vitiligo are more common among Graves' disease sufferers.

Management

The aims of management are symptom control and reduction of thyroid hormone output. For the latter, three modes are available:

- Pharmacological suppression.
- Radio-isotopic thyroid gland reduction/ablation.
- Surgical thyroid gland reduction/ablation.

Beta-blockers are used for symptom control while other therapy is initialized. This is effective because many of the effects of thyroid hormone are sympathomimetic and resemble those of adrenaline (epinephrine), including cardiac stimulation, tremor and anxiety (Table 9.23). *Propranolol* is preferred, probably because it is non-selective and crosses the blood–brain barrier, helping the anxiety. Agents with intrinsic sympathomimetic activity (e.g. *pindolol*; see Chapter 4) should not be used.

Patients may use different modes at different stages in their illness. Typical paths are shown in Figure 9.16. After initial stabilization with antithyroid drugs patients may go into remission after a year or so and drugs may be withdrawn. However, relapse is common and remission is then less likely. Thyroid gland reduction aims at a graded reduction in thyroid mass, hoping to leave enough remaining to produce normal amounts of thyroid hormone. However, judging this is difficult and it is always preferable to err on the side of greater destruction, obviating the need for further invasive therapy at a later date. Consequently, eventual iatrogenic hypothyroidism is common. Alternatively, a full ablation may be decided on at the outset, removing doubt and easing management by starting the patient on thyroxine replacement immediately. Thus the choice of options depends on the cause, severity, patient age and patient preference.

Pharmacotherapy

Antithyroid drugs are usually first-line treatment. They block thyroid peroxidase rapidly, but symptom control takes 2–4 weeks owing to stores of thyroid hormone and its long half-life. The most common agents are the thionamides. *Carbimazole* is preferred in the UK but *propylthiouracil* is used in the USA. The latter also blocks T_4–T_3 conversion but this may not be clinically significant. Most antithyroid drugs also have immunosuppressant activity, reducing TSH-receptor antibodies, which may account for the
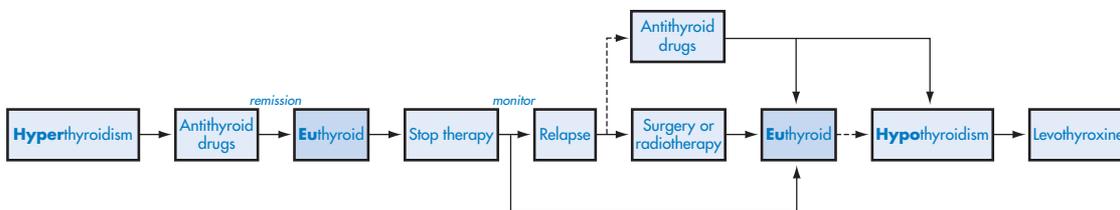
Figure 9.16   Treatment pathways for hyperthyroidism.

sustained remission seen in about half of patients after withdrawal of drug therapy It may also be related to the most serious side-effect, agranulocytosis.

A high initial dose (e.g. 40–60 mg *carbimazole*, depending on initial TFTs) is tapered after 4–6 weeks, with advice to the patient to be alert for overtreatment (sluggishness, constipation, slow pulse, etc). Repeated T_3/T_4 level estimations guide dose reduction at 4- to 8-week intervals. TSH takes longer to rise than thyroid hormone levels do to fall. A maintenance dose of 5–10 mg daily is continued for 18 months, after which a trial withdrawal can be attempted. About half of patients remain in remission and are monitored annually. Some eventually relapse; others develop autoimmune hypothyroidism. Those who relapse have less chance of a further remission and either long-term pharmacotherapy or an alternative mode of therapy is then indicated.

Block and replace
An alternative strategy is to continue antithyroid drugs at a high dose for the same period of 2 years, effectively producing a chemical ablation. Standard replacement doses of *levothyroxine* are given, eventually withdrawing all drugs if euthyroidism is achieved. This strategy is simpler, requiring less monitoring and titration, and it allows for a more sustained immunosuppressant action from higher doses of antithyroid drug. However, there is little evidence that it is more effective, and there is an increased risk of side-effects.

Side-effects include minor dermatological problems, avoided by changing to another antithyroid agent, and other minor non-specific drug side-effects. Most important, however, is bone marrow suppression and agranulocytosis, which can affect 0.1% of patients. This is usually rapid in onset, occurring during the first 3 months of treatment, so not easily detected from blood counts. All patients must be warned to watch for swollen glands, throat infections and bruising. If these occur they should stop their drug and consult their GP urgently. The problem is reversed on withdrawal but antimicrobial cover (for neutropenia) and *filgastrim* (to stimulate leucocyte recovery) may initially be required. A change of drug may subsequently be tried: the effect may not recur.

Iodide/iodine have an antithyroid effect and are sometimes used as an adjuvant in thyroid storm or before thryoidectomy, to reduce gland size, but they are no longer first-line therapy.

Radiotherapy

Selective thyroid reduction using sodium radioiodide (^{131}I) exploits the concentration of iodide in the thyroid, which minimizes exposure of other organs and allows a low total body dose. In the USA it it often the first line treatment for those over 50, owing to the potential cardiovascular risks of hyperthyroidism. In Europe it is preferred to surgery for medical failure to control hyperthyroidism or following relapse. Although the aim is to spare enough gland to permit normal thyroid hormone output, there is a 10–20% chance of hypothyroidism in the first year following treatment and subsequently up to a 5% annual incidence. Sodium radioiodide is taken as an oral solution. Little special contact avoidance is necessary afterwards, except for avoiding public transport and sustained close contact with children for about 4 weeks. It is contra-indicated in pregnancy.

Complications

The effect takes several months to develop, during which thyroid hormone levels may rise temporarily, and antithyroid drug or beta-blocker cover may be needed. Ophthalmopathy is a relative contraindication because it may be exacerbated. There is a small increase in the risk ot thyroid cancer.

Thyroidectomy

Surgery has a similar aim to radiotherapy, i.e. subtotal thyroid gland reduction, but has the same imprecision and is more invasive. It is particularly indicated if there is a large goitre. It is important that patients are rendered euthyroid before surgery, to avoid thyroid storm. Some are given oral iodine (Lugol's iodine) or potassium iodide for a few weeks before surgery, to inhibit thyroid hormone synthesis and reduce gland vascularity. As with radioiodine, many patients eventually become hypothyroid. Potential surgical complications include laryngeal or parathyroid damage.

Ophthalmopathy

Milder cases need symptomatic treatment, including artificial tears and eye protection. If sight is threatened, high-dose corticosteroids, surgery or radiation therapy may be indcated.

Thyroid storm

Urgent antithyroid therapy with thionamides and iodine are required to reduce thyroid hormone output. Symptomatic cover with beta-blockers, corticosteroids and possibly IV fluids will usually be necessary. The precipitating cause must be discovered and treated.

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Internet resources

http://www.diabetes.org.uk (website of Diabetes UK, the charity for people with diabetes).