26 Anti-inflammatory and immunosuppressant drugs

OVERVIEW

This chapter deals with the drugs used to treat inflammatory and immune disorders. While generally associated with diseases such as rheumatoid arthritis, it has become clear that inflammation forms a significant component of many, if not most, of the diseases encountered in the clinic and consequently anti-inflammatory drugs are extensively employed in virtually all branches of medicine.

The chief drugs used to treat inflammation may (somewhat arbitrarily) be divided into three major groups:

- **Drugs that inhibit the cyclo-oxygenase enzyme— the non-steroidal anti-inflammatory drugs (NSAIDs) and the coxibs.**
- **Antirheumatoid drugs—the disease-modifying antirheumatic drugs (DMARDs) including some immunosuppressants.**
- **The new anticytokine, and other biological agents.**

We first describe the therapeutic effects, mechanisms of action and unwanted effects common to all NSAIDs, and deal in a little more detail with aspirin, paracetamol and drugs that are selective for cyclo-oxygenase (COX)-2. The antirheumatoid drugs comprise a rather heterogeneous group, many of unknown mechanism of action. They include immunosuppressant drugs that are also used to prevent rejection of organ transplants. The glucocorticoids are covered in Chapter 32, but are briefly discussed in this chapter. We then consider the latest biologicals that are revolutionising treatment in many cases of severe disease. Finally, we consider drugs that do not fit easily into these categories: those used to treat gout and the histamine H$_1$ receptor antagonists used to treat acute allergic conditions.

CYCLO-OXYGENASE INHIBITORS

This group includes the 'traditional' (in the historical sense) NSAIDs[1] as well as the newer *coxibs* that are more selective for COX-2 (see below). These drugs, sometimes called the *aspirin-like drugs*, or *antipyretic analgesics* are among the most widely used of all agents. There are now more than 50 different NSAIDs on the global market; some current examples are listed in Table 26.1 and some structures given in Figure 26.1. These drugs provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteo- and rheumatoid arthritis, as well as in more acute inflammatory conditions such as fractures,

sprains, sports and other soft tissue injuries. They are also useful in the treatment of postoperative, dental and menstrual pain, and of headaches and migraine. Several NSAIDs are available over-the-counter and they are widely used for other types of minor aches and pains. There are many different NSAID formulations available, including tablets, injections and gels. Virtually all these drugs, particularly the 'traditional' NSAIDs, can have significant unwanted effects, especially in the elderly. Newer agents have fewer adverse actions.

While there are differences between individual NSAIDs, their primary pharmacology is related to their shared ability to inhibit the *fatty acid COX* enzyme, thereby inhibiting the production of prostaglandins and thromboxanes (see Ch. 17). There are two common isoforms of this enzyme, *COX-1* and *COX-2*. There may also be other COX enzymes that can generate prostaglandins but these have not been completely characterised. While COX-1 and COX-2 are closely related (> 60% sequence identity) and catalyse the same reaction, it is clear that there are important differences between the expression and role of these two isoforms. COX-1 is a *constitutive* enzyme expressed in most tissues, including blood platelets. It has a 'housekeeping' role in the body, being involved in tissue homeostasis, and is responsible for the production of prostaglandins involved in, for example, gastric cytoprotection (see Ch. 29), platelet aggregation (Ch. 24), renal blood flow autoregulation (Ch. 28) and the initiation of parturition (Ch. 34).

In contrast, COX-2 is *induced* in inflammatory cells when they are injured, infected or activated by, for example, the inflammatory cytokines—interleukin (IL)-1 and tumour necrosis factor (TNF)-α (see Ch. 17). Thus the COX-2 isoform is mainly responsible for the production of the prostanoid mediators of inflammation (Vane & Botting, 2001), although there are some significant exceptions. For example, there is a considerable pool of 'constitutive' COX-2 present in the central nervous system (CNS) and some other tissues, although its function at these sites is not yet completely clear.

Most 'traditional' NSAIDs inhibit both COX-1 and COX-2, although they vary in the degree to which they inhibit each isoform. It is believed that the anti-inflammatory action (and probably most analgesic and antipyretic actions) of the NSAIDs are related to inhibition of COX-2, while their unwanted effects—particularly those affecting the gastrointestinal tract—are largely a result of their inhibition of COX-1. Compounds with a selective inhibitory action on COX-2 are now in clinical use, but while these drugs show fewer gastrointestinal side effects, they are by no means as well tolerated as was once hoped. This is partly because many patients taking these drugs have already been exposed to less selective inhibitors and have already suffered some gastrointestinal damage. As COX-2 seems to be important in healing and resolution, one can see how problems might still occur. There is also a concern

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[1]Here, we use the term NSAID to include the coxibs but this is not a convention always followed in the literature.

Table 26.1   Comparison of some common anti-inflammatory cyclo-oxygenase inhibitors

Drug	Type	Indication	COX isoform selectivity	Comments
Aceclofenac	Phenylacetate	RA, OA, AS		
Acemetacin	Indole ester	RD, OA, MS, PO		Ester of indometacin
Aspirin	Salicylate		Weakly COX-1 selective	Mainly cardiovascular usage alone Component of many OTC preparations
Azapropazone	Pyrazolone	RD, AS, G		Used when other drugs have failed Severe gastrointestinal effects
Celecoxib	Coxib	RA, OA, AS, H&M	Moderately COX-2 selective	Fewer gastrointestinal effects
Dexibruprofen	Propionate	OA, MS, D, H&M		Active enantiomer of ibuprofen
Dexketoprofen	Propionate	PO, D, H&M		Isomer of ketoprofen
Diclofenac	Phenylacetate	RA, OA, G, MS, PO	Weakly COX-2 selective	Moderate potency
Etodolac	Pyranocarboxylate	RA, OA		Possibly fewer gastrointestinal effects
Etoricoxib	Coxib	RA, OA, G	Very COX-2 selective	
Fenbufen	Propionate	RA, OA, MS		
Fenoprofen	Propionate	RA, OA, MS, PO	Non-selective	Prodrug activated in liver
Flurbiprofen	Propionate	RA, OA, MS, PO, D, H&M	Very COX-1 selective	
Ibuprofen	Propionate	RA, OA, MS, PO, D, H&M	Weakly COX-1 selective	Suitable for children
Indometacin	Indole	RA, OA, G, MS, PO, D	Weakly COX-1 selective	Suitable for moderate to severe disease
Ketoprofen	Propionate	RA, OA, G, MS, PO		Suitable for mild disease
Ketorolac	Pyrrolizine	PO	Highly COX-1 selective	
Mefenamic acid	Fenamate	RA, OA, PO, D		Moderate activity
Meloxicam	Oxicam	RA, OA, AS		Possibly fewer gastrointestinal effects
Nabumetone	Naphthylalkenone	RA, OA		Prodrug activated in liver
Naproxen	Propionate	RA, OA, G, MS, PO, D	Weakly COX-1 selective	
Parecoxib	Coxib	PO		Prodrug activated in liver
Piroxicam	Oxicam	RA, OA, G, MS, PO	Weakly COX-2 selective	
Sulindac	Indene	RA, OA, G, MS	Weakly COX-2 selective	Prodrug
Tenoxicam	Oxicam	RA, OA, MS		
Tiaprofenic acid	Propionate	RA, OA, MS		
Tolfenamic acid	Fenamate	H&M		

AS, ankylosing spondylitis; D, dysmenorrhoea; G, acute gout; H&M, headache and migraine; MS, musculoskeletal injuries and pain; OA, osteoarthritis; OTC, over-the-counter; PO, postoperative pain; RA, rheumatoid arthritis.
(Data from British National Formulary and Warner T D, Mitchell J A 2004 FASEB J 18: 790–804.)

about the cardiovascular effects of all NSAIDs when these are taken over a long time (see below). Some notes on the relative selectivity of some currently available NSAIDs and coxibs are given in Table 26.1.

▼ While the pharmacological actions of NSAIDs are broadly similar (although there are marked differences in toxicity and degree of patient tolerance), there are exceptions. **Aspirin** has other qualitatively different pharmacological actions (see below), and **paracetamol** is an interesting exception to the general NSAID 'stereotype'. While it is an excellent analgesic and antipyretic, its anti-inflammatory activity is slight and seems to be restricted to a few special cases (e.g. inflammation following dental extraction; see Skjelbred et al., 1984). Paracetamol has been shown to inhibit prostaglandin biosynthesis in some experimental settings (e.g. during fever) but not in others. The

main pharmacological actions and the common side effects of the NSAIDs are outlined below, followed by a more detailed coverage of aspirin and paracetamol and an outline of the pharmacology of the selective COX-2 inhibitors.

MECHANISM OF ACTION

Vane and his colleagues established in 1971 that the main actions of NSAIDs were bought about through inhibition of arachidonic acid oxidation by the fatty acid COXs (see Fig. 26.2).

▼ These are bifunctional enzymes, having two distinct catalytic activities. The first, dioxygenase step incorporates two molecules of oxygen into the arachidonic (or other fatty acid substrate) chain at
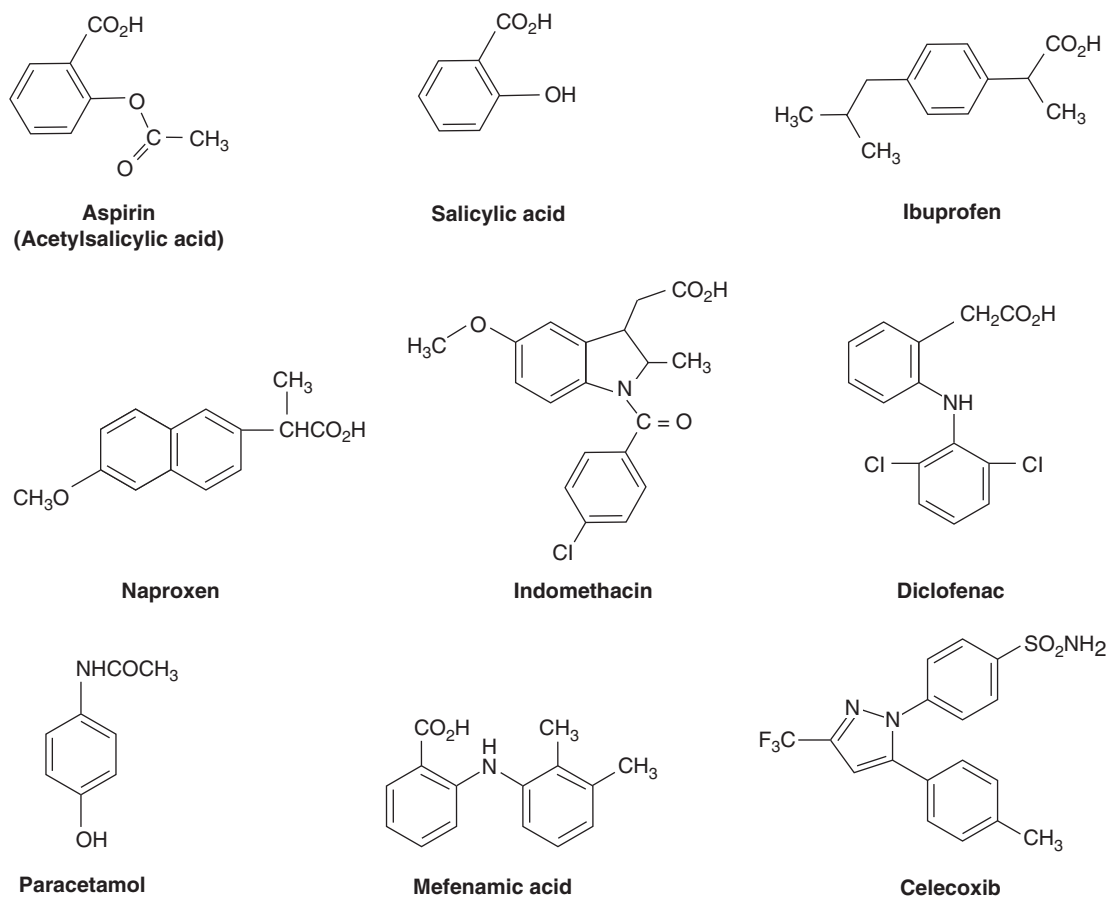
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Fig. 26.1 **Significant structural features of some non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs.** Aspirin contains an acetyl group that is responsible for the inactivation of the COX enzyme. Salicylic acid is the end product when aspirin is de-acetylated. Oddly it has anti-inflammatory activity in its own right. Paracetamol is a commonly used analgesic agent also of simple structure. Most 'classic' NSAIDs are carboxylic acids. Coxibs (celecoxib shown here as an example), however, often contain sulfonamide or sulfone groups. These are important in the selectivity of the molecule as they impede access to the hydrophobic channel in the COX-1 enzyme (see Fig. 26.2).

Cyclo-oxygenase inhibitors

These drugs have three major therapeutic actions, stemming from the suppression of prostanoid synthesis in inflammatory cells through inhibition of the cyclo-oxygenase (COX)-2 isoform of the arachidonic acid COX. They are as follows:

• *An anti-inflammatory action*: the decrease in prostaglandin E_2 and prostacyclin reduces vasodilatation and, indirectly, oedema. Accumulation of inflammatory cells is not directly reduced.

• *An analgesic effect*: decreased prostaglandin generation means less sensitisation of nociceptive nerve endings to inflammatory mediators such as bradykinin and 5-hydroxytryptamine. Relief of headache is probably a result of decreased prostaglandin-mediated vasodilatation.

• *An antipyretic effect*: interleukin-1 releases prostaglandins in the central nervous system, where they elevate the hypothalamic set point for temperature control, thus causing fever. NSAIDs prevent this.

Some important NSAIDs are **aspirin**, **ibuprofen**, **naproxen**, **indometacin**, **piroxicam** and **paracetamol**. Newer agents with more selective inhibition of COX-2 (and thus fewer adverse effects on the gastrointestinal tract) include **celecoxib** and **etoricoxib**.

C11 and C15, giving rise to the highly unstable endoperoxide inter-mediate PGG$_2$ with a hydroperoxy group at C15. A second, peroxi-dase function of the enzyme converts this to PGH$_2$ with a hydroxy group at C15 (see Ch. 17), which can then be transformed in a cell-specific manner by separate isomerase, reductase or synthase enzymes into other prostanoids. Both COX-1 and COX-2 are haem-

containing enzymes that exist as homodimers attached to intracel-lular membranes. Structurally, the isoforms are similar; both contain a hydrophobic channel into which the arachidonic or other substrate fatty acids dock so that the oxygenation reaction can proceed.

Most NSAIDs inhibit only the initial dioxygenation reaction. They are generally 'competitive reversible' inhibitors, but there are differences
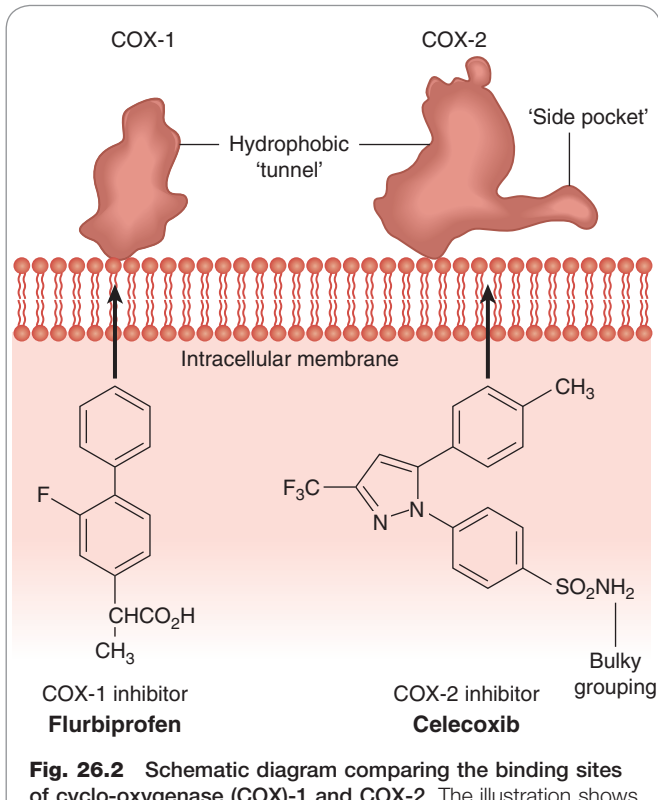
Fig. 26.2 **Schematic diagram comparing the binding sites of cyclo-oxygenase (COX)-1 and COX-2.** The illustration shows the differences in NSAID binding sites in the two isoforms. Note that the COX-2 binding site is characterised by a 'side pocket' that can accommodate the bulky groups, such as the sulfonamide moiety of celecoxib, which would impede its access to the COX-1 site. Other NSAIDs, such as flurbiprofen (shown here), can enter the active site of either enzyme. (After Luong et al. 1996 Nat Struct Biol 3: 927–933.)

in their time courses. Generally, these drugs inhibit COX-1 rapidly, but the inhibition of COX-2 is more time-dependent and the inhibition is often irreversible. To block the enzymes, NSAIDs enter the hydrophobic channel, forming hydrogen bonds with an arginine residue at position 120, thus preventing substrate fatty acids from entering into the catalytic domain. However, a single amino acid change (isoleucine to valine at position 523) in the structure of the entrance of this channel in COX-2 results in a bulky side pocket that is not found in COX-1. This is important in understanding why some drugs, especially those with large sulphur-containing side groups, are more selective for the COX-2 isoform (Fig. 26.2). Aspirin is, however, an anomaly. It enters the active site and acetylates a serine at position 530, irreversibly inactivating COX. This is the basis for aspirin's long-lasting effects on platelets (see below).

Other actions besides inhibition of COX may contribute to the anti-inflammatory effects of some NSAIDs. Reactive oxygen radicals produced by neutrophils and macrophages are implicated in tissue damage in some conditions, and some NSAIDs (e.g. **sulindac**) have oxygen radical-scavenging effects as well as COX inhibitory activity, so may decrease tissue damage. Aspirin also inhibits expression of the transcription factor NFκB (see Ch. 3), which has a key role in the transcription of the genes for inflammatory mediators.

PHARMACOLOGICAL ACTIONS

All the NSAIDs have actions very similar to those of aspirin, the archetypal NSAID, which was introduced into clinical medicine in the 1890s. Their main pharmacological profile is listed in the clinical box.

THERAPEUTIC ACTIONS

ANTI-INFLAMMATORY EFFECTS

As described in Chapter 17, many mediators coordinate inflammatory and allergic reactions. The NSAIDs reduce mainly those components of the inflammatory and immune response in which prostaglandins, mainly derived from COX-2, play a significant part. These include:

- *vasodilatation* (by reducing the synthesis of vasodilator prostaglandins)
- *oedema* (by an indirect action: the vasodilatation facilitates and potentiates the action of mediators such as histamine that increase the permeability of postcapillary venules; Ch. 17).

▼ While the NSAIDs suppress the signs and symptoms of inflammation, they have little or no action on underlying chronic disease itself. As a class, they are generally without direct effect on other aspects of inflammation, such as cytokine/chemokine release, leukocyte migration, lysosomal enzyme release and toxic oxygen radical production, which contribute to tissue damage in chronic inflammatory conditions such as rheumatoid arthritis, vasculitis and nephritis.

ANTIPYRETIC EFFECT

A centre in the hypothalamus that controls the balance between heat loss and heat production regulates normal body temperature. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', which leads to the set point of body temperature being raised. NSAIDs 'reset' this thermostat. Once there has been a return to the normal set point, the temperature-regulating mechanisms (dilatation of superficial blood vessels, sweating, etc.) then operate to reduce temperature. Normal body temperature in humans is not affected by NSAIDs.[2]

▼ The NSAIDs exert their antipyretic action largely through inhibition of prostaglandin production in the hypothalamus. During an inflammatory reaction, bacterial endotoxins cause the release from macrophages of IL-1 (Ch. 17), which stimulates the generation, in the hypothalamus, of E-type prostaglandins that elevate the temperature set point. COX-2 may have a role here, because IL-1 induces it in vascular endothelium in the hypothalamus. There is some evidence that prostaglandins are not the only mediators of fever, hence NSAIDs may have an additional antipyretic effect by mechanisms as yet unknown.

ANALGESIC EFFECT

The NSAIDs are effective against mild or moderate pain, especially that arising from inflammation or tissue damage. Two sites of action have been identified.

First, peripherally, they decrease production of prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin (see Chs 17 and 41) and they are therefore effective in arthritis, bursitis, pain of muscular and vascular origin, toothache, dysmenorrhoea, the pain of postpartum states and the pain of cancer metastases in

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[2]With possible exception of paracetamol which has been used clinically to lower body temperature during surgery.

bone. All conditions are associated with increased local prostaglandin synthesis probably as a result of COX-2 induction. Alone, or in combination with opioids, they decrease postoperative pain and in some cases can reduce the requirement for opioids by as much as one-third. Their ability to relieve headache may be related to the reduction in vasodilator prostaglandins acting on the cerebral vasculature.

In addition to these peripheral effects, there is a second, less well characterised central action, possibly in the spinal cord. Inflammatory lesions increase COX-2 and prostaglandin release within the cord, causing facilitation of transmission from afferent pain fibres to relay neurons in the dorsal horn.

UNWANTED EFFECTS

Overall, the burden of unwanted side effects is high, probably reflecting the fact that NSAIDs are used extensively in the more vulnerable elderly population, and often for extended periods of time. When used for joint diseases (which usually necessitates fairly large doses and long-continued use), there is a high incidence of side effects—particularly in the gastrointestinal tract but also in the liver, kidney, spleen, blood and bone marrow.

Because prostaglandins are involved in gastric cytoprotection, platelet aggregation, renal vascular autoregulation and induction of labour, among other effects, all NSAIDs share a broadly similar profile of mechanism-dependent side effects although there may be other additional unwanted effects peculiar to individual members of the group. COX-2-selective drugs have less, but not negligible, gastrointestinal toxicity (see below).

Gastrointestinal disturbances

Adverse gastrointestinal events are the commonest unwanted effects of the NSAIDs, and are believed to result mainly from inhibition of gastric COX-1, which is responsible for the synthesis of the prostaglandins that normally inhibit acid secretion and protect the mucosa (see Fig. 29.2).

These commonly include gastric discomfort, dyspepsia, diarrhoea (but sometimes constipation), nausea and vomiting, and in some cases gastric bleeding and ulceration. It has been estimated that 34–46% of users of NSAIDs will sustain some gastrointestinal damage that, while it may be asymptomatic, carries a risk of serious haemorrhage and/or perforation (Fries, 1983). Severe gastrointestinal effects (perforations, ulcers or bleeding) are said to result in the hospitalisation of over 100 000 people per year in the USA. Some 15% of these patients die from this iatrogenic disease (Fries, 1998). Damage is seen whether the drugs are given orally or systemically. However, in some cases (aspirin being a good example), local damage to the gastric mucosa caused directly by the drug itself may compound the damage. Figure 26.3 gives the relative risks of gastrointestinal damage with some common NSAIDs. Oral administration of prostaglandin analogues such as **misoprostol** (see Ch. 29) can diminish the gastric damage produced by these agents.

Based on extensive experimental evidence, it had been predicted that COX-2-selective agents would provide good anti-inflammatory and analgesic actions with less gastric damage, and some older drugs (e.g. **meloxicam**) that were believed to be better tolerated in the clinic turned out to have some COX-2 selectivity. Two large prospective studies
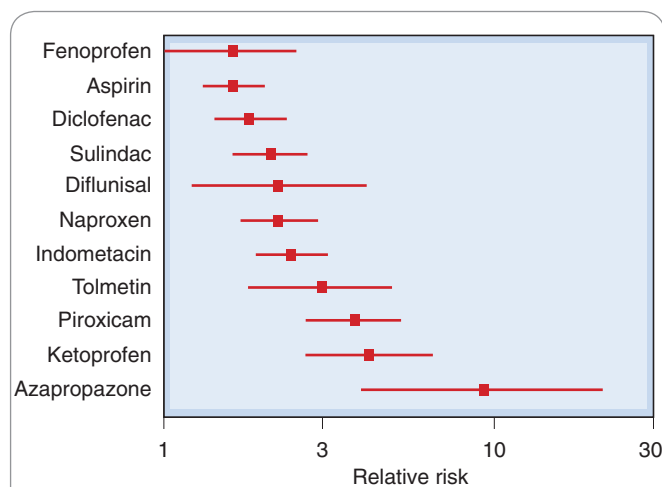

Fig. 26.3 **The risk of gastrointestinal complications with various non-steroidal anti-inflammatory drugs.** The risk is shown relative to ibuprofen (relative risk = 1). Ibuprofen, given in a dose of 1200 mg daily, itself carries a risk double that of placebo. The lines represent 95% confidence intervals. (From a figure by Hawkey, 2001; data derived from a meta-analysis of 12 comparative studies in Henry et al., 1996.)

compared the gastrointestinal side effects of celecoxib and rofecoxib with those of standard comparator NSAIDs in patients with arthritis and showed some benefit, although the results were not as clear-cut as had been hoped.

Other ideas have been proposed to explain the gastric side effects of NSAIDs. The administration of COX-1 inhibitors themselves causes COX-2 induction and, on the basis of experimental evidence, Wallace (2000) has argued that selective inhibitors of either isozyme will cause less gastric damage than non-selective drugs.

Skin reactions

Rashes are common idiosyncratic unwanted effects of NSAIDs, particularly with mefenamic acid (10–15% frequency) and sulindac (5–10% frequency). They vary from mild erythematous, urticarial and photosensitivity reactions to more serious and potentially fatal diseases including Stevens–Johnson syndrome (a blistering rash that extends into the gut), and toxic epidermal necrolysis,[3] characterised by widespread epithelial necrosis (fortunately rare). The mechanism is unclear.

Adverse renal effects

Therapeutic doses of NSAIDs in healthy individuals pose little threat to kidney function, but in susceptible patients they cause acute renal insufficiency, which is reversible on discontinuing the drug (see Ch. 57, Table 57.1). This occurs through the inhibition of the biosynthesis of those prostanoids (PGE_2 and PGI_2; prostacyclin) involved in the maintenance of renal blood flow, specifically in the PGE_2-mediated compensatory vasodilatation that occurs in response to the action of noradrenaline (norepinephrine) or angiotensin II (see Ch. 28). Neonates and the elderly are especially at risk,

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[3]A horrible condition where skin peels away in sheets as if scalded.

as are patients with heart, liver or kidney disease, or a reduced circulating blood volume.

Chronic NSAID consumption, especially NSAID 'abuse',[4] can cause *analgesic nephropathy* characterised by chronic nephritis and renal papillary necrosis (Ch. 28). **Phenacetin**, now withdrawn, was the main culprit; paracetamol, one of its major metabolites, is much less toxic. Regular use of prescribed doses of NSAIDs is less hazardous for the kidney than heavy and prolonged use of over-the-counter analgesics in a social context (e.g. Swiss workers manufacturing watches would hand round analgesics in the same way as sharing sweets or cigarettes!).

Cardiovascular side effects

While it had been recognised for some time that NSAIDs could oppose the effects of some antihypertensive drugs, there is currently fresh concern about the potential of these drugs, when given alone, to raise blood pressure, and therefore predispose to adverse cardiovascular events such as stroke and myocardial infarction.

▼ This first arose during trials of the COX-2 inhibitor **rofecoxib**. Uncertainty about the cardiovascular risk posed by this drug during clinical trials led to the addition of a 'warning label' in 2002, but the results from a later long-term trial designed to assess the anticancer activity of rofecoxib showed that the risk of cardiovascular events increased significantly after 18 months of drug treatment. As a result of this, the drug was withdrawn in 2004.

It now seems that adverse cardiovascular pharmacology, especially following prolonged use or in patients with pre-existing cardiovascular risk, may be an effect common to all NSAIDs, although some (e.g. **naproxen**) appear to be better tolerated in this respect than others (see Ray et al., 2009). At the time of writing it seems that the most likely explanation for this effect is that the hypertension is secondary to inhibition of COX-2 in the renin-secreting macula densa region of the kidney (Ch. 28). The hypertensive effect is dose- and time-dependent.

Other unwanted effects

Approximately 5% of patients exposed to NSAIDs may experience *aspirin-sensitive asthma*. The exact mechanism is unknown, but inhibition of COX is implicated (see Ch. 27) and the presence of a sensitising, pre-existing viral infection may be the culprit. Aspirin is the worst offender, but there is cross-reaction with all other NSAIDs, except possibly COX-2 inhibitors (see Ch. 27). Other, much less common, unwanted effects of NSAIDs include CNS effects, bone marrow disturbances and liver disorders, the last being more likely if there is already renal impairment.[5] Paracetamol overdose causes liver failure (see below). All NSAIDs (except COX-2 inhibitors) prevent platelet aggregation and therefore may prolong bleeding. Again, aspirin is the main problem in this regard (see below).

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[4]So called because the availability of NSAIDs in proprietary medicines over-the-counter, often in combination with other substances, such as caffeine, has tempted some people to consume them, often in prodigious quantities, for every conceivable malady.

[5]An odd side effect of the NSAID diclofenac came to light when a team of scientists investigated the curious decline in the population of several species of vulture in the Indian subcontinent. Dead cattle form an important part of the diet of these birds, and some animals had been treated with diclofenac for veterinary reasons. Apparently, residual amounts of the drug in the carcasses proved uniquely toxic to this species.

> ### General unwanted effects of cyclo-oxygenase inhibitors
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> Unwanted effects, many stemming from inhibition of the constitutive housekeeping enzyme cyclo-oxygenase (COX)-1 isoform of COX, are common, particularly in the elderly, and include the following:
>
> - *Dyspepsia, nausea, vomiting and other gastrointestinal effects*. Gastric and intestinal damage may occur in chronic users, with risk of haemorrhage, which can be life-threatening. The cause is suppression of gastroprotective prostaglandins in the gastric mucosa.
> - *Skin reactions*. Mechanism unknown.
> - *Reversible renal insufficiency*. Seen mainly in individuals with compromised renal function when the compensatory prostaglandin E_2-mediated vasodilatation is inhibited.
> - *Adverse cardiovascular effects*. These can occur with many NSAIDs and coxibs and may be related to inhibition of COX-2 in the macula densa leading to hypertension.
> - '*Analgesic-associated nephropathy*'. This can occur following long-term high-dose regimes of NSAIDs (e.g. paracetamol) and is often irreversible.
> - *Liver disorders, bone marrow depression*. Relatively uncommon.
> - *Bronchospasm*. Seen in 'aspirin-sensitive' asthmatics. Does not occur with coxibs.

SOME IMPORTANT NSAIDS AND COXIBS

Table 26.1 lists commonly used NSAIDs, and the clinical uses of the NSAIDs are summarised in the clinical box.

ASPIRIN

Aspirin (acetylsalicylic acid) was among the earliest drugs synthesised, and is still one of the most commonly consumed drugs worldwide. It is a common ingredient in many over-the-counter proprietary medicines. The drug itself is relatively insoluble, but its sodium and calcium salts are readily soluble.

While aspirin was previously thought of as an old anti-inflammatory workhorse, it is seldom used for this purpose now, having been supplanted by other, better tolerated NSAIDs. Today, in addition to its widespread use as an over-the-counter remedy, it is used clinically mainly as a cardiovascular drug because of its ability to provide a prolonged inhibition of platelet COX-1 and hence reduce aggregation.

▼ While inhibition of platelet function is a feature of most NSAIDs, the effect of aspirin is longer lasting. This is because it irreversibly acetylates COX enzymes, and while these proteins can be replaced in most cells, the platelet is not able to accomplish de novo protein synthesis. This means that a small dose of the drug can permanently inactivate platelets for their lifetime (approximately 10 days). Since a proportion of platelets is replaced each day from the bone marrow, this inhibition gradually abates but a small daily dose (e.g. 75 mg) is all that is required to suppress platelet function to levels which benefit patients at risk for myocardial infarction and other cardiovascular problems (Ch. 24). The view that even patients not at risk would

> ### Clinical uses of NSAIDs
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> NSAIDs are widely used but cause serious adverse effects (especially gastrointestinal, renal, pulmonary and cardiovascular effects related to their main pharmacological actions, as well as idiosyncratic effects). Elderly patients and those with pre-existing disorders are at particular risk. The main uses are:
> - *Antithrombotic*: e.g. **aspirin** (Ch. 24) for patients at high risk of arterial thrombosis (e.g. following myocardial infarction). (Other NSAIDs that cause less profound inhibition of platelet thromboxane synthesis than does aspirin, *increase* the risk of thrombosis and should be avoided in high-risk individuals if possible.)
> - *Analgesia* (e.g. for headache, dysmenorrhoea, backache, bony metastases, postoperative pain):
>   – short-term use: e.g. aspirin, paracetamol, ibuprofen
>   – chronic pain: more potent, longer-lasting drugs (e.g. naproxen, piroxicam) often combined with a low-potency opioid (e.g. codeine, Ch. 41)
>   – to reduce the requirement for narcotic analgesics (e.g. ketorolac postoperatively).
> - *Anti-inflammatory*: e.g. **ibuprofen**, **naproxen** for symptomatic relief in rheumatoid arthritis, gout, soft tissue disorders.
> - *Antipyretic*: **paracetamol**.

> ### Aspirin
>
> Aspirin (acetylsalicylic acid) is the oldest non-steroidal anti-inflammatory drug. It acts by irreversibly inactivating both cyclo-oxygenase (COX)-1 and COX-2.
> - In addition to its anti-inflammatory actions, aspirin inhibits platelet aggregation, and its main clinical importance now is in the therapy of cardiovascular disease.
> - It is given orally and is rapidly absorbed; 75% is metabolised in the liver.
> - Elimination of its metabolite salicylate follows first-order kinetics with low doses (half-life 4 h), and saturation kinetics with high doses (half-life over 15 h).
> - Unwanted effects:
>   – with therapeutic doses: some gastric bleeding (usually slight and asymptomatic) is common
>   – with large doses: dizziness, deafness and tinnitus ('salicylism'); compensated respiratory alkalosis may occur
>   – with toxic doses (e.g. from self-poisoning): uncompensated metabolic acidosis may occur, particularly in children
>   – aspirin has been linked with a rare but serious postviral encephalitis (Reye's syndrome) in children.
> - If given concomitantly with warfarin, aspirin can cause a potentially hazardous increase in the risk of bleeding.

benefit from taking the drug prophylactically (primary prevention) was challenged by a recent meta-analysis (Baigent et al., 2009) suggesting that in the normal population, the risk from gastrointestinal bleeding outweighs the protective action. Whether or not this is the case, the use of aspirin to prevent recurrence (secondary prevention) seems unassailable.

Aspirin has also been canvassed for other conditions. These include:

- *colonic and rectal cancer*: aspirin (and COX-2 inhibitors) may reduce some types of colorectal cancer
- *Alzheimer's disease*: this was suggested on the basis of epidemiological evidence, but so far, clinical trial results have been disappointing (Ch. 39)
- *radiation-induced diarrhoea*.

Pharmacokinetic aspects

Aspirin, being a weak acid, is protonated in the acid environment of the stomach, thus facilitating its passage across the mucosa. Most absorption, however, occurs in the ileum, because of the extensive surface area of the microvilli.

▼ Aspirin is rapidly (probably within 30 min) hydrolysed by esterases in plasma and tissues, particularly the liver, yielding **salicylate**. This compound itself has anti-inflammatory actions (indeed, it was the original anti-inflammatory from which aspirin was derived); the mechanism is not clearly understood, although it probably involves the COX system. Oral salicylate is no longer used for treating inflammation, although it is a component of some topical preparations. Approximately 25% of the salicylate is oxidised; some is conjugated to give the glucuronide or sulfate before excretion, and about 25% is excreted unchanged, the rate of excretion being higher in alkaline urine (see Ch. 8).

The plasma half-life of aspirin will depend on the dose, but the duration of action is not directly related to the plasma half-life because of the irreversible nature of the action of the acetylation reaction by which it inhibits COX activity.

Unwanted effects

Salicylates (of which the main examples are aspirin, diflunisal and sulfasazine) may produce both local and systemic toxic effects. Aspirin shares many of the general unwanted effects of NSAIDs outlined above. In addition, there are certain specific unwanted effects that occur with aspirin and other salicylates.

- *Salicylism*, characterised by tinnitus, vertigo, decreased hearing and sometimes also nausea and vomiting, occurs with chronic overdosage of any salicylate.
- *Reye's syndrome*, a rare disorder of children that is characterised by hepatic encephalopathy following an acute viral illness and 20–40% mortality. Since the withdrawal of aspirin for paediatric use in the UK, the incidence of Reye's syndrome has fallen dramatically.

▼ Acute salicylate poisoning (a medical emergency, which occurs mainly in children and suicide attempts) causes major disturbance of acid–base and electrolyte balance. These drugs can uncouple oxidative phosphorylation (mainly in skeletal muscle), leading to increased oxygen consumption and thus increased production of carbon dioxide. This stimulates respiration, which is also stimulated by a direct action of the drugs on the respiratory centre. The resulting hyperventilation causes a respiratory alkalosis that is normally compensated by renal mechanisms involving increased bicarbonate excretion. Larger doses can cause a depression of the respiratory centre, which leads eventually to retention of carbon dioxide and thus an increase in plasma carbon dioxide. Because this is superimposed on a reduction in plasma bicarbonate, an uncompensated respiratory acidosis will occur. This may be complicated by a metabolic acidosis, which results from the accumulation of metabolites of pyruvic, lactic and acetoacetic acids (an indirect consequence of interference with

carbohydrate metabolism). Hyperpyrexia secondary to the increased metabolic rate is also likely to be present, and dehydration may follow repeated vomiting. In the CNS, initial stimulation with excitement is followed eventually by coma and respiratory depression. Bleeding can also occur, mainly as a result of depressed platelet aggregation.

Drug interactions

Aspirin may cause a potentially hazardous increase in the effect of **warfarin**, partly by displacing it from plasma proteins (Ch. 56) and partly because its effect on platelets interferes with haemostatic mechanisms (see Ch. 24). Aspirin also interferes with the effect of some antihypertensives and with uricosuric agents such as **probenecid** and **sulfinpyrazone**. Because low doses of aspirin may, on their own, reduce urate excretion (Ch. 28), it should not be used in gout.

PARACETAMOL

Paracetamol (called *acetaminophen* in the USA) is one of the most commonly used non-narcotic analgesic–antipyretic agents and is a component of many over-the-counter proprietary preparations. In some ways, the drug constitutes an anomaly: while it has excellent analgesic and antipyretic activity, which can be traced to inhibition of CNS prostaglandin synthesis, it has weak anti-inflammatory activity (except in some specific instances) and does not share the gastric or platelet side effects of the other NSAIDs. For this reason, paracetamol is sometimes not classified as an NSAID at all. In man however, it is a selective though weak COX-2 inhibitor (Hinz et al 2008).

▼ A potential solution to this puzzle was supplied by the observation that a further COX isoform, COX-3 (an alternate splice product of COX-1) existed predominantly in the CNS of some species, and that paracetamol, as well as some other drugs with similar properties (e.g. **antipyrine** and **dipyrone**), were selective inhibitors of this enzyme (Chandrasekharan et al., 2002). This elegant idea is still under investigation. Alternative explanations for the ability of paracetamol selectively to inhibit COX in the CNS alone have been provided by Ouellet & Percival (2001) and Boutaud et al. (2002).

Paracetamol

Paracetamol is a commonly used drug available over-the-counter. It has potent analgesic and antipyretic actions but rather weaker anti-inflammatory effects than other NSAIDs. It may act through inhibition of a central nervous system-specific cyclo-oxygenase (COX) isoform, although this is not yet conclusive.

- It is given orally and metabolised in the liver (half-life 2–4 h).
- Toxic doses cause nausea and vomiting, then, after 24–48 h, potentially fatal liver damage by saturating normal conjugating enzymes, causing the drug to be converted by mixed function oxidases to *N*-acetyl-*p*-benzoquinone imine. If not inactivated by conjugation with glutathione, this compound reacts with cell proteins and kills the cell.
- Agents that increase glutathione (intravenous **acetylcysteine** or oral **methionine**) can prevent liver damage if given early.

Pharmacokinetic aspects

Paracetamol is given orally and is well absorbed, with peak plasma concentrations reached in 30–60 min. The plasma half-life of therapeutic doses is 2–4 h, but with toxic doses it may be extended to 4–8 h. Paracetamol is inactivated in the liver, being conjugated to give the glucuronide or sulfate.

Unwanted effects

With therapeutic doses, side effects are few and uncommon, although allergic skin reactions sometimes occur. It is possible that regular intake of large doses over a long period may cause kidney damage.

Toxic doses (10–15 g) cause potentially fatal *hepatotoxicity*. This occurs when the liver enzymes catalysing the normal conjugation reactions are saturated, causing the drug to be metabolised instead by mixed function oxidases. The resulting toxic metabolite, N-*acetyl*-p-*benzoquinone imine*, is inactivated by conjugation with glutathione, but when glutathione is depleted the toxic intermediate accumulates and causes necrosis in the liver and also in the kidney tubules.

▼ The initial symptoms of acute paracetamol poisoning are nausea and vomiting, the hepatotoxicity being a delayed manifestation that occurs 24–48 h later. Further details of the toxic effects of paracetamol are given in Chapter 57. If the patient is seen sufficiently soon after ingestion, the liver damage can be prevented by giving agents that increase glutathione formation in the liver (**acetylcysteine** intravenously, or **methionine** orally). If more than 12 h have passed since the ingestion of a large dose, the antidotes, which themselves can cause adverse effects (nausea, allergic reactions), are less likely to be useful. Regrettably, ingestion of large amounts of paracetamol is a common method of suicide.

COXIBS

Three coxibs are currently available for clinical use in the UK; others may be available elsewhere. Several have been withdrawn, and the overall licensing situation is somewhat volatile. Current advice restricts the use of coxibs to patients for whom treatment with conventional NSAIDs would pose a high probability of serious gastrointestinal side effects, and they are prescribed only after an assessment of cardiovascular risk. Gastrointestinal disturbances may still occur with these agents, perhaps because COX-2 has been implicated in the healing of pre-existing ulcers, so inhibition could delay recovery from earlier lesions.

Celecoxib and etoricoxib

Celecoxib and etoricoxib are licensed in the UK for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis and some other conditions. Both are administered orally and have similar pharmacokinetic profiles, being well absorbed with peak plasma concentrations being achieved within 1–3 h. They are extensively (> 99%) metabolised in the liver, and plasma protein binding is high (> 90%).

Common unwanted effects may include headache, dizziness, skin rashes and peripheral oedema caused by fluid retention. Consideration should be given to the possibility of adverse cardiovascular events prior to administration. Because of the potential role of COX-2 in the healing of ulcers, patients with pre-existing disease should avoid the drugs, if possible.

Parecoxib

Parecoxib is a prodrug of **valdecoxib**. The latter drug has now been withdrawn, but parecoxib is licensed for the short-term treatment of postoperative pain. It is given by intravenous or intramuscular injection, and is rapidly and virtually completely (> 95%) converted into the active valdecoxib by enzymatic hydrolysis in the liver. Maximum blood levels are achieved within approximately 30–60 min, depending on the route of administration. Plasma protein binding is high. The active metabolite, valdecoxib, is converted in the liver to various inactive metabolites, and has a plasma half-life of about 8 h.

Skin reactions, some of them serious, have been reported with the active metabolite valdecoxib, and patients should be monitored carefully. The drug should also be given with caution to patients with impaired renal function, and renal failure has been reported in connection with this drug. Postoperative anaemia may also occur.

ANTIRHEUMATOID DRUGS

Arthritic disease is one of the commonest chronic inflammatory conditions in developed countries, and rheumatoid arthritis is a common cause of disability. One in three patients with rheumatoid arthritis is likely to become severely disabled. The joint changes, which are probably driven by an autoimmune reaction, involve inflammation, proliferation of the synovium and erosion of cartilage and bone. The primary inflammatory cytokines, IL-1 and TNF-α, have a major role in pathogenesis (Ch. 17). The pathogenesis of rheumatoid arthritis, and the action of therapeutic drugs, are summarised in Figure 26.4.

The drugs most frequently used in initial therapy are the 'disease-modifying antirheumatic drugs' (DMARDs) and the NSAIDs. Unlike the NSAIDs, which reduce the symptoms but not the progress of the disease, the former group may halt or reverse the underlying disease itself. Although such claims may be optimistic, these drugs are nevertheless
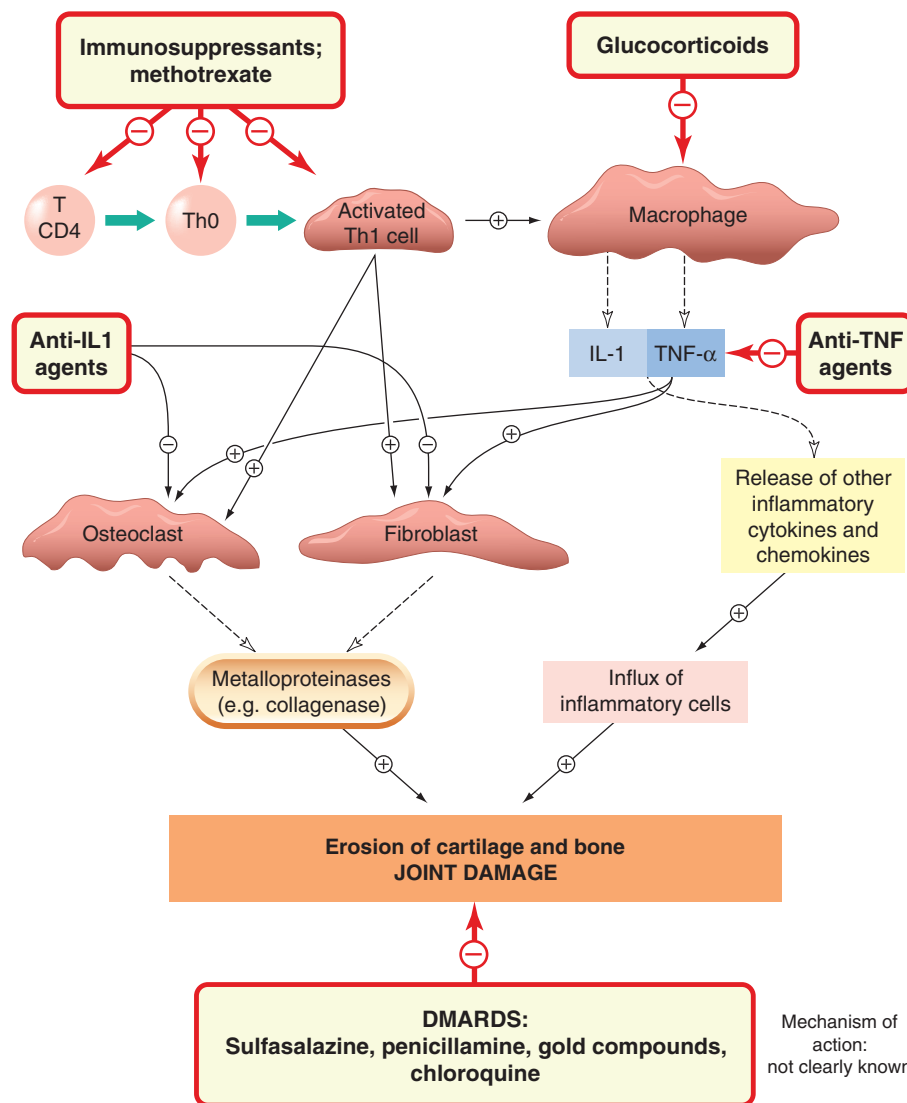

Fig. 26.4 A schematic diagram of the cells and mediators involved in the pathogenesis of rheumatoid joint damage, indicating the sites of action of antirheumatoid drugs. DMARD, disease-modifying antirheumatic drug. For details of the anti-TNF, IL-1 and IL-2 receptor agents, see Table 26.3

Table 26.2 Comparison of some common 'disease-modifying' and immunosuppressive drugs used in the treatment of the arthritides

Type	Drug	Indication	Severity	Comments
Gold complexes	Sodium aurothiomalate	RA, JRA		
	Auranofin	RA		
Antimalarials	Chloroquine	RA, SLE	Moderate	Used when other therapies fail
	Hydroxychloroquine sulfate	RA, SLE	Moderate	Also useful for some skin disorders
Immunomodulators	Methotrexate	RA, PS	Moderate to severe	A 'first-choice' drug Also used in Crohn's disease, psoriasis and cancer treatment
	Azathioprine	RA		Used when other therapies fail Also used in transplant rejection
	Ciclosporin	RA, AD, PS	Severe	Used when other therapies fail Also used in some skin diseases and transplant rejection
	Cyclophosphamide	RA	Severe	Used when other therapies fail
	Leflunamide	RA, PA	Moderate to severe	Also used in psoriatic arthritis
NSAID	Sulfasalazine	RA, PA		A 'first-choice' drug Also used in ulcerative colitis
Penicillin metabolite	Penicillamine	RA	Severe	

AD, atopic dermatitis; JRA, juvenile rheumatoid arthritis; NSAID, non-steroidal anti-inflammatory drug; PS, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
(Data from various sources including the British National Formulary.)

useful in the treatment of discrete groups of patients, and Rau (2005) has argued for their continuing use even when the newer anticytokine agents are available. Some immunosuppressants (e.g. **azathioprine**, **ciclosporin**) are also used, as are the glucocorticoids (covered in Chs 3 and 32).

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

The term 'DMARD' is a latex concept that can be stretched to cover a heterologous group of agents with unrelated chemical structures and different mechanisms of action. Included in this category are **methotrexate**, **sulfasalazine**, **gold** compounds, **penicillamine** and **chloroquine** and other antimalarials (see Table 26.2) and various immunosuppressant drugs.

▼ The antirheumatoid action of most of these agents was usually discovered through a mixture of serendipity and clinical intuition. When the drugs were introduced, nothing was known about their mechanism of action and decades of in vitro experiments have generally resulted in further bewilderment rather than understanding. DMARDs generally improve symptoms and can reduce disease activity in rheumatoid arthritis, as measured by reduction in the number of swollen and tender joints, pain score, disability score, X-ray appearance and serum concentration of acute-phase proteins and of rheumatoid factor (an immunoglobulin [Ig] M antibody against host IgG).

The DMARDs were often referred to as *second-line drugs*, with the implication that they are only resorted to when other therapies (e.g. NSAIDs) failed. Today, however, DMARD therapy may be initiated as soon as a definite diagnosis has been reached. Their clinical effects are usually slow (months) in onset, and it is usual to provide NSAID 'cover' during this induction phase. If therapy is successful (and the success rate is not invariably high), concomitant NSAID (or glucocorticoid) therapy can generally be dramatically reduced. Some DMARDs have a place in the treatment of other chronic inflammatory diseases, whereas others (e.g. penicillamine) are not thought to have a general anti-inflammatory action. Putative mechanisms of action of DMARDs have been reviewed by Bondeson (1997) and Cutolo (2002).

METHOTREXATE

Methotrexate is a folic acid antagonist with cytotoxic and immunosuppressant activity (see below and Chs 49 and 55) and potent antirheumatoid action. It is a common first-choice drug. It has a more rapid onset of action than other DMARDs, but treatment must be closely monitored because of potential blood dyscrasias (some fatal) and liver cirrhosis. It is, however, superior to most other DMARDs in terms of efficacy and unwanted effects, and is often given in conjunction with the anticytokine drugs.

SULFASALAZINE

Sulfasalazine, a common first-choice DMARD in the UK, produces remission in active rheumatoid arthritis and is also used for chronic inflammatory bowel disease (see Ch. 29). It may act by scavenging the toxic oxygen metabolites produced by neutrophils. The drug is a complex of a sulfonamide (**sulfapyridine**) and salicylate. It is split

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into its component parts by bacteria in the colon, the **5-aminosalicylic** acid being the putative radical scavenger. It is poorly absorbed after oral administration. The common side effects include gastrointestinal disturbances, malaise and headache. Skin reactions and leucopenia can occur but are reversible on stopping the drug. The absorption of folic acid is sometimes impaired; this can be countered by giving folic acid supplements. A reversible decrease in sperm count has also been reported. As with other sulfonamides, bone marrow depression and anaphylactic-type reactions may occur in a few patients. Hematological monitoring may be necessary.

PENICILLAMINE

Penicillamine is dimethylcysteine; it is produced by hydrolysis of **penicillin** and appears in the urine after treatment with that drug. The D-isomer is used in the therapy of rheumatoid disease. About 75% of patients with rheumatoid arthritis respond to penicillamine. In responders, therapeutic effects are seen within weeks but do not reach a plateau for several months. Penicillamine is thought to modify rheumatoid disease partly by decreasing the immune response, IL-1 generation and/or partly by an effect on collagen synthesis, preventing the maturation of newly synthesised collagen. However, the precise mechanism of action is still a matter of conjecture. The drug has a highly reactive thiol group and also has metal-chelating properties, which are put to good use in the treatment of *Wilson's disease* (pathological copper deposition causing neurodegeneration) or heavy metal poisoning.

Penicillamine is given orally, and only half the dose administered is absorbed. It reaches peak plasma concentrations in 1–2 h and is excreted in the urine. Dosage is started low and increased only gradually to minimise unwanted effects.

Unwanted effects occur in about 40% of patients treated and may necessitate cessation of therapy. Rashes and stomatitis are the most common unwanted effects but may resolve if the dosage is lowered. Anorexia, fever, nausea and vomiting, and disturbances of taste (the last related to the chelation of zinc) are seen, but often disappear with continued treatment. Proteinuria occurs in 20% of patients and should be monitored. Hematological monitoring is also required when treatment is initiated. Thrombocytopenia may require lowering the dose. Leucopenia or aplastic anaemia are absolute contraindications, as are the various autoimmune conditions (e.g. thyroiditis, myasthenia gravis) that sometimes supervene. Because penicillamine is a metal chelator, it should not be given with gold compounds.

GOLD COMPOUNDS

Gold is administered in the form of organic complexes; **sodium aurothiomalate** and **auranofin** are the two most common preparations. The effect of gold compounds develops slowly over 3–4 months. Pain and joint swelling subside, and the progression of bone and joint damage diminishes. The mechanism of action is not clear, but auranofin, although not aurothiomalate, inhibits the induction of IL-1 and TNF-α.

Sodium aurothiomalate is given by deep intramuscular injection; auranofin is given orally. The compounds gradually become concentrated in the tissues, not only in synovial cells in joints but also in liver cells, kidney tubules, the adrenal cortex and macrophages throughout the body. The gold complexes remain in the tissues for some time after treatment is stopped. Excretion is mostly renal, but some is eliminated in the gastrointestinal tract. The half-life is 7 days initially but increases with treatment, so the drug is usually given first at weekly, then at monthly intervals.

Unwanted effects with aurothiomalate are seen in about one-third of patients treated, and serious toxic effects in about 1 patient in 10. Unwanted effects with auranofin are less frequent and less severe. Important unwanted effects include skin rashes (which can be severe), mouth ulcers, non-specific flu-like symptoms, proteinuria, thrombocytopenia and blood dyscrasias. Encephalopathy, peripheral neuropathy and hepatitis can occur. If therapy is stopped when the early symptoms appear, the incidence of serious toxic effects is relatively low.

ANTIMALARIAL DRUGS

Hydroxychloroquine and **chloroquine** are 4-aminoquinoline drugs used mainly in the prevention and treatment of malaria (Ch. 53), but they are also used as DMARDs. Chloroquine is usually reserved for cases where other treatments have failed. They are also used to treat another autoimmune disease, *lupus erythematosus*, but are contraindicated in patients with *psoriatic arthropathy* because they make the skin lesions worse. The related compound, **mepacrine**, is also sometimes used for discoid lupus. The antirheumatic effects do not appear until a month or more after the drug is started, and only about half the patients treated respond. The pharmacokinetic aspects and unwanted effects of chloroquine are dealt with in Ch. 53; screening for ocular toxicity is particularly important.

IMMUNOSUPPRESSANT DRUGS

▼ Immunosuppressants are used in the therapy of autoimmune disease and also to prevent and/or treat transplant rejection. Because they impair immune responses, they carry the hazard of a decreased response to infections and may facilitate the emergence of malignant cell lines. However, the relationship between these adverse effects and potency in preventing graft rejection varies with different drugs. The clinical use of immunosuppressants is summarised in the clinical box.

Most of these drugs act during the induction phase of the immunological response (see Ch. 6), reducing lymphocyte proliferation, although others also inhibit aspects of the effector phase. They can be roughly characterised as:

- drugs that inhibit IL-2 production or action (e.g. **ciclosporin**, **tacrolimus**)
- drugs that inhibit cytokine gene expression (e.g. the corticosteroids)
- drugs that inhibit purine or pyrimidine synthesis (e.g. **azathioprine**, **mycophenolate mofetil**).

CICLOSPORIN

Ciclosporin is a naturally occurring compound first found in fungus. It is a cyclic peptide of 11 amino acid residues (including some not found in animals) with potent immunosuppressive activity but no effect on the acute inflammatory reaction per se. Its unusual activity, which (unlike most earlier immunosuppressants) does not involve cytotoxicity, was discovered in 1972 and was crucial for the development of transplant surgery (for a detailed review,

Clinical uses of immunosuppressant drugs

Immunosuppressant drugs are used by specialists, often in combination with glucorticoid and/or cytotoxic drugs:

- To slow the progress of rheumatoid and other arthritic diseases including psoriatic arthritis, ankylosis spondylitis, juvenile arthritis: disease-modifying antirheumatic drugs (DMARDs), e.g. **methotrexate**, **leflunomide**, **ciclosporin**; *cytokine modulators* (e.g. **adalimumab**, **etanercept**, **infliximab**) are used when the response to methotrexate or other DMARDs has been inadequate.
- To suppress rejection of transplanted organs, e.g. **ciclosporin**, **tacrolimus**, **sirolimus**.
- To suppress graft-versus-host disease following bone marrow transplantation, e.g. **ciclosporin**.
- In autoimmune disorders including idiopathic thrombocytopenic purpura, some forms of haemolytic anaemias and of glomerulonephritis and myasthenia gravis.
- In severe inflammatory bowel disease (e.g. **ciclosporin** in ulcerative colitis, **infliximab** in Crohn's disease).
- In severe skin disease (e.g. **pimecrolimus**, **tacrolimus** for atopic eczema uncontrolled by maximal topical glucocorticoids; **etanercept**, **infliximab** for very severe plaque psoriasis which has failed to respond to methotrexate or ciclosporin).

Immunosuppressants

- Clonal proliferation of T-helper cells can be decreased through inhibition of transcription of interleukin (IL)-2: **ciclosporin**, **tacrolimus** and glucocorticoids act in this way.
- Ciclosporin and tacrolimus bind to cytosolic proteins (immunophilins) and produce their effects on gene transcription by inhibiting calcineurin or activating protein kinases.
- Ciclosporin and tacrolimus are given orally or intravenously; a common adverse effect is nephrotoxicity.
- For glucocorticoids, see separate box.
- DNA synthesis is inhibited by:
  - **azathioprine**, through its active metabolite mercaptopurine
  - **mycophenolate mofetil**, through inhibition of de novo purine synthesis.
- T cell signal transduction events are blocked by **basiliximab** and **daclizumab**, which are monoclonal antibodies against the α chain of the IL-2 receptor.

see Borel et al., 1996). The drug has numerous actions on several cell types; in general, the actions of relevance to immunosuppression are:

- *decreased clonal proliferation* of T cells, primarily by inhibiting IL-2 synthesis and possibly also by decreasing expression of IL-2 receptors

- *reduced induction*, and clonal proliferation, of cytotoxic T cells from CD8$^+$ precursor T cells
- *reduced function* of the effector T cells that are responsible for cell-mediated responses (e.g. decreased delayed-type hypersensitivity)
- *some reduction* of T cell-dependent B cell responses.

The main action is a relatively selective inhibitory effect on IL-2 gene transcription, although a similar effect on interferon (IFN)-γ and IL-3 has also been reported. Normally, interaction of antigen with a T-helper (Th) cell receptor results in increased intracellular Ca^{2+} (Chs 2 and 6), which in turn stimulates a phosphatase, *calcineurin*. This activates various transcription factors that initiate IL-2 transcription. Ciclosporin binds to *cyclophilin*, a cytosolic protein member of the immunophilins (a group of proteins that act as intracellular receptors for such drugs). The drug–immunophilin complex binds to and inhibits *calcineurin* (a protein phosphatase that acts in opposition to the many protein kinases involved in signal transduction, see Ch. 3), thereby preventing activation of Th cells and production of IL-2 (Ch. 6).

Ciclosporin itself is poorly absorbed by mouth but can be given orally in a more readily absorbed formulation, or given by intravenous infusion. After oral administration, peak plasma concentrations are usually attained in about 3–4 h. The plasma half-life is approximately 24 h. Metabolism occurs in the liver, and most of the metabolites are excreted in the bile. Ciclosporin accumulates in most tissues at concentrations three to four times that seen in the plasma. Some of the drug remains in lymphomyeloid tissue and remains in fat depots for some time after administration has stopped.

The commonest and most serious unwanted effect of ciclosporin is nephrotoxicity, which is thought to be unconnected with calcineurin inhibition. It may be a limiting factor in the use of the drug in some patients (see also Ch. 57). Hepatotoxicity and hypertension can also occur. Less important unwanted effects include anorexia, lethargy, hirsutism, tremor, paraesthesia (tingling sensation), gum hypertrophy (especially when co-prescribed with calcium antagonists for hypertension; Ch. 22) and gastrointestinal disturbances. Ciclosporin has no depressant effects on the bone marrow.

TACROLIMUS

Tacrolimus is a macrolide antibiotic of fungal origin with a very similar mechanism of action to ciclosporin, but higher potency. The main difference is that the internal receptor for this drug is not cyclophilin but a different immunophilin termed *FKBP* (FK-binding protein, so-called because tacrolimus was initially termed FK506). The tacrolimus–FKBP complex inhibits calcineurin with the effects described above. It is mainly used in organ transplantation and severe atopic eczema. **Pimecrolimus** (used topically for atopic eczema) acts in a similar way. **Sirolimus** (used to prevent organ rejection after transplantation, and also in coating on stents to prevent restenosis; Ch. 22) also combines with an immunophilin, but activates a protein kinase to produce its immunosuppressant effect.

Tacrolimus can be given orally, by intravenous injection or as an ointment for topical use in inflammatory disease of the skin. It is 99% metabolised by the liver and has a half-life of approximately 7 h.

The unwanted effects of tacrolimus are similar to those of ciclosporin but are more severe. The incidence of nephrotoxicity and neurotoxicity is higher, but that of hirsutism is lower. Gastrointestinal disturbances and metabolic disturbances (hyperglycaemia) can occur. Thrombocytopenia and hyperlipidaemia have been reported but decrease when the dosage is reduced.

AZATHIOPRINE

Azathioprine interferes with purine synthesis and is cytotoxic. It is widely used for immunosuppression, particularly for control of autoimmune diseases such as rheumatoid arthritis and to prevent tissue rejection in transplant surgery. This drug is metabolised to give mercaptopurine, a purine analogue that inhibits DNA synthesis (see Ch. 55). Both cell-mediated and antibody-mediated immune reactions are depressed by this drug, because it inhibits clonal proliferation during the induction phase of the immune response (see Ch. 6) through a cytotoxic action on dividing cells. As is the case with mercaptopurine itself, the main unwanted effect is depression of the bone marrow. Other toxic effects are nausea and vomiting, skin eruptions and a mild hepatotoxicity.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil is a semisynthetic derivative of a fungal antibiotic used for preventing organ rejection. In the body, it is converted to *mycophenolic acid*, which restrains proliferation of both T and B lymphocytes and reduces the production of cytotoxic T cells by inhibiting *inosine monophosphate dehydrogenase*, an enzyme crucial for de novo purine biosynthesis in both T and B cells (other cells can generate purines through another pathway), so the drug has a fairly selective action. It is mainly used to curtail transplant rejection.

Mycophenolate mofetil is given orally and is well absorbed. Magnesium and aluminium hydroxides impair absorption, and **colestyramine** reduces plasma concentrations. The metabolite mycophenolic acid undergoes enterohepatic cycling and is eliminated by the kidney as the inactive glucuronide. Unwanted gastrointestinal effects are common.

LEFLUNOMIDE

Leflunomide has a relatively specific inhibitory effect on activated T cells. It is transformed to a metabolite that inhibits de novo synthesis of pyrimidines by inhibiting *dihydro-orotate dehydrogenase*. It is orally active and well absorbed from the gastrointestinal tract. It has a long plasma half-life, and the active metabolite undergoes enterohepatic circulation. Unwanted effects include diarrhoea, alopecia, raised liver enzymes and indeed a risk of hepatic failure. The long half-life increases the risk of cumulative toxicity.

GLUCOCORTICOIDS

Immunosuppression by glucocorticoids involves both their effects on the immune response and their anti-inflammatory actions. These are described in Chapter 32, and the sites of action of the agents on cell-mediated immune reactions are indicated in Figure 26.4. Glucocorticoids are immunosuppressant chiefly because, like ciclosporin, they restrain the clonal proliferation of Th cells, through decreasing transcription of the gene for IL-2. However, they also decrease the transcription of many other cytokine genes (including those for TNF-α, IFN-γ, IL-1 and many other interleukins) in both the induction and effector phases of the immune response. The synthesis and release of anti-inflammatory proteins (e.g. annexin 1, protease inhibitors, etc.) is also increased. These effects on transcription are mediated through inhibition of the action of transcription factors, such as *activator protein-1* and *NFκB*.

ANTICYTOKINE DRUGS AND OTHER BIOPHARMACEUTICALS

The drugs in this section probably represent the greatest technological and conceptual breakthrough in the treatment of severe chronic inflammation for decades (see Maini, 2005). By their use, treatment can, for the first time, be targeted at specific aspects of the disease processes in rheumatoid arthritis and other inflammatory diseases. The drugs are *biopharmaceuticals*, that is to say, they are engineered recombinant antibodies and other proteins (see Ch. 59). As such, they are difficult and expensive to produce, and this limits their use. In the UK, their use (in the National Health Service) is generally restricted to patients who do not respond adequately to other DMARD therapy and they are usually provided under specialist supervision only. Some of these drugs are administered in combination with methotrexate.

The drugs currently available, and some of their characteristics and indications, are shown in Table 26.3. **Adalimumab**, **etanercept** and **infliximab** target TNF-α; **anakinra** targets IL-1. **Rituximab**, **abatacept**, **natalizumab** and **efalizumab** target receptors on leukocytes, disrupting immune signalling or cell trafficking or other functions. While they are not used for treating arthritis, **basiliximab** and **daclizumab** are included in the table as they act to prevent the rejection of transplanted organs in a similar way—by blocking the IL-2 receptor and suppressing T cell proliferation.

There is debate over the precise target of the anti-TNF agents. Some target both soluble and membrane-bound forms of TNF whereas others are more selective. Antibodies that target membrane-bound TNF (infliximab and adalimumab) may kill the host cell by complement-induced lysis. This produces a different quality of effect than simple immunoneutralisation of the soluble mediator (by, for example, etanercept). This fact is probably the reason why some of these drugs exhibit a slightly different pharmacological profile despite apparently acting through the same mechanism (see Arora et al., 2009, for further details).

As proteins, none of these drugs can be given orally. Administration is usually by subcutaneous injection or intravenous infusion and their pharmacokinetic profiles vary enormously. Dosing regimes differ but anakinra is usually given daily, efalizumab and etanercept once or twice per week, adalimumab, infliximab and rituximab every 2 weeks, and abatacept and natalizumab every month. Sometimes a loading dose of these drugs is given as a preliminary to regular administration. Some patients to not respond for reasons that are not entirely clear and therapy is generally discontinued if no therapeutic benefit is evident within a defined time span (usually 2–4 weeks).

Cytokines are crucial to the regulation of host defence systems (see Ch. 17), and leukocytes are key players in its

Table 26.3 Biologics used in the treatment of inflammatory disease

Drug	Type	Target	Indication
Adalimumab	Humanised monoclonal ab	TNF (neutralises)	RA (moderate–severe), PA, AS, PP, CD
Etanercept	Fusion protein (soluble TNF receptor/Ig)	TNF (decoy receptor)	RA (moderate–severe), PA, AS, PP
Infliximab	Chimeric ab	TNF (neutralises)	RA[a] (moderate–severe), PA, AS, PP
Rituximab	Chimeric monoclonal ab	CD20 (B cells: receptor antagonist)	RA[a] (moderate–severe), some malignancies
Anakinra	Recombinant protein	IL-1 (receptor antagonist)	RA[a] (moderate–severe)
Abatacept	Fusion protein	B7 (antigen presenting cells)	RA[a] (moderate–severe)
Efalizumab	Humanised monoclonal ab	CD11a (leukocytes: neutralises)	PP (moderate–severe)
Basiliximab	Chimeric monoclonal ab	IL-2 receptor antagonist (lymphocytes)	Transplantation surgery
Daclizumab	Humanised monoclonal ab	IL-2 receptor antagonist (lymphocytes)	Transplantation surgery
Natalizumab	Humanised monoclonal ab	VLA-4 on lymphocytes (neutralises)	Severe multiple sclerosis

[a] Used in conjunction with methotrexate.
ab, antibody; AS, ankylosing spondylitis; CD, Crohn's disease; PA, psoriatic arthritis; PP, plaque psoriasis (e.g. skin); RA, rheumatoid arthritis.

functioning and execution. One might predict, therefore, that anticytokine or antileukocyte therapy—like any treatment that interferes with immune function—may precipitate latent disease (e.g. tuberculosis and hepatitis B) or encourage opportunistic infections. Reports suggest that this may be a problem with adalimumab, etanercept, infliximab, natalizumab and rituximab. The area has been reviewed by Bongartz et al. (2006). Another unexpected, but fortunately rare, effect seen with these drugs is the onset of psoriasis-like syndrome (Fiorino et al., 2009). Hypersensitivity, injection site reactions or mild gastrointestinal symptoms may be seen with any of these drugs.

DRUGS USED IN GOUT

Gout is a metabolic disease in which plasma urate concentration is raised. Sometimes this is linked to overindulgence in alcoholic beverages, especially beer, or purine-rich foods such as offal. Increased cell turnover in haematological malignancies, particularly after treatment with cytotoxic drugs (see Ch. 55), or impaired excretion of uric acid are other causes. It is characterised by very painful intermittent attacks of acute arthritis produced by the deposition of crystals of sodium urate (a product of purine metabolism) in the synovial tissue of joints and elsewhere. An inflammatory response is evoked, involving activation of the kinin, complement and plasmin systems (see Ch. 17 and Fig. 6.1), generation of lipoxygenase products such as leukotriene B$_4$ (Fig. 17.1), and local accumulation of neutrophil granulocytes. These engulf the crystals by phagocytosis, releasing tissue-damaging toxic oxygen metabolites and subsequently causing lysis of the cells with release of proteolytic enzymes. Urate crystals also induce the production of IL-1 and possibly other cytokines.

Drugs used to treat gout act in the following ways:

- By inhibiting uric acid synthesis (**allopurinol**, the main prophylactic drug).
- By increasing uric acid excretion (uricosuric agents: **probenecid**, **sulfinpyrazone**).
- By inhibiting leukocyte migration into the joint (**colchicine**).
- By a general anti-inflammatory and analgesic effect (NSAIDs and occasionally glucocorticoids).

Their clinical uses are summarised in the clinical box, below.

ALLOPURINOL

Allopurinol is an analogue of hypoxanthine that reduces the synthesis of uric acid by competitive inhibition of *xanthine oxidase* (Fig. 26.5). It is first converted to alloxanthine by xanthine oxidase, and this metabolite, which remains in

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Drugs used in gout and hyperuricaemia

- To treat acute gout:
  - an NSAID, e.g. **ibuprofen**, **naproxen**
  - **colchicine** is useful if NSAIDs are contraindicated
  - a glucocorticoid, e.g. **hydrocortisone** (oral, intramuscular or intra-articular) is another alternative to an NSAID.
- For prophylaxis (must not generally be started until the patient is asymptomatic):
  - **allopurinol**
  - a uricosuric drug (e.g. **probenecid**, **sulphinpyrazone**), for patients allergic to allopurinol
  - **rasburicase** by intravenous infusion for prevention and treatment of acute hyperuricaemia in patients with haematological malignancy at risk of rapid lysis.
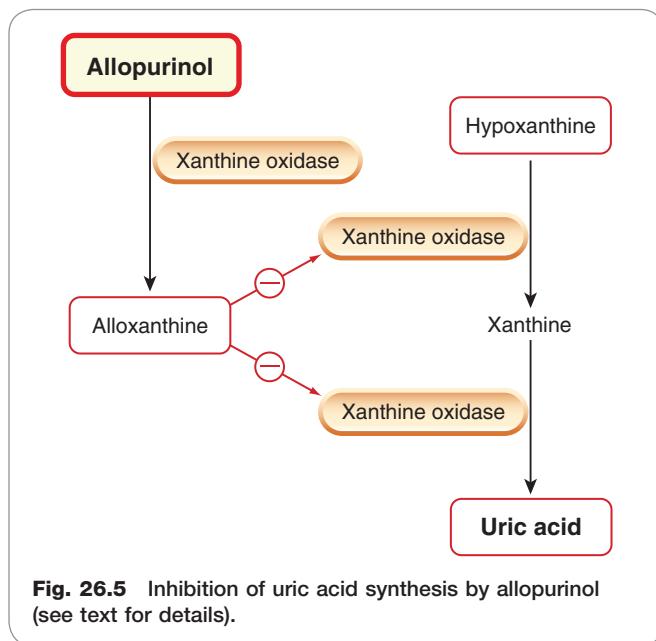
Fig. 26.5 Inhibition of uric acid synthesis by allopurinol (see text for details).

the tissue for a considerable time, is an effective non-competitive inhibitor of the enzyme. Some inhibition of de novo purine synthesis also occurs.

Allopurinol reduces the concentration of the relatively insoluble urates and uric acid in tissues, plasma and urine, while increasing the concentration of their more soluble precursors, the xanthines and hypoxanthines. The deposition of urate crystals in tissues (*tophi*) is reversed, and the formation of renal stones is inhibited. Allopurinol is the drug of choice in the long-term treatment of gout, but it is ineffective in the treatment of an acute attack and may even exacerbate the inflammation.

Allopurinol is given orally and is well absorbed. Its half-life is 2–3 h: its active metabolite alloxanthine (Fig. 26.5) has a half-life of 18–30 h. Renal excretion is a balance between glomerular filtration and probenecid-sensitive tubular reabsorption.

Unwanted effects are few. Gastrointestinal disturbances, allergic reactions (mainly rashes) and some blood problems can occur but usually disappear if the drug is stopped. Potentially fatal skin diseases such as Stevens–Johnson syndrome are rare—but devastating. Re-challenge under these circumstances is never justified. Acute attacks of gout occur commonly during the early stages of therapy (possibly as a result of physicochemical changes in the surfaces of urate crystals as these start to re-dissolve), so treatment with allopurinol is never initiated during an acute attack and is usually combined with an NSAID initially.

Allopurinol increases the effect of **mercaptopurine**, an antimetabolite used in cancer chemotherapy (Ch. 55), and also that of **azathioprine** (an immunosuppressant used to prevent transplant rejection; see below), which is metabolised to mercaptopurine. Allopurinol also enhances the effect of another anticancer drug, **cyclophosphamide** (Ch. 55). The effect of **warfarin** is increased because its metabolism is inhibited.

URICOSURIC AGENTS

Uricosuric drugs increase uric acid excretion by a direct action on the renal tubule (see Ch. 28). Common drugs

used are **probenecid** and **sulfinpyrazone**. **Benzbromarone** is also available on a named patient basis for treatment of patients with renal impairment. They remain useful as prophylaxis for patients with severe recurrent gout who have severe adverse reactions to allopurinol. Sulfinpyrazone also has NSAID activity. Treatment with uricosuric drugs is initiated with an NSAID, as for allopurinol. Aspirin and salicylates antagonise the action of uricosuric drugs and should not be used concurrently.

Although not strictly speaking in this group, **rasburicase**, a preparation containing the enzyme *uric acid oxidase*, is sometimes used for aggressive treatment. It oxidises uric acid in the blood to allantoin, which is more soluble and thus more readily excreted.

COLCHICINE

Colchicine is an alkaloid extracted from the autumn crocus. It has a specific effect in gouty arthritis and can be used both to prevent and to relieve acute attacks. It prevents migration of neutrophils into the joint by binding to *tubulin*, resulting in the depolymerisation of the microtubules and reduced cell motility. Colchicine-treated neutrophils develop a 'drunken walk'. Colchicine may also prevent the production of a putative inflammatory glycoprotein by neutrophils that have phagocytosed urate crystals, and other mechanisms may also be important in bringing about its effects.

Colchicine is given orally, and is excreted partly in the gastrointestinal tract and partly in the urine.

The acute unwanted effects of colchicine are largely gastrointestinal and include nausea, vomiting and abdominal pain. Severe diarrhoea[6] may be a problem, and with large doses may be associated with gastrointestinal haemorrhage and kidney damage. Prolonged treatment can, rarely, cause blood dyscrasias, rashes or peripheral neuropathy.

ANTAGONISTS OF HISTAMINE

There are three groups: H_1, H_2 and H_3 receptor antagonists. The first group was introduced by Bovet and his colleagues in the 1930s, at a time when histamine receptors had not been classified (indeed, this was possible only *because* these agents were available). For historical reasons, then, the generic term *antihistamine* conventionally refers only to the H_1 receptor antagonists that are used for treating various inflammatory and allergic conditions, and it is these drugs that are discussed in this section. The main clinical effect of H_2 receptor antagonists is inhibition of gastric secretion (see Ch. 29). Several H_3 receptor agonists and antagonists are now available, and the potential for their clinical use (mainly in CNS conditions) is being explored.

H_1 RECEPTOR ANTAGONISTS (ANTIHISTAMINES)

Details of some typical systemic H_1 receptor antagonists are shown in Table 26.4. In addition to these there are several others that are primarily used topically (e.g. in nasal sprays or eye drops) in the treatment of hay fever and other allergic symptoms. These include **antazoline**, **azelastine**, **epinastine**, **ketotifen**, **olapatadine** and **emadastine**. In addition to H_1 antagonist activities, some of these drugs

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[6]Because the therapeutic margin is so small, it used to be said by rheumatologists that 'patients must run before they can walk'.

Table 26.4 Comparison of some commonly used systemic H$_1$ receptor antagonists

Drug	Type	Common use	Comments
Cetirizine	Non-sedating	H, U	
Desloratadine	Non-sedating	H, U	'Cardio-safe' metabolite of loratadine
Fexofenadine	Non-sedating	H, U	'Cardio-safe' metabolite of terfenidine
Levocetrizine	Non-sedating	H, U	Isomer of cetirizine
Loratadine	Non-sedating	H, U	
Mizolastine	Sedating	H, U	May cause QT interval prolongation
Alimemazine	Sedating	U	Used for anaesthetic premedication
Clorphenamine	Sedating	H, U, AE	
Clemastine	Sedating	H, U	
Cyproheptadine	Sedating	H, U	Also used for migraine
Hydroxyzine	Sedating	U,	Also used to treat anxiety
Promethazine	Sedating	H, U, AE, S	Also used to treat motion sickness
Cinnarizine	Sedating	–	Used to treat nausea, vomiting, motion sickness
Cyclizine	Sedating	–	Used to treat nausea, vomiting, motion sickness

AE, allergic emergency (e.g. anaphylactic shock); H, hay fever; S, sedation; U, urticaria and/or pruritus.
(From *British National Formulary*.)

(e.g. ketotifen) may also have 'mast cell stabilising' and other anti-inflammatory properties unrelated to histamine antagonism (see Assanasen & Naclerio, 2002).

Pharmacological actions
Conventionally, the antihistamines are divided into 'first-generation' drugs, that cross the blood–brain barrier and have sedating actions, and 'second-generation' drugs, which do not. Some second-generation agents (e.g. **terfenadine**) exhibited some cardiac toxicity (torsade de pointes, see Ch. 21). While the risk was extremely low, it was increased when the drug was taken with grapefruit juice or with agents that inhibit cytochrome P450 in the liver (see Chs 9 and 56). These drugs were withdrawn and replaced by 'third-generation' 'cardio-safe' drugs (often active metabolites of the original drugs, e.g. **fexofenadine**).

▼ Pharmacologically, many of the actions of the H$_1$ receptor antagonists follow from the actions of histamine outlined in Ch. 17. In vitro, for example, they decrease histamine-mediated contraction of the smooth muscle of the bronchi, the intestine and the uterus. They inhibit histamine-induced increases in vascular permeability and bronchospasm in the guinea pig in vivo, but are unfortunately of little value in allergic bronchospasm in humans. The clinical uses of H$_1$ receptor antagonists are summarised in the clinical box, opposite.

The CNS 'side effects' of some older H$_1$ receptor antagonists are sometimes more clinically useful than the peripheral H$_1$ antagonist effects. Some are fairly strong sedatives and may be used for this action (e.g. **clorphenamine**; see Table 26.4). Several are antiemetic and are used to prevent motion sickness (e.g. **promethazine**; see Ch. 29).

Several H$_1$ receptor antagonists show weak blockade of α_1-adrenoceptors (an example is the phenothiazine promethazine). **Cyproheptadine** is a 5-hydroxytryptamine antagonist as well as an H$_1$ receptor antagonist.

Clinical uses of histamine H$_1$ receptor antagonists

- Allergic reactions (see Ch. 16):
  - non-sedating drugs (e.g. **fexofenadine**, **cetirizine**) are used for allergic rhinitis (hay fever) and urticaria
  - topical preparations may be used for insect bites
  - injectable formulations are useful as an adjunct to adrenaline (epinephrine) for severe drug hypersensitivity reactions and emergency treatment of anaphylaxis.
- As antiemetics (see Ch. 29):
  - prevention of motion sickness (e.g. **cyclizine**, **cinnarizine**)
  - other causes of nausea, especially labyrinthine disorders.
- For sedation (see Ch. 43, e.g. **promethazine**).

Pharmacokinetic aspects
Most H$_1$ receptor antagonists are well absorbed when given orally, and remain effective for 3–6 h, although there are exceptions. Most appear to be widely distributed throughout the body, but some do not penetrate the blood–brain barrier, for example the non-sedative drugs mentioned above (see Table 26.4). They are mainly metabolised in the liver and excreted in the urine.

When antihistamines are used to treat allergies, the sedative CNS effects are generally unwanted, but there are other occasions (e.g. in small children approaching bedtime) when such effects are more desirable. Even under

these circumstances, other CNS effects, such as dizziness and fatigue, are unwelcome.

Many antihistamines have peripheral antimuscarinic side effects. The commonest of these is dryness of the mouth, but blurred vision, constipation and retention of urine can also occur. Unwanted effects that are not mechanism based are also seen; gastrointestinal disturbances are fairly common, while allergic dermatitis can follow topical application.

POSSIBLE FUTURE DEVELOPMENTS

Undoubtedly the most exciting area of current development is in 'biologicals' (see Ch. 59). The success of the anti-TNF agents has been very gratifying and the skilful use of recombinant and protein engineering to produce antibodies that neutralise inflammogens or block key leukocyte receptors or adhesion molecules is likely to continue. Particularly encouraging has been the news that early clinical results using rituximab and methotrexate in combination may actually abort the development of rheumatoid arthritis if given early enough. Several other biologics are in advanced state of clinical testing including **toclizumab** (anti-IL6), **certilizumab-pegol** (anti-TNF), **golimumab** (anti-TNF), **ofatumumab** (anti-CD 20) and **ocrelizumab** (anti-CD 20). The main problem with this sector is not the efficacy of the drugs but their cost and lack of oral availability, which places a severe strain on budgets and prevents them from being used as a first-line therapy. Hopefully, ways will be found to reduce the cost of production and development in this important technology.

Clearly a low-cost alternative to a neutralising anti-TNF antibody would be a welcome development. *TNF converting enzyme (TACE)* cleaves membrane-bound TNF thus releasing the soluble active form and so might be an attractive target. A number of putative small-molecule inhibitors of this enzyme are in phase II clinical trials and the results are awaited (see Moss et al., 2008, for a review).

A major blow to the NSAID area (and indeed to the pharmaceutical industry in general) has been the recent controversy surrounding the increased incidence of coronary thrombosis in patients taking COX-2 inhibitors and the withdrawal of some prominent members of this class for this and other reasons. The emerging evidence that 'traditional' NSAIDs may also have similar cardiovascular side effects has cast a pall over our existing therapies.[7] At the time of writing, it is too early to say exactly how this awkward situation will be resolved (see Ray et al., 2009).

One of the few innovations in the beleaguered NSAID area has been the design and synthesis of nitric oxide (NO)-NSAIDs—conventional NSAIDs that have NO-donating groups attached to them by ester linkages. The ability of these drugs to release NO following hydrolysis in plasma and tissue fluid is aimed at reducing the risk of ulcerogenic events and increasing the anti-inflammatory activity, presumably due to the beneficial effects of low concentrations of NO (see Ch. 20). Some of these drugs (e.g. **naproxcinod**, a derivative of naproxen) are currently in clinical trial (see Stefano & Distrutti, 2007). Yedgar et al. (2007) discuss some alternative approaches to manipulating the production or action of eicosanoid mediators of inflammation.

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[7]This does not, of course, apply to low-dose aspirin.

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27 Respiratory system

OVERVIEW

Basic aspects of respiratory physiology (regulation of airway smooth muscle, pulmonary vasculature and glands) are considered as a basis for a discussion of pulmonary disease and its treatment. We devote most of the chapter to asthma, dealing first with pathogenesis and then the main drugs used in its treatment and prevention—inhaled bronchodilators and anti-inflammatory agents. We also discuss chronic obstructive pulmonary disease (COPD). There are short sections on allergic emergencies, surfactants and the treatment of cough. Other important pulmonary diseases, such as bacterial infections (e.g. tuberculosis and acute pneumonias) and malignancies, are addressed in Chapters 50 and 55, respectively, or are not yet amenable to drug treatment (e.g. occupational and interstitial lung diseases). Antihistamines, important in treatment of hay fever, are covered in Chapter 26. Pulmonary hypertension is covered in Chapter 22.

THE PHYSIOLOGY OF RESPIRATION

CONTROL OF BREATHING

Respiration is controlled by spontaneous rhythmic discharges from the respiratory centre in the medulla, modulated by input from pontine and higher central nervous system (CNS) centres and vagal afferents from the lungs. Various chemical factors affect the respiratory centre, including the partial pressure of carbon dioxide in arterial blood ($P_A CO_2$) by an action on medullary chemoreceptors, and of oxygen ($P_A O_2$) by an action on the chemoreceptors in the carotid bodies.

Some voluntary control can be superimposed on the automatic regulation of breathing, implying connections between the cortex and the motor neurons innervating the muscles of respiration. Bulbar poliomyelitis and certain lesions in the brain stem result in loss of the automatic regulation of respiration without loss of voluntary regulation.[1]

REGULATION OF MUSCULATURE, BLOOD VESSELS AND GLANDS OF THE AIRWAYS

Irritant receptors and C fibres respond to chemical irritants and cold air, and also to inflammatory mediators (see

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below). Efferent pathways controlling the airways include cholinergic parasympathetic nerves and non-noradrenergic non-cholinergic (NANC) inhibitory nerves (see Ch. 12). Inflammatory mediators (see Ch. 17) and NANC bronchoconstrictor mediators also have a role in diseased airways.

The tone of bronchial muscle influences airway resistance, which is also affected by the state of the mucosa and activity of the glands in patients with asthma and bronchitis. Airway resistance can be measured indirectly by instruments that record the volume or flow of forced expiration. FEV_1 is the forced expiratory volume in 1 second. The peak expiratory flow rate (PEFR) is the maximal flow (expressed as l/min) after a full inhalation; this is simpler to measure at the bedside than FEV_1, which it follows closely.

EFFERENT PATHWAYS

Autonomic innervation

The autonomic innervation of human airways is reviewed by van der Velden & Hulsmann (1999).

Parasympathetic innervation. Parasympathetic innervation of bronchial smooth muscle predominates. Parasympathetic ganglia are embedded in the walls of the bronchi and bronchioles, and the postganglionic fibres innervate airway smooth muscle, vascular smooth muscle and glands. Three types of muscarinic (M) receptors are present (see Ch. 13, Table 13.2). M_3 receptors are pharmacologically the most important. They are found on bronchial smooth muscle and glands, and mediate bronchoconstriction and mucus secretion. M_1 receptors are localised in ganglia and on postsynaptic cells, and facilitate nicotinic neurotransmission, whereas M_2 receptors are inhibitory autoreceptors mediating negative feedback on acetylcholine release by postganglionic cholinergic nerves. Stimulation of the vagus causes bronchoconstriction—mainly in the larger airways. The possible clinical relevance of the heterogeneity of muscarinic receptors in the airways is discussed below.

A distinct population of NANC nerves (see Ch. 12) also regulates the airways. Bronchodilators released by these nerves include *vasoactive intestinal polypeptide* (Table 12.2) and *nitric oxide* (NO; Ch. 20).

Sympathetic innervation. Sympathetic nerves innervate tracheobronchial blood vessels and glands, but not human airway smooth muscle. β-Adrenoceptors are, however, abundantly expressed on human airway smooth muscle (as well as mast cells, epithelium, glands and alveoli) and β agonists relax bronchial smooth muscle, inhibit mediator release from mast cells and increase mucociliary clearance (see below). In humans, β-adrenoceptors in the airways are of the $β_2$ variety.

In addition to the autonomic innervation, non-myelinated sensory fibres linked to irritant receptors in the lungs release tachykinins such as *substance P*, *neurokinin A* and

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[1]Referred to as Ondine's curse. Ondine was a water nymph who fell in love with a mortal. When he was unfaithful to her, the king of the water nymphs put a curse on him—that he must stay awake in order to breathe. When exhaustion finally supervened and he fell asleep, he died.

> ### Regulation of airway muscle, blood vessels and glands
>
> **Afferent pathways**
> - Irritant receptors and C fibres respond to exogenous chemicals, inflammatory mediators and physical stimuli (e.g. cold air).
>
> **Efferent pathways**
> - Parasympathetic nerves cause bronchoconstriction and mucus secretion through M_3 receptors.
> - Sympathetic nerves innervate blood vessels and glands, but not airway smooth muscle.
> - β_2-Adrenoceptor agonists relax airway smooth muscle. This is pharmacologically important.
> - Inhibitory non-noradrenergic non-cholinergic (NANC) nerves relax airway smooth muscle by releasing nitric oxide and vasoactive intestinal peptide.
> - Excitation of sensory nerves causes neuroinflammation by releasing tachykinins: substance P and neurokinin A.

neurokinin B (see Chs 19 and 41), which act on smooth muscle, secretory and inflammatory cells, producing *neurogenic inflammation.*

SENSORY RECEPTORS AND AFFERENT PATHWAYS

Slowly adapting *stretch receptors* control respiration via the respiratory centre. Unmyelinated sensory *C fibres* and rapidly adapting *irritant receptors* associated with myelinated vagal fibres are also important.

Physical or chemical stimuli, acting on irritant receptors on myelinated fibres in the upper airways and/or C-fibre receptors in the lower airways, cause coughing, bronchoconstriction and mucus secretion. Such stimuli include cold air and irritants such as ammonia, sulfur dioxide, cigarette smoke and the experimental tool *capsaicin* (Ch. 41), as well as endogenous inflammatory mediators.

PULMONARY DISEASE AND ITS TREATMENT

Common symptoms of pulmonary disease include shortness of breath, wheeze, chest pain and cough with or without sputum production or haemoptysis—blood in the sputum. Ideally, treatment is of the underlying disease, but sometimes symptomatic treatment, for example of cough, is all that is possible. The lung is an important target organ of many diseases addressed elsewhere in this book, including infections (Chs 50–54), malignancy (Ch. 55) and occupational and rheumatological diseases; drugs (e.g. **amiodarone methotrexate**) can damage lung tissue and cause pulmonary fibrosis. Heart failure leads to pulmonary oedema (Ch. 22). Thromboembolic disease (Ch. 24) and pulmonary hypertension (Ch. 22) affect the pulmonary circulation. In this present chapter, we concentrate on two important diseases of the airways: asthma and COPD.

BRONCHIAL ASTHMA

Asthma is the commonest chronic disease in children in economically developed countries, and is also common in adults. It is increasing in prevalence and severity. It is an inflammatory condition in which there is recurrent reversible airways obstruction in response to irritant stimuli that are too weak to affect non-asthmatic subjects. The obstruction usually causes wheeze and merits drug treatment, although the natural history of asthma includes spontaneous remissions.[2] Reversibility of airways obstruction in asthma contrasts with COPD, where the obstruction is either not reversible or at best incompletely reversible by bronchodilators.

CHARACTERISTICS OF ASTHMA

Asthmatic patients experience intermittent attacks of wheezing, shortness of breath—with difficulty especially in breathing out—and sometimes cough. As explained above, acute attacks are reversible, but the underlying pathological disorder can progress in older patients to a chronic state superficially resembling COPD.

Acute severe asthma (also known as *status asthmaticus*) is not easily reversed and causes hypoxaemia. Hospitalisation is necessary, as the condition, which can be fatal, requires prompt and energetic treatment.

Asthma is characterised by:

- inflammation of the airways
- bronchial hyper-reactivity
- reversible airways obstruction.

The term *bronchial hyper-reactivity* (or hyper-responsiveness) refers to abnormal sensitivity to a wide range of stimuli, such as irritant chemicals, cold air and stimulant drugs, all of which can result in bronchoconstriction. In allergic asthma, these features may be initiated by sensitisation to allergen(s), but, once established, asthma attacks can be triggered by various stimuli such as viral infection, exercise (in which the stimulus may be cold air and/or drying of the airways) and atmospheric pollutants such as sulfur dioxide. Immunological desensitisation to allergens such as pollen or dust mites is popular in some countries but is not superior to conventional inhaled drug treatment.

PATHOGENESIS OF ASTHMA

The pathogenesis of asthma involves both genetic and environmental factors, and the asthmatic attack itself consists, in many subjects, of two main phases: an immediate and a late (or delayed) phase (see Fig. 27.1).

Numerous cells and mediators play a part, and the full details of the complex events involved are still a matter of debate (Walter & Holtzman, 2005). The following simplified account is intended to provide a basis for understanding the rational use of drugs in the treatment of asthma.

Asthmatics have activated T cells, with a T-helper (Th)2 profile of cytokine production (see Ch. 17 and Table 6.2)

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[2]William Osler, 19th-century doyen of American and British clinicians, wrote that 'the asthmatic pants into old age'—this at a time when the most effective drug that he could offer was to smoke stramonium cigarettes, a herbal remedy the antimuscarinic effects of which were offset by direct irritation from the smoke. Its use persisted in English private schools into the 1950s as one author can attest—much to the envy of his fellows!

in their bronchial mucosa. How these cells are activated is not fully understood, but allergens (Fig. 27.2) are one mechanism. The Th2 cytokines that are released do the following:

• Attract other inflammatory granulocytes, especially eosinophils, to the mucosal surface. Interleukin (IL)-5 and granulocyte–macrophage colony-stimulating factor prime eosinophils to produce cysteinyl leukotrienes, and to release granule proteins that damage the epithelium. This damage is one cause of bronchial hyper-responsiveness.

• Promote immunoglobulin (Ig)E synthesis and responsiveness in some asthmatics (IL-4 and IL-13 'switch' B cells to IgE synthesis and cause expression
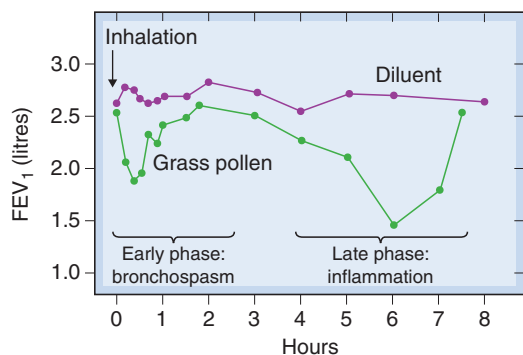
of IgE receptors on mast cells and eosinophils; they also enhance adhesion of eosinophils to endothelium).

Some asthmatics, in addition to these mechanisms, are also *atopic*—i.e. they make allergen-specific IgE that binds to mast cells in the airways. Inhaled allergen cross-links IgE molecules on mast cells, triggering degranulation with release of histamine and leukotriene B_4, both of which are powerful bronchoconstrictors to which asthmatics are especially sensitive because of their airway hyper-responsiveness. This provides a mechanism for acute exacerbation of asthma in atopic individuals exposed to allergen. The effectiveness of **omalizumab** (an anti-IgE antibody; see below) serves to emphasise the importance of IgE in the pathogenesis of asthma as well as in other allergic diseases. Noxious gases (e.g. sulfur dioxide, ozone) and airway dehydration can also cause mast cell degranulation.

Clinicians often refer to atopic or 'extrinsic' asthma and non-atopic or 'intrinsic' asthma; we prefer the terms allergic and non-allergic.

The immediate phase of the asthmatic attack

In allergic asthma, the immediate phase (i.e. the initial response to allergen provocation) occurs abruptly and is mainly caused by spasm of the bronchial smooth muscle. Allergen interaction with mast cell-fixed IgE causes release of histamine, leukotriene B_4 and prostaglandin (PG) D_2 (Ch. 17).

Other mediators released include IL-4, IL-5, IL-13, macrophage inflammatory protein-1α and tumour necrosis factor (TNF)-α.

Various chemotaxins and chemokines (see Ch. 17) attract leukocytes—particularly eosinophils and mononuclear cells—into the area, setting the stage for the delayed phase (Fig. 27.3).
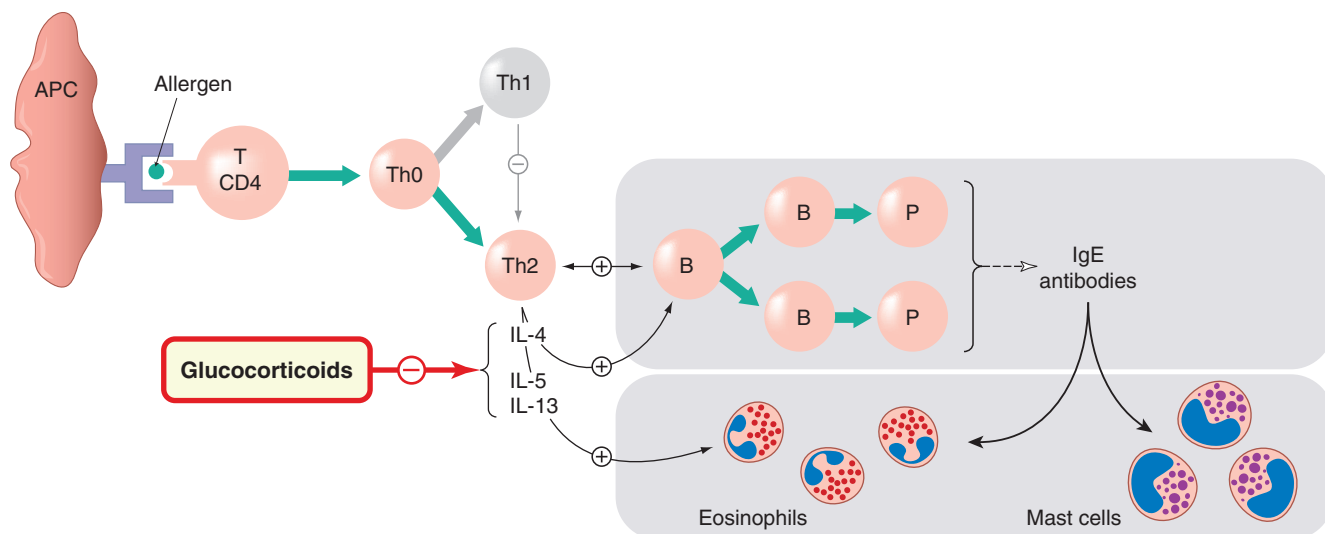

Fig. 27.1 **Two phases of asthma demonstrated by the changes in forced expiratory volume in 1 second (FEV₁) after inhalation of grass pollen in an allergic subject.** (From Cockcroft D W 1983 Lancet ii: 253.)

Fig. 27.2 **The part played by T lymphocytes in allergic asthma.** In genetically susceptible individuals, allergen (green circle) interacts with dendritic cells and CD4⁺ T cells, leading to the development of Th0 lymphocytes, which give rise to a clone of Th2 lymphocytes. These then (1) generate a cytokine environment that switches B cells/plasma cells to the production and release of immunoglobulin (Ig)E; (2) generate cytokines, such as interleukin (IL)-5, which promote differentiation and activation of eosinophils; and (3) cytokines (e.g. IL-4 and IL-13) that induce expression of IgE receptors. Glucocorticoids inhibit the action of the cytokines specified. APC, antigen-presenting dendritic cell; B, B cell; P, plasma cell; Th, T-helper cell.
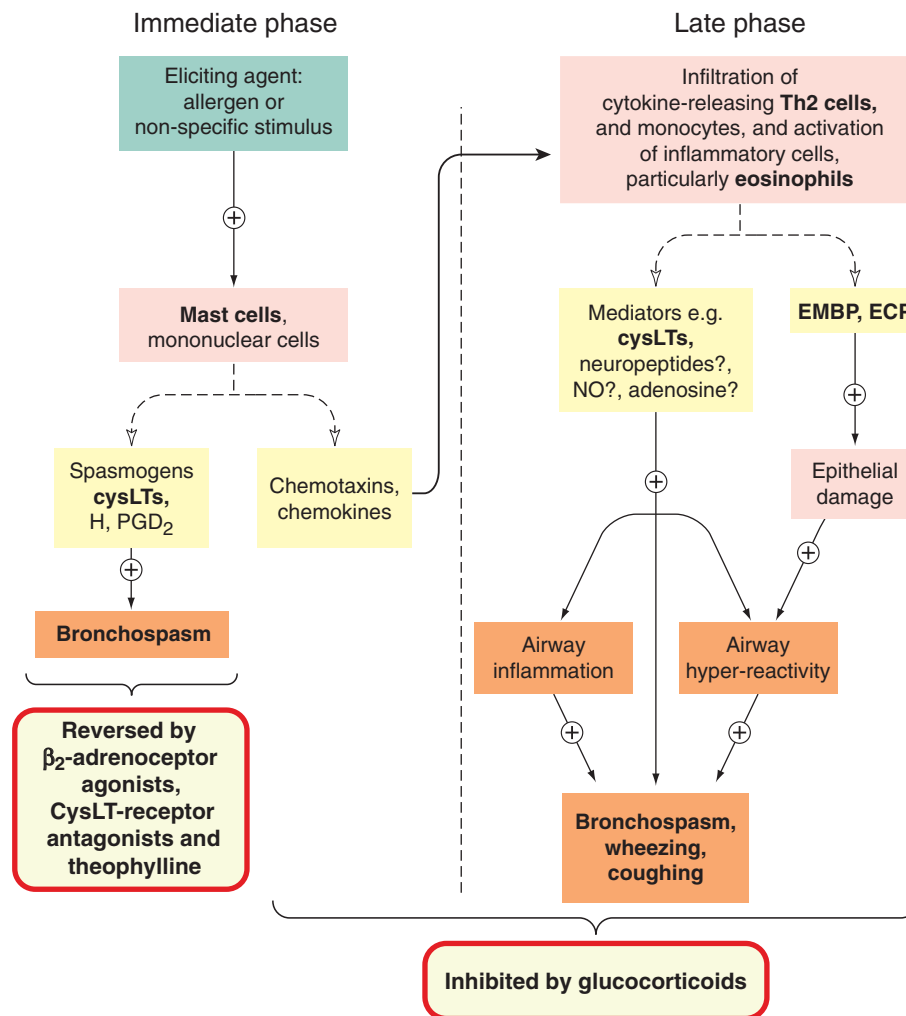
Fig. 27.3   Immediate and late phases of asthma, with the actions of the main drugs. CysLTs, cysteinyl leukotrienes (leukotrienes C_4 and D_4); ECP, eosinophil cationic protein; EMBP, eosinophil major basic protein; H, histamine; iNO, induced nitric oxide. (For more detail of the Th2-derived cytokines and chemokines, see Ch. 17 and Fig. 6.4.)

The late phase

The late phase or delayed response (see Figs 27.1 and 27.3) may be nocturnal. It is, in essence, a progressing inflammatory reaction, initiation of which occurred during the first phase, the influx of Th2 lymphocytes being of particular importance. The inflammatory cells include activated eosinophils. These release *cysteinyl leukotrienes*, *interleukins IL-3, IL-5* and *IL-8*, and the toxic proteins, *eosinophil cationic protein*, *major basic protein* and *eosinophil-derived neurotoxin*. These play an important part in the events of the late phase, the toxic proteins causing damage and loss of epithelium (see, for example, Larche et al., 2003; Kay, 2005). Other putative mediators of the inflammatory process in the delayed phase are adenosine (acting on the A_1 receptor; see Ch. 16), induced NO (see Ch. 20) and neuropeptides (see Ch. 19).

Growth factors released from inflammatory cells act on smooth muscle cells, causing hypertrophy and hyperplasia, and the smooth muscle can itself release proinflammatory mediators and autocrine growth factors (Chs 5 and 17). Figure 27.4 shows schematically the changes that take place in the bronchioles. Epithelial cell loss means that irritant receptors and C fibres are more accessible to irritant stimuli—an important mechanism of bronchial hyper-reactivity.

'Aspirin-sensitive' asthma

▼ Non-steroidal anti-inflammatory drugs (NSAIDs), especially **aspirin**, can precipitate asthma in sensitive individuals. Such aspirin-sensitive asthma is relatively uncommon (< 10% of asthmatic subjects), and is often associated with nasal polyps. Individuals sensitive to one NSAID are usually also sensitive to other chemically unrelated cyclo-oxygenase (COX) inhibitors, including sometimes **paracetamol** (Ch. 26). Abnormal leukotriene production and sensitivity are implicated. Patients with aspirin-sensitive asthma produce more cysteinyl leukotriene and have greater airway hyper-responsiveness to inhaled cysteinyl leukotrienes than aspirin-tolerant asthmatics. Such airway hyper-responsiveness reflects elevated expression of cysteinyl leukotriene receptors on inflammatory cells, and this is downregulated by aspirin desensitisation (Sousa et al., 2002). In addition, aspirin and similar drugs directly activate eosinophils and mast cells in these patients through IgE-independent mechanisms.

Asthma

- Asthma is defined as recurrent reversible airway obstruction, with attacks of wheeze, shortness of breath and often nocturnal cough. Severe attacks cause hypoxaemia and are life-threatening.
- Essential features include:
  - airways inflammation, which causes
  - bronchial hyper-responsiveness, which in turn results in
  - recurrent reversible airway obstruction.
- Pathogenesis involves exposure of genetically disposed individuals to allergens; activation of Th2 lymphocytes and cytokine generation promote:
  - differentiation and activation of eosinophils
  - IgE production and release
  - expression of IgE receptors on mast cells and eosinophils.
- Important mediators include leukotriene B_4 and cysteinyl leukotrienes (C_4 and D_4); interleukins IL-4, IL-5, IL-13; and tissue-damaging eosinophil proteins.
- Antiasthmatic drugs include:
  - bronchodilators
  - anti-inflammatory agents.
- Treatment is monitored by measuring forced expiratory volume in 1 second (FEV_1) or peak expiratory flow rate and, in acute severe disease, oxygen saturation and arterial blood gases.

DRUGS USED TO TREAT AND PREVENT ASTHMA

There are two categories of antiasthma drugs: *bronchodilators* and *anti-inflammatory agents*. Bronchodilators reverse the bronchospasm of the immediate phase; anti-inflammatory agents inhibit or prevent the inflammatory components of both phases (Fig. 27.3). These two categories are not mutually exclusive: some drugs classified as bronchodilators also have some anti-inflammatory effect.

How best to use these drugs to treat asthma is complex. A guideline (see www.brit-thoracic.org.uk, updated in 2009) specifies five therapeutic steps for adults and children with chronic asthma. Very mild disease may be controlled with short-acting bronchodilator alone (step 1), but if patients need this more than once a day, a regular inhaled corticosteroid should be added (step 2). If the asthma remains uncontrolled, the next step is to add a long-acting bronchodilator (**salmeterol** or **formoterol**); this minimises the need for increased doses of inhaled corticosteroid (step 3). **Theophylline** and leukotriene antagonists, such as **montelukast**, also exert a corticosteroid-sparing effect, but this is less reliable. One or other is added in for patients with more severe asthma who remain symptomatic and/or the dose of inhaled corticosteroid increased to the maximum recommended (step 4). If the patient's condition is still poorly controlled, it may be necessary to add a regular oral corticosteroid (e.g. **prednisolone**)—step 5. Corticosteroids are the mainstay of therapy because they are the only asthma drugs that potently inhibit T-cell activation, and thus the inflammatory response, in the asthmatic airways. **Cromoglicate** (see below) has only a weak effect and is now seldom used.

BRONCHODILATORS

The main drugs used as bronchodilators are β_2-adrenoceptor agonists; others include **theophylline**, cysteinyl leukotriene receptor antagonists and muscarinic receptor antagonists.

β-Adrenoceptor agonists

The β_2-adrenoceptor agonists are dealt with in Chapter 14. Their primary effect in asthma is to dilate the bronchi by a direct action on the β_2 adrenoceptors of smooth muscle. Being physiological antagonists of bronchoconstrictors (see Ch. 2), they relax bronchial muscle whatever the spasmogens involved. They also inhibit mediator release from mast cells and TNF-α release from monocytes, and increase mucus clearance by an action on cilia.

The β_2-adrenoceptor agonists are usually given by inhalation of aerosol, powder or nebulised solution (i.e. solution that has been converted into a cloud or mist of fine
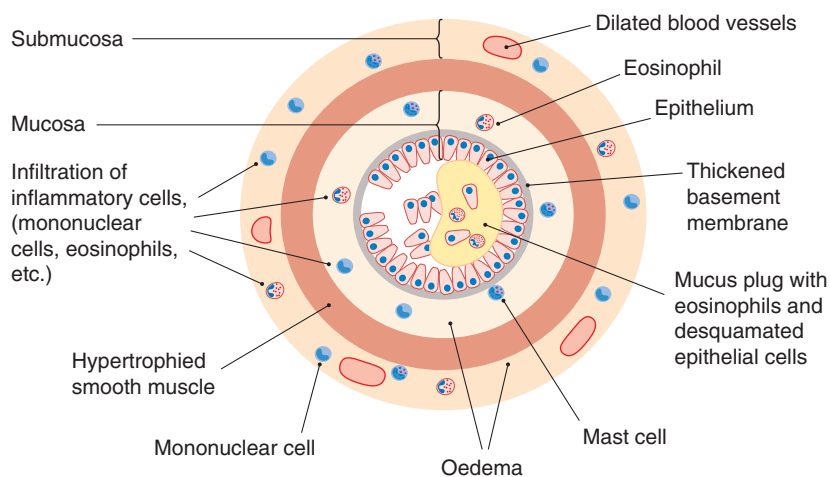
Fig. 27.4   Schematic diagram of a cross-section of a bronchiole, showing changes that occur with severe chronic asthma. The individual elements depicted are not, of course, drawn to scale.

Submucosa
Dilated blood vessels
Eosinophil
Mucosa
Epithelium
Infiltration of inflammatory cells, (mononuclear cells, eosinophils, etc.)
Thickened basement membrane
Mucus plug with eosinophils and desquamated epithelial cells
Hypertrophied smooth muscle
Mononuclear cell
Oedema
Mast cell

Antiasthma drugs: bronchodilators

- β_2-Adrenoceptor agonists (e.g. **salbutamol**) are first-line drugs (for details, see Ch. 14):
  - they act as physiological antagonists of the spasmogenic mediators but have little or no effect on the bronchial hyper-reactivity
  - salbutamol is given by inhalation; its effects start immediately and last 3–5 h, and it can also be given by intravenous infusion in status asthmaticus
  - **salmeterol** or **formoterol** are given regularly by inhalation; their duration of action is 8–12 h.
- **Theophylline** (often formulated as **aminophylline**):
  - is a methylxanthine
  - inhibits phosphodiesterase and blocks adenosine receptors
  - has a narrow therapeutic window: unwanted effects include cardiac dysrhythmia, seizures and gastrointestinal disturbances
  - is given intravenously (by slow infusion) for status asthmaticus, or orally (as a sustained-release preparation) as add-on therapy to inhaled corticosteroids and long-acting β_2 agonists (step 4)
  - is metabolised in the liver by P450; liver dysfunction and viral infections increase its plasma concentration and half-life (normally approximately 12 h)
  - interacts importantly with other drugs; some (e.g. some antibiotics) increase the half-life of theophylline, others (e.g. anticonvulsants) decrease it.
- Cysteinyl leukotriene receptor antagonists (e.g. **montelukast**) are third-line drugs for asthma. They:
  - compete with cysteinyl leukotrienes at $CysLT_1$ receptors
  - are used mainly as add-on therapy to inhaled corticosteroids and long-acting β_2 agonists (step 4).

Clinical use of β_2-adrenoceptor agonists as bronchodilators

- Short-acting drugs (**salbutamol** or **terbutaline**, usually by inhalation) to prevent or treat wheeze in patients with reversible obstructive airways disease.
- Long-acting drugs (**salmeterol**, **formoterol**) to prevent bronchospasm (e.g. at night or with exercise) in patients requiring long-term bronchodilator therapy.

Xanthine drugs (see Chs 15 and 45)

Theophylline (1,3-dimethylxanthine), which is also used as theophylline ethylenediamine (known as **aminophylline**), is the main therapeutic drug of this class, and has long been used as a bronchodilator.[3] Here we consider it in the context of respiratory disease, its only current therapeutic use.

Mechanism of action

The mechanism of theophylline is still unclear. The relaxant effect on smooth muscle has been attributed to inhibition of phosphodiesterase (PDE) isoenzymes, with resultant increase in cAMP and/or cGMP (see Fig. 4.10). However, the concentrations necessary to inhibit the isolated enzymes exceed the therapeutic range of plasma concentrations.

Competitive antagonism of adenosine at adenosine A_1 and A_2 receptors (Ch. 16) may contribute, but the PDE inhibitor **enprofylline**, which is a potent bronchodilator, is not an adenosine antagonist.

Type IV PDE is implicated in inflammatory cells (see below), and methylxanthines may have some anti-inflammatory effect. (**Roflumilast**, a type IV PDE inhibitor, is mentioned below in the context of COPD.)

Theophylline activates *histone deacetylase* (HDAC) and may thereby reverse resistance to the anti-inflammatory effects of corticosteroids (Barnes, 2006).

Methylxanthines stimulate the CNS (Ch. 47) and respiratory stimulation may be beneficial in patients with COPD and reduced respiration evidenced by a tendency to retain CO_2 (see below).

Unwanted effects

When theophylline is used in asthma, its other actions (CNS, cardiovascular, gastrointestinal and diuretic) result in unwanted side effects (e.g. insomnia, nervousness). The therapeutic plasma concentration range is 30–100 μmol/l, and adverse effects are common with concentrations greater than 110 μmol/l; thus, there is a relatively narrow therapeutic window. Serious cardiovascular and CNS effects can occur when the plasma concentration exceeds 200 μmol/l. The most serious cardiovascular effect is *dysrhythmia* (especially during intravenous administration of aminophylline), which can be fatal. *Seizures* can occur with theophylline concentrations at or slightly above the upper limit of the therapeutic range, and can be fatal in patients with impaired respiration due to severe asthma. Monitoring the concentration of theophylline in plasma is useful for optimising the dose.

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droplets), but some may be given orally or by injection. A metered-dose inhaler is used for aerosol preparations.

Two categories of β_2-adrenoceptor agonists are used in asthma.

- Short-acting agents: **salbutamol** and **terbutaline**. These are given by inhalation; the maximum effect occurs within 30 min and the duration of action is 3–5 h; they are usually used on an 'as needed' basis to control symptoms.
- Longer-acting agents: e.g. **salmeterol** and **formoterol**. These are given by inhalation, and the duration of action is 8–12 h. They are not used 'as needed' but are given regularly, twice daily, as adjunctive therapy in patients whose asthma is inadequately controlled by glucocorticoids.

Unwanted effects

The unwanted effects of β_2-adrenoceptor agonists result from systemic absorption and are given in Chapter 14. In the context of their use in asthma, the commonest adverse effect is *tremor*; other unwanted effects include *tachycardia* and *cardiac dysrhythmia*.

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[3]Over 200 years ago, William Withering recommended 'coffee made very strong' as a remedy for asthma. Coffee contains caffeine, a related methylxanthine.

> ### Clinical use of theophylline
>
> - In addition to steroids, in patients whose asthma does not respond adequately to β_2-adrenoceptor agonists.
> - In addition to steroids in COPD.
> - Intravenously (as aminophylline, a combination of theophylline with ethylenediamine to increase its solubility in water) in acute severe asthma.

> ### Clinical use of inhaled muscarinic receptor antagonists (e.g. ipratropium)
>
> - For asthma, as an adjunct to β_2-adrenoceptor antagonists and steroids.
> - For some patients with COPD, especially long-acting drugs (e.g. **tiotropium**).
> - For bronchospasm precipitated by β_2-adrenoceptor antagonists.
> - For clinical uses of muscarinic receptor antagonists in other organ systems, see clinical box in Chapter 13, p. 162.

Pharmacokinetic aspects

Theophylline is given orally as a sustained-release preparation. Aminophylline can be given by slow intravenous injection of a loading dose followed by intravenous infusion.

Theophylline is well absorbed from the gastrointestinal tract. It is metabolised by P450 enzymes in the liver; the mean elimination half-life is approximately 8 h in adults but there is wide inter-individual variation. The half-life is increased in liver disease, cardiac failure and viral infections, and is decreased in heavy cigarette smokers (as a result of enzyme induction). Unwanted drug interactions are clinically important: its plasma concentration is decreased by drugs that induce P450 enzymes (including **rifampicin**, **phenytoin** and **carbamazepine**). The concentration is increased by drugs that inhibit P450 enzymes, such as **erythromycin**, **clarithromycin**, **ciprofloxacin**, **diltiazem** and **fluconazole**. This is important in view of the narrow therapeutic window; antibiotics such as clarithromycin are often started when asthmatics are hospitalised because of a severe attack precipitated by a chest infection, and if the dose of theophylline is unaltered, severe toxicity can result.

Muscarinic receptor antagonists

Muscarinic receptor antagonists are dealt with in Chapter 13. The main compound used as a bronchodilator is **ipratropium**. **Tiotropium** is also available; it is a longer-acting drug used in maintenance treatment of COPD (see below). Ipratropium is seldom used on a regular basis in asthma but can be useful for cough caused by irritant stimuli in such patients.

Ipratropium is a quaternary derivative of *N*-isopropylatropine. It does not discriminate between muscarinic receptor subtypes (see Ch. 13), and it is possible that its blockade of M_2 autoreceptors on the cholinergic nerves increases acetylcholine release and reduces the effectiveness of its antagonism at the M_3 receptors on smooth muscle. It is not particularly effective against allergen challenge, but it inhibits the augmentation of mucus secretion that occurs in asthma and may increase the mucociliary clearance of bronchial secretions. It has no effect on the late inflammatory phase of asthma.

Ipratropium is given by aerosol inhalation. As a quaternary nitrogen compound, it is highly polar and is not well absorbed into the circulation (Ch. 8), limiting systemic effects. The maximum effect occurs approximately 30 min after inhalation and persists for 3–5 h. It has few unwanted effects and is, in general, safe and well tolerated. It can be used with β_2-adrenoceptor agonists. See the clinical box, above, for clinical uses.

Cysteinyl leukotriene receptor antagonists

Two receptors for cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) have been cloned, *CysLT*$_1$ and *CysLT*$_2$ (see Ch. 17), and both are expressed in respiratory mucosa and infiltrating inflammatory cells, but the functional significance of each is unclear. The 'lukast' drugs (**montelukast** and **zafirlukast**) antagonise only CysLT$_1$.

Lukasts reduce acute reactions to aspirin in sensitive patients, but have not been shown to be particularly effective for aspirin-sensitive asthma (see above) in the clinic. They inhibit exercise-induced asthma and decrease both early and late responses to inhaled allergen. They relax the airways in mild asthma but are less effective than salbutamol, with which their action is additive. They reduce sputum eosinophilia, but there is no clear evidence that they modify the underlying inflammatory process in chronic asthma.

The lukasts are taken by mouth, in combination with an inhaled corticosteroid. They are generally well tolerated, adverse effects consisting mainly of headache and gastrointestinal disturbances.

Histamine H$_1$-receptor antagonists

Although mast cell mediators play a part in the immediate phase of allergic asthma (Fig. 27.3) and in some types of exercise-induced asthma, histamine H$_1$-receptor antagonists have no routine place in therapy, although they may be modestly effective in mild atopic asthma, especially when this is precipitated by acute histamine release in patients with concomitant allergy such as severe hay fever.

ANTI-INFLAMMATORY AGENTS

Glucocorticoids

Glucocorticoids (see Ch. 30) are the main drugs used for their anti-inflammatory action in asthma. They are not bronchodilators, but prevent the progression of chronic asthma and are effective in acute severe asthma (see below).[4]

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[4]In 1900, Solis-Cohen reported that dried bovine adrenals had antiasthma activity. He noted that the extract did not serve acutely 'to cut short the paroxysm' but was 'useful in averting recurrence of paroxysms'. Mistaken for the first report on the effect of adrenaline, his astute observation was probably the first on the efficacy of steroids in asthma.

Actions and mechanism

The basis of the anti-inflammatory action of glucocorticoids is discussed in Chapter 32. An important action, of relevance for asthma, is that they decrease formation of cytokines, in particular the Th2 cytokines that recruit and activate eosinophils and are responsible for promoting the production of IgE and the expression of IgE receptors. Glucocorticoids also inhibit the generation of the vasodilators PGE_2 and PGI_2, by inhibiting induction of COX-2 (Fig. 17.1). By inducing *annexin-1*,[5] they could inhibit production of leukotrienes and platelet-activating factor, although there is currently no direct evidence that annexin-1 is involved in the therapeutic action of glucocorticoids in human asthma.

Corticosteroids inhibit the allergen-induced influx of eosinophils into the lung. Glucocorticoids upregulate β_2-adrenoceptors, decrease microvascular permeability and indirectly reduce mediator release from eosinophils by inhibiting the production of cytokines (e.g. IL-5 and granulocyte-macrophage colony stimulating factor) that activate eosinophils. Reduced synthesis of IL-3 (the cytokine that regulates mast cell production) may explain why long-term steroid treatment eventually reduces the number of mast cells in the respiratory mucosa, and hence suppresses the early-phase response to allergens and exercise.

Glucocorticoids are sometimes ineffective, even in high doses, for reasons that are incompletely understood (reviewed by Adcock & Ito, 2004). Many individual mechanisms could contribute to glucocorticoid resistance. The phenomenon has been linked to the number of glucocorticoid receptors, but in some situations other mechanisms are clearly in play—for example, reduced activity of *histone deacetylase* (HDAC) may be important in cigarette smokers (see below).

The main compounds used are **beclometasone**, **budesonide**, **fluticasone**, **mometasone** and **ciclesonide**. These are given by inhalation with a metered-dose or dry powder inhaler, the full effect on bronchial hyper-responsiveness being attained only after weeks or months of therapy.

Unwanted effects

Serious unwanted effects are uncommon with inhaled steroids. Oropharyngeal candidiasis (thrush; Ch. 52) can occur (T lymphocytes are important in protection against fungal infection), as can sore throat and croaky voice, but use of 'spacing' devices, which decrease oropharyngeal deposition of the drug and increase airway deposition, reduces these problems. Regular high doses can produce some adrenal suppression, particularly in children, and necessitate carrying a 'steroid card' (Ch. 32). This is less likely with fluticasone, mometasone and ciclesonide, as these drugs are poorly absorbed from the gastrointestinal tract and undergo almost complete presystemic metabolism. The unwanted effects of oral glucocorticoids are given in Chapter 32 and Figure 32.7.

Cromoglicate and nedocromil

These two drugs, of similar chemical structure and properties, are now hardly used for the treatment of asthma. Although very safe, they have only weak anti-inflammatory

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Clinical use of glucocorticoids in asthma

- Patients who require regular bronchodilators should be considered for glucocorticoid treatment (e.g. with inhaled **beclometasone**).
- More severely affected patients are treated with high-potency inhaled drugs (e.g. **budesonide**).
- Patients with acute exacerbations of asthma may require intravenous **hydrocortisone** and oral **prednisolone**.
- A 'rescue course' of oral prednisolone may be needed at any stage of severity if the clinical condition is deteriorating rapidly.
- Prolonged treatment with oral prednisolone, in addition to inhaled bronchodilators and steroids, is needed by a few severely asthmatic patients.

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effects and short duration of action. They are given by inhalation as aerosols or dry powders, and can be also be used topically for allergic conjunctivitis or rhinitis. They are not bronchodilators, having no direct effects on smooth muscle, nor do they inhibit the actions of any of the known smooth muscle stimulants. Given prophylactically, they reduce both the immediate- and late-phase asthmatic responses and reduce bronchial hyper-reactivity.

Their mechanism of action is not fully understood. Cromoglicate is a 'mast cell stabiliser', preventing histamine release from mast cells. However, this is not the basis of its action in asthma, because compounds that are more potent than cromoglicate at inhibiting mast cell histamine release are ineffective against asthma.

Cromoglicate depresses the exaggerated neuronal reflexes that are triggered by stimulation of the 'irritant receptors'; it suppresses the response of sensory C fibres to capsaicin and may inhibit the release of T-cell cytokines. Various other effects, of uncertain importance, on the inflammatory cells and mediators involved in asthma have been described.

Anti-IgE treatment

Omalizumab is a humanised monoclonal anti-IgE antibody. It is effective in patients with allergic asthma as well as in allergic rhinitis. It is of considerable theoretical interest (see review by Holgate et al., 2005), but it is expensive and its place in therapeutics is unclear.

SEVERE ACUTE ASTHMA (STATUS ASTHMATICUS)

Severe acute asthma is a medical emergency requiring hospitalisation. Treatment includes **oxygen** (in high concentration, usually ≥ 60%), inhalation of nebulised **salbutamol**, and intravenous **hydrocortisone** followed by a course of oral **prednisolone**. Additional measures occasionally used include nebulised **ipratropium**, intravenous salbutamol or **aminophylline**, and antibiotics (if bacterial infection is present). Monitoring is by PEFR or FEV_1, and by measurement of arterial blood gases and oxygen saturation.

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[5]Previously known as lipocortin-1—the nomenclature was changed in order to comply with the latest genomics data, which indicate there are approximately 30 members of this family!

> ### Antiasthma drugs: anti-inflammatory agents
>
> **Glucocorticoids (for details, see Ch. 32)**
> - These reduce the inflammatory component in chronic asthma and are life-saving in status asthmaticus (acute severe asthma).
> - They do not prevent the immediate response to allergen or other challenges.
> - The mechanism of action involves decreased formation of cytokines, particularly those generated by Th2 lymphocytes (see key points box), decreased activation of eosinophils and other inflammatory cells.
> - They are given by inhalation (e.g. **beclometasone**); systemic unwanted effects are uncommon at moderate doses, but oral thrush and voice problems can occur. Systemic effects can occur with high doses but are less likely with **mometasone** because of its presystemic metabolism. In deteriorating asthma, an oral glucocorticoid (e.g. **prednisolone**) or intravenous **hydrocortisone** is also given.

ALLERGIC EMERGENCIES

Anaphylaxis (Ch. 6) and *angio-oedema* are emergencies involving acute airways obstruction; **adrenaline** (epinephrine) is potentially life-saving. It is administered intramuscularly (or occasionally intravenously, as in anaphylaxis occurring in association with general anaesthesia). Patients at risk of acute anaphylaxis, for example from food or insect sting allergy, may self-administer intramuscular adrenaline using a spring-loaded syringe. Oxygen, an antihistamine such as **chlorphenamine**, and **hydrocortisone** are also indicated.

Angio-oedema is the intermittent occurrence of focal swelling of the skin or intra-abdominal organs caused by plasma leakage from capillaries. Most often, it is mild and 'idiopathic', but it can occur as part of acute allergic reactions, when it is generally accompanied by urticaria—'hives'—caused by histamine release from mast cells. If the larynx is involved, it is life-threatening; swelling in the peritoneal cavity can be very painful and mimic a surgical emergency. It can be caused by drugs, especially *angiotensin-converting enzyme inhibitors*—perhaps because they block the inactivation of peptides such as bradykinin (Ch. 19)—and by **aspirin** and related drugs in patients who are aspirin sensitive (see above and Ch. 26). The hereditary form is associated with lack of C1 esterase inhibitor—C1 esterase is an enzyme that degrades the complement component C1 (see Ch. 6). **Tranexamic acid** (Ch. 24) or **danazol** (Ch. 34) may be used to prevent attacks in patients with hereditary angioneurotic oedema, and administration of partially purified C1 esterase inhibitor or fresh plasma, with antihistamines and glucocorticoids, can terminate acute attacks. **Icatibant**, a peptide bradykinin B_2 receptor antagonist (Ch. 16) is effective for acute attacks of hereditary angio-oedema. It is administered subcutaneously and can cause nausea, abdominal pain and nasal stuffiness.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease is a major global health problem. Cigarette smoking is the main cause, and is increasing in the developing world. Air pollution, also aetiologically important, is also increasing, and there is a huge unmet need for effective drugs. Despite this, COPD has received much less attention than asthma. A recent resurgence of interest in new therapeutic approaches (see Barnes, 2008) has yet to bear fruit.

Clinical features. The clinical picture starts with attacks of morning cough during the winter, and progresses to chronic cough with intermittent exacerbations, often initiated by an upper respiratory infection, when the sputum becomes purulent ('bronchitis'). There is progressive breathlessness. Some patients have a reversible component of airflow obstruction identifiable by an improved FEV_1 following a dose of bronchodilator. Pulmonary hypertension (Ch. 22) is a late complication, causing symptoms of heart failure (*cor pulmonale*). Exacerbations may be complicated by respiratory failure (i.e. reduced P_AO_2) requiring hospitalisation and intensive care. Tracheostomy and artificial ventilation, while prolonging survival, may serve only to return the patient to a miserable life.

Pathogenesis. There is small airways fibrosis, resulting in obstruction, and/or destruction of alveoli and of elastin fibres in the lung parenchyma. The latter features are hallmarks of emphysema,[6] thought to be caused by proteases, including elastase, released during the inflammatory response. It is emphysema that causes respiratory failure, because it destroys the alveoli, impairing gas transfer. There is chronic inflammation, predominantly in small airways and lung parenchyma, characterised by increased numbers of macrophages, neutrophils and T lymphocytes. The inflammatory mediators have not been as clearly defined as in asthma. Lipid mediators, inflammatory peptides, reactive oxygen and nitrogen species, chemokines, cytokines and growth factors are all implicated (Barnes, 2004).

Principles of treatment. Stopping smoking (Ch. 46) slows the progress of COPD. Patients should be immunised against influenza and *Pneumococcus*, because superimposed infections with these organisms are potentially lethal. Glucocorticoids are generally ineffective, in contrast to asthma, but a trial of glucocorticoid treatment is worthwhile because asthma may coexist with COPD and have been overlooked. This contrast with asthma is puzzling, because in both diseases multiple inflammatory genes are activated, which might be expected to be turned off by glucocorticoids. Inflammatory gene activation results from acetylation of nuclear histones around which DNA is wound. Acetylation opens up the chromatin structure, allowing gene transcription and synthesis of inflammatory proteins to proceed. HDAC is a key molecule in suppressing production of proinflammatory cytokines. Corticosteroids recruit HDAC to activated genes, reversing acetylation and switching off inflammatory gene transcription (Barnes et al., 2004). There is a link between the severity of COPD (but not of asthma) and reduced HDAC activity in lung tissue (Ito et al., 2005); furthermore, HDAC activity is

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[6]Emphysema is a pathological condition sometimes associated with COPD, in which lung parenchyma is destroyed and replaced by air spaces that coalesce to form bullae—blister-like air-filled spaces in the lung tissue.

inhibited by smoking-related oxidative stress, which may explain the lack of effectiveness of glucocorticoids in COPD.

Long-acting bronchodilators give modest benefit, but do not deal with the underlying inflammation. No currently licensed treatments reduce the progression of COPD or suppress the inflammation in small airways and lung parenchyma. Several new treatments that target the inflammatory process are in clinical development (Barnes & Stockley, 2005). Some, such as chemokine antagonists, are directed against the influx of inflammatory cells into the airways and lung parenchyma, whereas others target inflammatory cytokines such as TNF-α. PDE IV inhibitors (e.g. **roflumilast**; Rabe et al., 2005) show some promise. Other drugs that inhibit cell signalling (see Chs 3 and 5) include inhibitors of p38 mitogen-activated protein kinase, nuclear factor κβ and phosphoinositide-3 kinase-γ. More specific approaches are to give antioxidants, inhibitors of inducible NO synthase and leukotriene B_4 antagonists. Other treatments have the potential to combat mucus hypersecretion, and there is a search for serine protease and matrix metalloprotease inhibitors to prevent lung destruction and the development of emphysema.

Specific aspects of treatment. Short- and long-acting inhaled bronchodilators can provide useful palliation in patients with a reversible component. The main short-acting drugs are ipratropium and salbutamol; long-acting drugs include **tiotropium** and **salmeterol** or **formoterol** (Chs 13 and 14). Theophylline (Ch. 16)) can be given by mouth but is of uncertain benefit. Its respiratory stimulant effect may be useful for patients who tend to retain CO_2. Other respiratory stimulants (e.g. **doxapram**; see Ch. 47) are sometimes used briefly in acute respiratory failure (e.g. postoperatively) but have largely been replaced by ventilatory support (intermittent positive-pressure ventilation).

Long-term oxygen therapy administered at home prolongs life in patients with severe disease and hypoxaemia (at least if they refrain from smoking — an oxygen fire is not a pleasant way to go, especially for one's neighbours!).

Acute exacerbations. Acute exacerbations of COPD are treated with inhaled O_2 in a concentration (initially, at least) of only 24% O_2, i.e. only just above atmospheric O_2 concentration (approximately 20%). The need for caution is because of the risk of precipitating CO_2 retention as a consequence of terminating the hypoxic drive to respiration. Blood gases and tissue oxygen saturation are monitored, and inspired O_2 subsequently adjusted accordingly. Broad-spectrum antibiotics (e.g. **cefuroxime**; Ch. 50), including activity against *Haemophilus influenzae*, are used if there is evidence of infection. Inhaled bronchodilators may provide some symptomatic improvement.

A systemically active glucocorticoid (intravenous **hydrocortisone** or oral **prednisolone**) is also administered routinely, although efficacy is modest. Inhaled steroids do not influence the progressive decline in lung function in patients with COPD, but do improve the quality of life,

probably as a result of a modest reduction in hospital admissions.

SURFACTANTS

Pulmonary surfactants are not true drugs in Ehrlich's sense (Ch. 2), acting as a result of their physicochemical properties within the airways rather than by binding to specific receptors. They are effective in the prophylaxis and management of *respiratory distress syndrome* in newborn babies, especially if premature. Examples include **beractant** and **poractant alpha**, which are derivatives of the physiological pulmonary surfactant protein. They are administered directly into the tracheobronchial tree via an endotracheal tube. (The mothers of premature infants are sometimes treated with glucocorticoids before birth in an attempt to accelerate maturation of the fetal lung and minimise incidence of this disorder.)

COUGH

Cough is a protective reflex that removes foreign material and secretions from the bronchi and bronchioles. It is a very common adverse effect of angiotensin-converting enzyme inhibitors, in which case the treatment is usually to substitute an alternative drug, notably an angiotensin receptor antagonist, less likely to cause this adverse effect (Ch. 22). It can be triggered by inflammation in the respiratory tract, for example by undiagnosed asthma or chronic reflux with aspiration, or by neoplasia. In these cases, cough suppressant (antitussive) drugs are sometimes useful, for example for the dry painful cough associated with bronchial carcinoma, but are to be avoided in cases of chronic pulmonary infection, as they can cause undesirable thickening and retention of sputum, and in asthma because of the risk of respiratory depression.

DRUGS USED FOR COUGH

Antitussive drugs in clinical use are all opioid analgesics (Ch. 41), which act by an ill-defined effect in the brain stem, depressing an even more poorly defined 'cough centre'. They suppress cough in doses below those required for pain relief. Those used as cough suppressants have minimal analgesic actions and addictive properties. New opioid analogues that suppress cough by inhibiting release of excitatory neuropeptides through an action on μ receptors (see Table 41.1) on sensory nerves in the bronchi are being assessed.

Codeine (methylmorphine) is a weak opioid (see Ch. 41) with considerably less addiction liability than the main opioids, and is a mild cough suppressant. It decreases secretions in the bronchioles, which thickens sputum, and inhibits ciliary activity. Constipation is common. **Dextromethorphan** and **pholcodine** have similar but possibly less intense adverse effects. Respiratory depression is a risk with all drugs of this type. **Morphine** is used for palliative care in cases of lung cancer associated with distressing cough.

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The kidney 28

OVERVIEW

We set the scene with a brief outline of renal physiology based on the functional unit of the kidney—the nephron—before describing drugs that affect renal function. Subsequent emphasis is on diuretics—drugs that increase the excretion of Na⁺ ions and water. We also consider briefly other drugs that are used in treatment of patients with renal failure and urinary tract disorders.

INTRODUCTION

The main drugs that work by altering renal function—the diuretics—are crucial for the management of cardiovascular disease (Chs 21 and 22) as well as patients with renal disease. The kidneys are the main organ by which drugs and their metabolites are eliminated from the body (Ch. 9), and so in renal impairment dosing regimens of many drugs must be adapted. Furthermore, the kidneys are a target for various kinds of drug toxicity (Ch. 57). Antihypertensive drugs (commonly indicated in kidney disease) are covered in Chapter 22, immunosuppressant drugs (effective in several of the diseases that can cause renal failure, and crucial for maintaining the health of patients who have received a kidney transplant) in Chapter 26 and antibacterial drugs (used to treat renal and urinary tract infections) in Chapter 50. Patients with anaemia due to chronic renal failure benefit greatly from **epoetin** (Ch. 25). In the present chapter we focus on the main drugs that act on the renal tubules, namely diuretics—drugs that increase the excretion of Na⁺ ions and water. We also consider briefly other drugs that are used in treating renal failure (concentrating on acid–base and electrolyte aspects) and urinary tract disorders.

OUTLINE OF RENAL FUNCTION

The main function of the kidney is to maintain the constancy of the 'interior environment' by eliminating waste products and by regulating the volume, electrolyte content and pH of the extracellular fluid in the face of varying dietary intake and other environmental (e.g. climatic) demands.

The kidneys receive about a quarter of the cardiac output. From the several hundred litres of plasma that flow through them each day, they filter (in a 70 kg human) approximately 120 litres per day, 11 times the total extracellular fluid volume. This filtrate is similar to plasma apart from the absence of protein. As it passes through the renal tubule, about 99% of the filtered water, and much of the filtered Na⁺, is reabsorbed, and some substances are secreted into it from the blood. Eventually, approximately 1.5 litres is voided as urine per 24 h under usual conditions (Table 28.1).

Each kidney consists of an outer cortex, an inner medulla and a hollow pelvis, which empties into the ureter. The functional unit is the nephron, of which there are approximately 1.4×10^6 in each kidney (approximately half this number in people with hypertension), with considerable variation between individuals and an age-related decline.

THE STRUCTURE AND FUNCTION OF THE NEPHRON

Each nephron consists of a *glomerulus*, *proximal tubule*, *loop of Henle*, *distal convoluted tubule* and *collecting duct*—Figure 28.1. The glomerulus comprises a tuft of capillaries projecting into a dilated end of the renal tubule. Most nephrons lie largely or entirely in the cortex. The remaining 12%, called the *juxtamedullary nephrons*, have their glomeruli and convoluted tubules next to the junction of the medulla and cortex, and their loops of Henle pass deep into the medulla.

THE BLOOD SUPPLY TO THE NEPHRON

Nephrons possess the special characteristic of having two capillary beds in series with each other (see Fig. 28.1). The afferent arteriole of each cortical nephron branches to form the glomerulus; glomerular capillaries coalesce into the efferent arteriole which, in turn, branches to form a second capillary network in the cortex, around the convoluted tubules and loops of Henle, before converging on venules and thence on renal veins. By contrast, efferent arterioles of juxtamedullary nephrons lead to vessel loops (*vasa recta*) that pass deep into the medulla with the thin loops of Henle, and play a key role in counter-current exchange (see below).

THE JUXTAGLOMERULAR APPARATUS

A conjunction of afferent arteriole, efferent arteriole and distal convoluted tubule near the glomerulus forms the juxtaglomerular apparatus (Fig. 28.2). At this site, there are specialised cells in both the afferent arteriole and in the tubule. The latter, termed *macula densa* cells, respond to changes in the rate of flow and the composition of tubule fluid, and they control *renin* release from specialised granular renin-containing cells in the afferent arteriole (Ch. 22). Other mediators also influence renin secretion, including β_2 agonists, vasodilator prostaglandins and feedback inhibition from angiotensin II acting on AT_1 receptors (see Fig. 22.4). The role of the juxtaglomerular apparatus in the control of Na⁺ balance is dealt with below.

GLOMERULAR FILTRATION

Fluid is driven from the capillaries into the tubular capsule (Bowman's capsule) by hydrodynamic force opposed by the oncotic pressure of the plasma proteins, to which the
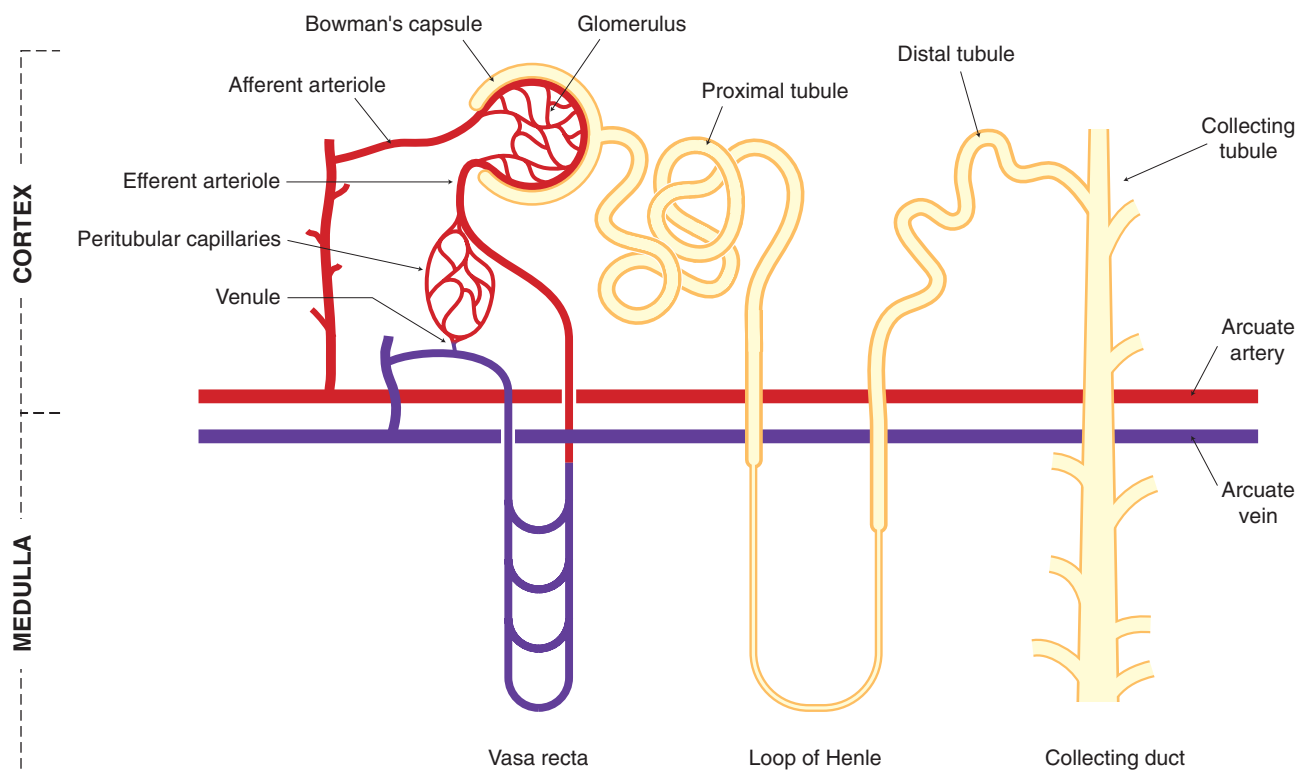
Fig. 28.1   Simplified diagram of a juxtamedullary nephron and its blood supply. The tubules and the blood vessels are shown separately for clarity. In the kidney, the peritubular capillary network surrounds the convoluted tubules, and the distal convoluted tubule passes close to the glomerulus, between the afferent and efferent arterioles. (This last is shown in more detail in Fig. 28.2.)

Table 28.1   Reabsorption of fluid and solute in the kidney[a]

	Filtered/day	Excreted/day[b]	Percentage reabsorbed
Na^+ (mmol)	25 000	150	99+
K^+ (mmol)	600	90	93+
Cl^- (mmol)	18 000	150	99+
HCO_3^- (mmol)	4900	0	100
Total solute (mosmol)	54 000	700	87
H_2O (litres)	180	~1.5	99+

[a] Typical values for a healthy young adult: renal blood flow, 1200 ml/min (20–25% of cardiac output); renal plasma flow, 660 ml/min; glomerular filtration rate, 125 ml/min.
[b] These are typical figures for an individual eating a Western diet. The kidney excretes more or less of each of these substances to maintain the constancy of the internal milieu, so on a low-sodium diet (for instance in the Yanomami Indians of the upper Amazon basin), NaCl excretion may be reduced to below 10 mmol/day! At the other extreme, individuals living in some fishing communities in Japan eat (and therefore excrete) several hundred mmol/day.
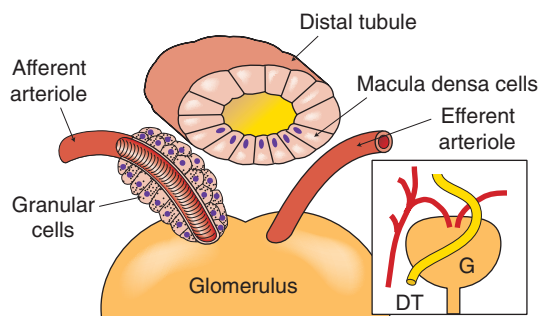

Fig. 28.2   The juxtaglomerular apparatus. The cutaway sections show the granular renin-containing cells round the afferent arteriole, and the macula densa cells in the distal convoluted tubule. The inset shows the general relationships between the structures. DT, distal tubule; G, glomerulus. (Modified from Sullivan & Grantham, 1982.)

glomerular capillaries are impermeable. All the low-molecular-weight constituents of plasma appear in the filtrate, while albumin and larger proteins are retained in the blood.

TUBULAR FUNCTION

The apex (lumenal surface) of each tubular cell is surrounded by a tight junction, as in all epithelia. This is a specialised region of membrane that separates the intercellular space from the lumen. The movement of ions and water across the epithelium can occur *through* cells (the transcellular pathway) and *between* cells through the tight junctions (the paracellular pathway). A common theme is that energy is expended to pump Na^+ out of the cell by Na^+-K^+-ATPase situated in the basolateral cell membrane and the resulting gradient of Na^+ concentration drives the entry of Na^+ from the lumen via various transporters that facilitate Na^+ entry coupled with movement of other ions. These transporters vary in different parts of the nephron as described below.

THE PROXIMAL CONVOLUTED TUBULE

The epithelium of the proximal convoluted tubule is 'leaky', i.e. the tight junctions in the proximal tubule are not so 'tight' after all, being permeable to ions and water, and permitting passive flow in either direction. This prevents the build-up of large concentration gradients; thus, although approximately 60–70% of Na^+ reabsorption occurs in the proximal tubule, this transfer is accompanied by passive absorption of water so that fluid leaving the proximal tubule remains approximately isotonic to the filtrate entering Bowman's capsule.

Some of the transport processes in the proximal tubule are shown in Figures 28.3–28.5. The most important mechanism for Na^+ entry into proximal tubular cells from the filtrate occurs by Na^+/H^+ exchange (Fig. 28.5). Intracellular carbonic anhydrase is essential for production of H^+ for secretion into the lumen. Na^+ is reabsorbed in exchange for H^+, and transported out of the cells into the interstitium and thence into the blood by a Na^+-K^+-ATPase (sodium pump) in the basolateral membrane. This is the main active transport mechanism of the nephron in terms of energy consumption.

▼ Bicarbonate is normally completely reabsorbed in the proximal tubule. This is achieved by combination with protons, yielding carbonic acid, which dissociates to form carbon dioxide and water—a reaction catalysed by carbonic anhydrase present in the lumenal brush border of the proximal tubule cells (Fig. 28.5A)—followed by passive reabsorption of the dissolved carbon dioxide.[1] The selective removal of sodium bicarbonate, with accompanying water, in the early proximal tubule causes a secondary rise in the concentration of chloride ions. Diffusion of chloride down its concentration gradient via the paracellular shunt leads, in turn, to a lumen-positive potential difference that favours reabsorption of sodium. The other mechanism involved in movement via the paracellular route is that sodium ions are secreted by Na^+-K^+-ATPase into the lateral intercellular space, slightly raising its osmolality because of its 3:2 stoichiometry. This leads to osmotic movement of water across the tight junction, in turn causing sodium reabsorption by convection (solvent drag).

Many organic acids and bases are actively secreted into the tubule from the blood by specific transporters (see below, Fig. 28.3 and Ch. 9).

After passage through the proximal tubule, tubular fluid (now 30–40% of the original volume of the filtrate) passes on to the loop of Henle.

THE LOOP OF HENLE, MEDULLARY COUNTER-CURRENT MULTIPLIER AND EXCHANGER

The loop of Henle consists of a descending and an ascending portion (Figs 28.1 and 28.4), the ascending portion having both thick and thin segments. This part of the nephron enables the kidney to excrete urine that is either more or less concentrated than plasma, and hence to regulate the osmotic balance of the body as a whole. The loops of Henle of the juxtamedullary nephrons function as counter-current multipliers, and the vasa recta as counter-current exchangers. NaCl is actively reabsorbed in the thick ascending limb, causing hypertonicity of the interstitium. In the descending limb, water moves out and the tubular fluid becomes progressively more concentrated as it approaches the bend.

▼ The *descending limb* is permeable to water, which exits passively because the interstitial fluid of the medulla is kept hypertonic by the counter-current concentrating system. In juxtamedullary nephrons with long loops, there is extensive movement of water out of the tubule so that the fluid eventually reaching the tip of the loop has a high osmolality—normally approximately 1200 mosmol/kg, but up to 1500 mosmol/kg under conditions of dehydration—compared with plasma and extracellular fluid, which is approximately 300 mosmol/kg.[2] The hypertonic milieu of medulla, through which the collecting ducts of all nephrons pass on the way to the renal pelvis, is important in providing a mechanism by which the osmolarity of the urine is controlled.
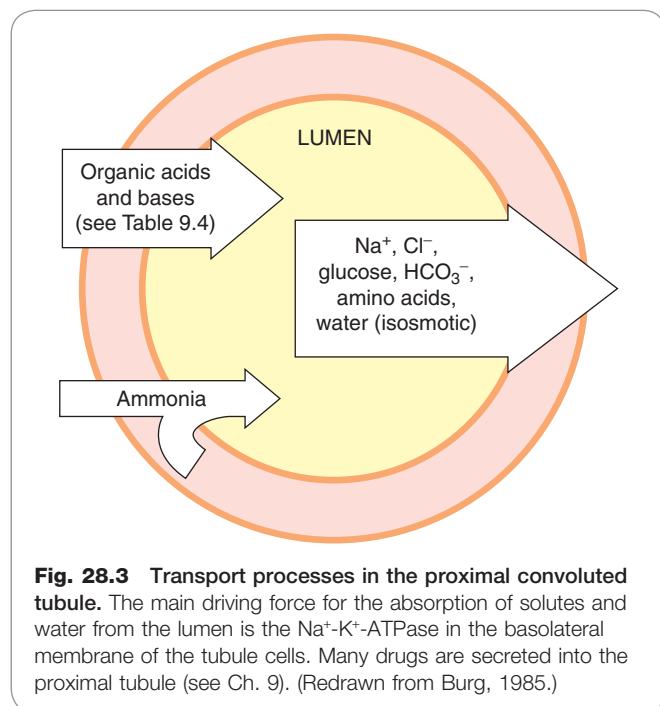

Fig. 28.3 Transport processes in the proximal convoluted tubule. The main driving force for the absorption of solutes and water from the lumen is the Na^+-K^+-ATPase in the basolateral membrane of the tubule cells. Many drugs are secreted into the proximal tubule (see Ch. 9). (Redrawn from Burg, 1985.)

Labels in figure: LUMEN; Organic acids and bases (see Table 9.4); Na^+, Cl^-, glucose, HCO_3^-, amino acids, water (isosmotic); Ammonia

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[1]The reaction is reversible, and the enzyme (as any catalyst) does not alter the equilibrium, just speeds up the rate with which it is attained. The concentrations inside the cell are such that carbon dioxide combines with water to produce carbonic acid: the same enzyme (carbonic anhydrase) catalyses this as well (Fig. 28.5A).

[2]These figures are for humans; some other species, notably the desert rat, can do much better, with urine osmolalities up to 5000 mosmol/kg.

Fig. 28.4 **Schematic showing the absorption of sodium and chloride in the nephron and the main sites of action of drugs.** Cells are depicted as an orange border round the yellow tubular lumen. Mechanisms of ion absorption at the apical margin of the tubule cell: (1) Na$^+$/H$^+$ exchange; (2) Na$^+$/K$^+$/2Cl$^-$ co-transport; (3) Na$^+$/Cl$^-$ co-transport; (4) Na$^+$ entry through sodium channels. Sodium is pumped out of the cells into the interstitium by the Na$^+$-K$^+$-ATPase in the basolateral margin of the tubular cells (not shown). The numbers in the boxes give the concentration of ions as millimoles per litre of filtrate, and the percentage of filtered ions still remaining in the tubular fluid at the sites specified. CT, collecting tubule; DT, distal tubule; PCT, proximal convoluted tubule; TAL, thick ascending loop. (Data from Greger, 2000.)
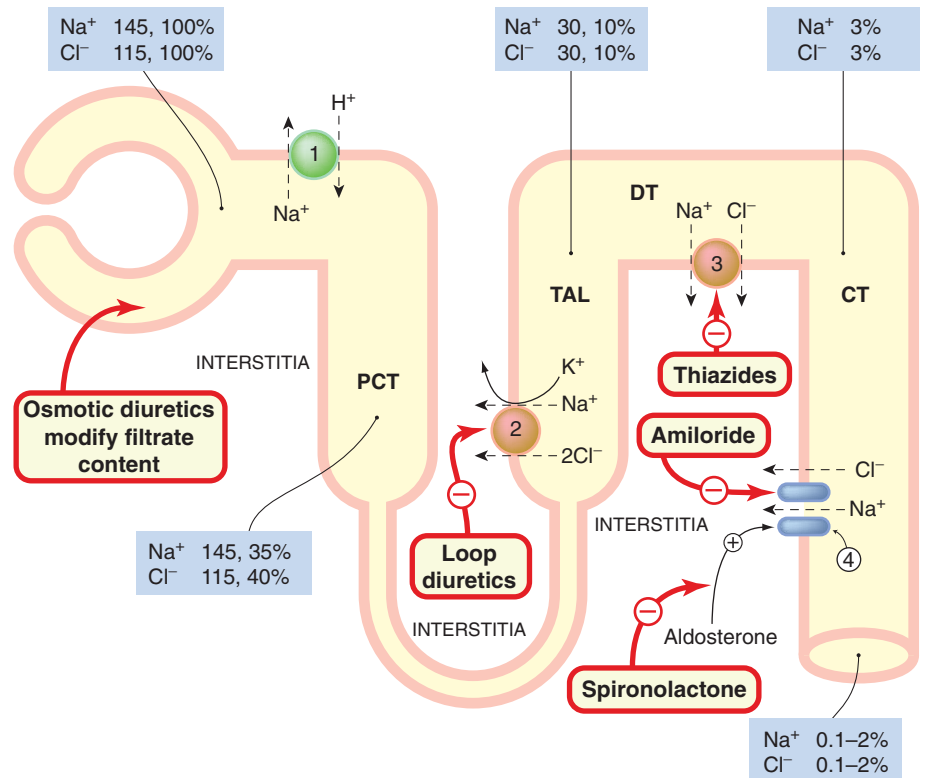
The *ascending limb* has very low permeability to water, i.e. the tight junctions really are 'tight', enabling the build-up of a substantial concentration gradient across the wall of the tubule. It is here, in the thick ascending limb of the loop of Henle, that 20–30% of filtered Na$^+$ is reabsorbed. There is active reabsorption of NaCl, unaccompanied by water, reducing the osmolarity of the tubular fluid and making the interstitial fluid of the medulla hypertonic. The osmotic gradient in the medullary interstitium is the key consequence of the counter-current multiplier system, the main principle being that small horizontal osmotic gradients 'stack up' to produce a large vertical gradient. Urea contributes to the gradient because it is more slowly reabsorbed than water and may be added to fluid in the descending limb, so its concentration rises along the nephron until it reaches the collecting tubules, where it diffuses out into the interstitium. It is thus 'trapped' in the inner medulla.

Ions move into cells of the thick ascending limb of the loop of Henle across the apical membrane by a Na$^+$/K$^+$/2Cl$^-$ co-transporter, driven by the Na$^+$ gradient produced by Na$^+$-K$^+$-ATPase in the basolateral membrane (Fig. 28.5B). Most of the K$^+$ taken into the cell by the Na$^+$/K$^+$/2Cl$^-$ co-transporter returns to the lumen through apical potassium channels, but some K$^+$ is reabsorbed, along with Mg^{2+} and Ca^{2+}.

Reabsorption of salt from the thick ascending limb is not balanced by reabsorption of water, so tubular fluid is hypotonic with respect to plasma as it enters the distal convoluted tubule (Fig. 28.4). The thick ascending limb is therefore sometimes referred to as the 'diluting segment'.

THE DISTAL TUBULE

In the early distal tubule, NaCl reabsorption, coupled with impermeability of the *zonula occludens* to water, further dilutes the tubular fluid. Transport is driven by Na$^+$-K$^+$-ATPase in the basolateral membrane. This lowers cytoplas-

mic Na$^+$ concentration, and consequently Na$^+$ enters the cell from the lumen down its concentration gradient, accompanied by Cl$^-$, by means of a Na$^+$/Cl$^-$ co-transporter (Fig. 28.5C).

The excretion of Ca^{2+} is regulated in this part of the nephron, *parathormone* and *calcitriol* both increasing Ca^{2+} reabsorption (see Ch. 35).

THE COLLECTING TUBULE AND COLLECTING DUCT

Distal convoluted tubules empty into collecting tubules, which coalesce to form collecting ducts (Fig. 28.1). Collecting tubules include principal cells, which reabsorb Na$^+$ and secrete K$^+$ (Fig. 28.5D), and two populations of intercalated cells, α and β, which secrete acid and base, respectively.

The tight junctions in this portion of the nephron are impermeable to water and ions. The movement of ions and water in this segment is under independent hormonal control: absorption of NaCl by *aldosterone* (Ch. 22), and absorption of water by *antidiuretic hormone* (ADH), also termed *vasopressin* (Ch. 32).

Aldosterone enhances Na$^+$ reabsorption and promotes K$^+$ excretion. It promotes Na$^+$ reabsorption by:

- a rapid effect, stimulating Na$^+$/H$^+$ exchange by an action on membrane aldosterone receptors[3]
- a delayed effect, via nuclear receptors (see Ch. 3), directing the synthesis of a specific protein mediator that activates sodium channels in the apical membrane (Fig. 28.5D)

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[3]A mechanism distinct from regulation of gene transcription, which is the normal transduction mechanism for steroid hormones (Ch. 3).
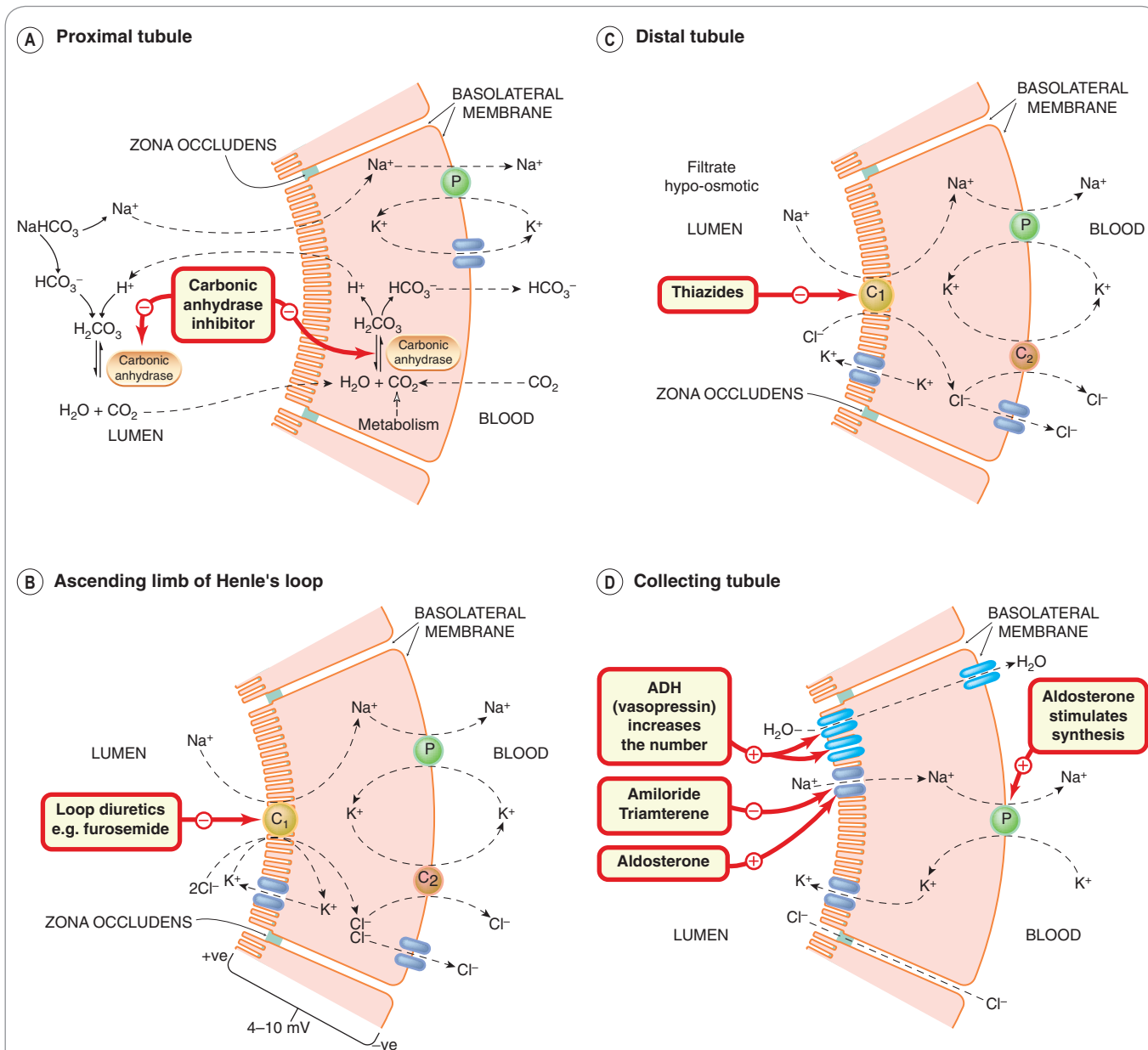
A Proximal tubule

B Ascending limb of Henle's loop

C Distal tubule

D Collecting tubule

Fig. 28.5 **Drug effects on renal tubular ion transport.** The primary active transport mechanism is the Na^+ pump (P) in the basolateral membrane. The diagram is simplified: the Na^+ pump (in each panel) exchanges $3Na^+$ for $2K^+$. [**A**] Bicarbonate ion reabsorption in the proximal convoluted tubule, showing the action of carbonic anhydrase inhibitors. Sodium ions are absorbed and H^+ secreted at the lumenal surface by an antiport mechanism (Na^+/H^+ exchanger). [**B**] Ion transport in the thick ascending limb of Henle's loop, showing the site of action of loop diuretics. Na^+, K^+ and Cl^- enter by a co-transport system (C_1). Chloride leaves the cell both through basolateral chloride channels and by an electroneutral K^+/Cl^- co-transport system (C_2). Some K^+ returns to the lumen via potassium channels in the apical membrane, and some Na^+ is absorbed paracellularly through the zonula occludens. [**C**] Salt transport in the distal convoluted tubule, showing the site of action of thiazide diuretics. Sodium and chloride ions enter by an electroneutral co-transport carrier (C_1). Some Cl^- is transported out of the cell by a K^+/Cl^- co-transport carrier (C_2); some leaves the cell through chloride channels. Some K^+ is transported out of the cell by the co-transport carrier (C_2), and some passes back into the tubule lumen through potassium channels. [**D**] Actions of hormones and drugs on the collecting tubule. The cells are impermeable to water in the absence of antidiuretic hormone (ADH), and to Na^+ in the absence of aldosterone. Aldosterone acts on a nuclear receptor within the tubule cell and on membrane receptors. Chloride ions exit the tubule through the paracellular pathway. Potassium ions are added to the filtrate, as is H^+ (not shown). (Adapted from Greger, 2000.)

• long-term effects, by increasing the number of basolateral Na^+ pumps (Fig. 28.5D).

ADH and nephrogenic diabetes insipidus. ADH is secreted by the posterior pituitary (Ch. 32) and binds V_2 receptors in the basolateral membranes of cells in the col-

lecting tubules and ducts, increasing expression of *aquaporin* (water channels; see Ch. 8) in the apical membranes (Fig. 28.5D). This renders this part of the nephron permeable to water, allowing passive reabsorption of water as the collecting duct traverses the hyperosmotic region of the medulla, and hence the excretion of concentrated urine.

Conversely, in the absence of ADH, collecting duct epithelium is impermeable to water, so hypotonic fluid that leaves the distal tubule remains hypotonic as it passes down the collecting ducts, leading to the excretion of dilute urine. Defective ADH secretion (Ch. 32) or action on the kidney results in *diabetes insipidus*, a disorder in which patients excrete large volumes of dilute urine.

Ethanol (Ch. 48) inhibits the secretion of ADH, causing a water diuresis (possibly familiar to some of our readers) as a kind of transient diabetes insipidus. **Nicotine** enhances ADH secretion (perhaps contributing to the appeal of an after-dinner cigar?).

Several drugs inhibit the action of ADH: **lithium** (used in psychiatric disorders; see Ch. 45), **demeclocycline** (a tetracycline used not as an antibiotic, but rather to treat inappropriate secretion of ADH from tumours or in other conditions), **colchicine** (Ch. 26) and *vinca alkaloids* (Ch. 55). Recently, more specific antagonists of ADH (e.g. **conivaptan**,

> ### Renal tubular function
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> - Protein-free glomerular filtrate enters via Bowman's capsule.
> - Na^+-K^+-ATPase in the basolateral membrane is the main active transporter. It provides the gradients for passive transporters in the apical membranes.
> - 60–70% of the filtered Na^+ and > 90% of HCO_3^- is absorbed in the proximal tubule.
> - Carbonic anhydrase is key for $NaHCO_3$ reabsorption and distal tubular urine acidification.
> - The thick ascending limb of Henle's loop is impermeable to water; 20–30% of the filtered NaCl is actively reabsorbed in this segment.
> - Ions are reabsorbed from tubular fluid by a $Na^+/K^+/2Cl^-$ co-transporter in the apical membranes of the thick ascending limb.
> - $Na^+/K^+/2Cl^-$ co-transport is inhibited by loop diuretics.
> - Filtrate is diluted as it traverses the thick ascending limb as ions are reabsorbed, so that it is hypotonic when it leaves.
> - The tubular counter-current multiplier actively generates a concentration gradient—small horizontal differences in solute concentration between tubular fluid and interstitium are multiplied vertically. The deeper in the medulla, the more concentrated is the interstitial fluid.
> - Medullary hypertonicity is preserved passively by counter-current exchange in the vasa recta.
> - Na^+/Cl^- co-transport (inhibited by thiazide diuretics) reabsorbs 5–10% of filtered Na^+ in the distal tubule.
> - K^+ is secreted into tubular fluid in the distal tubule and the collecting tubules and collecting ducts.
> - In the absence of antidiuretic hormone (ADH), the collecting tubule and collecting duct have low permeability to salt and water. ADH increases water permeability.
> - Na^+ is reabsorbed from the collecting duct through epithelial sodium channels.
> - These are stimulated by aldosterone and inhibited by **amiloride**. K^+ or H^+ is secreted into the tubule in exchange for Na^+ in this distal region.

tolvaptan) have been introduced for treatment of hyponatraemia (see Ch. 22). All these drugs can cause acquired forms of *nephrogenic* diabetes insipidus, caused by a failure of the renal collecting ducts to respond to ADH. Nephrogenic diabetes insipidus can also be caused by two genetic disorders affecting the V_1 receptor or aquaporin.

ACID–BASE BALANCE

The kidneys (together with the lungs; Ch. 27) regulate the H^+ concentration of body fluids. Acid or alkaline urine can be excreted according to need, the usual requirement being to form acid urine to eliminate phosphoric and sulfuric acids generated during the metabolism of nucleic acids, and sulfur-containing amino acids consumed in the diet. Consequently, metabolic acidosis is a common accompaniment of renal failure. Altering urine pH to alter drug excretion is mentioned below.

POTASSIUM BALANCE

Extracellular K^+ concentration—critically important for excitable tissue function (see Ch. 4)—is tightly controlled through regulation of K^+ excretion by the kidney. Urinary K^+ excretion matches dietary intake, usually approximately 50–100 mmol in 24 h in Western countries. Most diuretics cause K^+ loss (see below). This can cause problems if they are co-administered with cardiac glycosides or class III antidysrhythmic drugs whose toxicity is increased by low plasma K^+ (Ch. 22)—clinically important drug interactions (see Ch. 56).

Potassium ions are transported into collecting duct and collecting tubule cells from blood and interstitial fluid by Na^+-K^+-ATPase in the basolateral membrane, and leak into the lumen through a K^+-selective ion channel. Na^+ passes from tubular fluid through sodium channels in the apical membrane down the electrochemical gradient created by the Na^+-K^+-ATPase; a lumen-negative potential difference across the cell results, increasing the driving force for K^+ secretion into the lumen. Thus K^+ secretion is coupled to Na^+ reabsorption.

Consequently, K^+ is lost when:

- more Na^+ reaches the collecting duct, as occurs with any diuretic acting proximal to the collecting duct
- Na^+ reabsorption in the collecting duct is increased directly (e.g. in hyperaldosteronism).

K^+ is retained when:

- Na^+ reabsorption in the collecting duct is decreased, for example by **amiloride** or **triamterene**, which block the sodium channel in this part of the nephron, or **spironolactone** or **eplerenone**, which antagonise aldosterone (see below).

EXCRETION OF ORGANIC MOLECULES

There are distinct mechanisms (see Ch. 9, Table 9.4) for secreting organic anions and cations into the proximal tubular lumen. Secreted anions include several important drugs, for example *thiazides*, **furosemide**, **salicylate** (Ch. 26), and most *penicillins* and *cephalosporins* (Ch. 50). Similarly, several secreted organic cations are important drugs, for example **triamterene**, **amiloride**, **atropine** (Ch. 13), **morphine** (Ch. 41) and **quinine** (Ch. 53). Both anion and cation transport mechanisms are, like other renal ion

transport processes, indirectly powered by active transport of Na^+ and K^+, the energy being derived from Na^+-K^+-ATPase in the basolateral membrane.

Organic anions are exchanged with α-ketoglutarate by an antiport in the basolateral membrane, and diffuse passively into the tubular lumen (Fig. 28.3).

Organic cations diffuse into the cell from the interstitium and are then actively transported into the tubular lumen in exchange for H^+.

NATRIURETIC PEPTIDES

Endogenous A, B and C natriuretic peptides (ANP, BNP and CNP; see Chs 21 and 22) are involved in the regulation of Na^+ excretion. They are released from the heart in response to stretch (A and B), from endothelium (C) and from brain (B). They activate guanylyl cyclase (Ch. 3), and cause natriuresis both by renal haemodynamic effects (increasing glomerular capillary pressure by dilating afferent and constricting efferent arterioles) and by direct tubular actions. The tubular actions include the inhibition of angiotensin II-stimulated Na^+ and water reabsorption in the proximal convoluted tubule, and of the action of ADH in promoting water reabsorption in the collecting tubule.

Within the kidney, the post-translational processing of ANP prohormone differs from that in other tissues, resulting in an additional four amino acids being added to the amino terminus of ANP to yield a related peptide, *urodilatin*, that promotes Na^+ excretion by acting on receptors on the lumenal side of the collecting duct cells.

PROSTAGLANDINS AND RENAL FUNCTION

Prostaglandins (PGs; see Ch. 17) generated in the kidney modulate its haemodynamic and excretory functions. The main renal prostaglandins in humans are vasodilator and natriuretic, namely PGE_2 in the medulla and PGI_2 (prostacyclin) in glomeruli. Factors that stimulate their synthesis include ischaemia, angiotensin II, ADH and bradykinin.

Prostaglandin biosynthesis is low under basal conditions. However, when vasoconstrictors (e.g. angiotensin II, noradrenaline) are released, PGE_2 and PGI_2 modulate their effects on the kidney by causing compensatory vasodilatation.

The influence of renal prostaglandins on salt balance and haemodynamics can be inferred from the effects of non-steroidal anti-inflammatory drugs (NSAIDs, which inhibit prostaglandin production; see Ch. 26). NSAIDs have little or no effect on renal function in healthy people, but predictably cause acute renal failure in clinical conditions in which renal blood flow depends on vasodilator prostaglandin biosynthesis. These include cirrhosis of the liver, heart failure, nephrotic syndrome, glomerulonephritis and extracellular volume contraction (see Ch. 57, Table 57.1). NSAIDs increase blood pressure in patients treated for hypertension by impairing PG-mediated vasodilatation and salt excretion. They exacerbate salt and water retention in patients with heart failure (see Ch. 22), partly by this same direct mechanism.[4]

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[4]Additionally, NSAIDs make many of the diuretics used to treat heart failure less effective by competing with them for the organic anion transport (OAT) mechanism mentioned above; loop diuretics and thiazides act from within the lumen by inhibiting exchange mechanisms—see later in this chapter—so blocking their secretion into the lumen reduces their effectiveness by reducing their concentrations at their sites of action.

DIURETICS

Diuretics increase the excretion of Na^+ and water. They decrease the reabsorption of Na^+ and (usually) Cl^- from the filtrate, increased water loss being secondary to the increased excretion of NaCl (natriuresis). This can be achieved:

- by a direct action on the cells of the nephron
- indirectly, by modifying the content of the filtrate.

Because a very large proportion of salt (NaCl) and water that passes into the tubule via the glomerulus is reabsorbed (Table 28.1), a small decrease in reabsorption can cause a marked increase in Na^+ excretion. A summary diagram of the mechanisms and sites of action of various diuretics is given in Figure 28.4 and more detailed information on different classes of drugs in Figure 28.5.

Most diuretics with a direct action on the nephron act from within the tubular lumen and reach their sites of action by being secreted into the proximal tubule (**spironolactone** is an exception).

DIURETICS ACTING DIRECTLY ON CELLS OF THE NEPHRON

The main therapeutically useful diuretics act on the:

- thick ascending loop of Henle
- early distal tubule
- collecting tubules and ducts.

For a more detailed review of the actions and clinical uses of the diuretics, see Greger et al. (2005).

Loop diuretics

Loop diuretics (Fig. 28.5B) are the most powerful diuretics (see Fig. 28.6 for a comparison with thiazides), capable of causing the excretion of 15–25% of filtered Na^+. Their action is often described—in a phrase that conjures up a rather uncomfortable picture—as causing 'torrential urine flow'. The main example is **furosemide**; **bumetanide** is an alternative agent. These drugs act on the thick ascending limb, inhibiting the $Na^+/K^+/2Cl^-$ carrier in the lumenal membrane by combining with its Cl^- binding site.

Loop diuretics also have incompletely understood vascular actions. Intravenous administration of furosemide to patients with pulmonary oedema caused by acute heart failure (see Ch. 22) causes a therapeutically useful vasodilator effect before the onset of diuresis. Possible mechanisms that have been invoked include decreased vascular responsiveness to vasoconstrictors such as angiotensin II and noradrenaline; increased formation of vasodilating prostaglandins (see above); decreased production of the endogenous ouabain-like natriuretic hormone (Na^+-K^+-ATPase inhibitor; see Ch. 21), which has vasoconstrictor properties; and potassium channel-opening effects in resistance arteries (see Greger et al., 2005).

Loop diuretics increase the delivery of Na^+ to the distal nephron, causing loss of H^+ and K^+. Because Cl^- but not HCO_3^- is lost in the urine, the plasma concentration of HCO_3^- increases as plasma volume is reduced—a form of metabolic alkalosis therefore referred to as 'contraction alkalosis'.

Loop diuretics increase excretion of Ca^{2+} and Mg^{2+} and decrease excretion of uric acid.
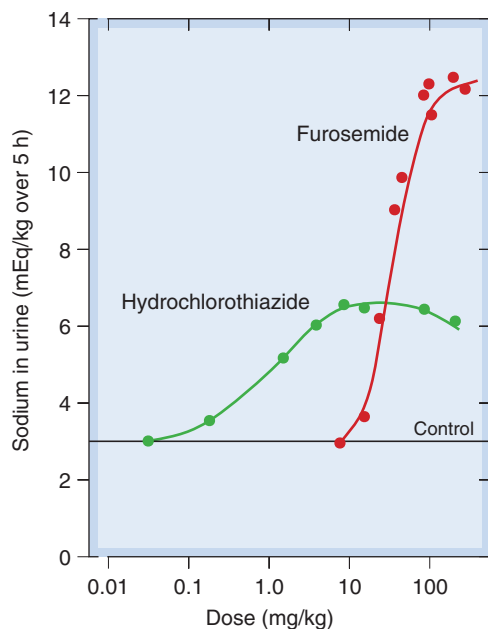
Fig. 28.6 Dose–response curves for furosemide (frusemide) and hydrochlorothiazide, showing differences in potency and maximum effect 'ceiling'. Note that these doses are not used clinically. (Adapted from Timmerman R J et al. 1964 Curr Ther Res 6: 88.)

> **Clinical uses of loop diuretics (e.g. furosemide)**
>
> - Loop diuretics are used (cautiously!), in conjunction with dietary salt restriction and often with other classes of diuretic, in the treatment of salt and water overload associated with:
>   – *acute pulmonary oedema*
>   – *chronic heart failure*
>   – *cirrhosis* of the liver complicated by *ascites*
>   – *nephrotic syndrome*
>   – *renal failure*.
> - Treatment of *hypertension* complicated by renal impairment (thiazides are preferred if renal function is preserved).
> - Treatment of *hypercalcaemia* after replacement of plasma volume with intravenous NaCl solution.

Pharmacokinetic aspects

Loop diuretics are absorbed from the gastrointestinal tract, and are usually given by mouth. They may also be given intravenously in urgent situations (e.g. acute pulmonary oedema) or when intestinal absorption is impaired, for example as a result of reduced intestinal perfusion in patients with chronic congestive heart failure, who can become resistant to the action of orally administered diuretics. Given orally, they act within 1 h; given intravenously, they produce a peak effect within 30 min. Loop diuretics are strongly bound to plasma protein, and so do not pass directly into the glomerular filtrate. They reach their site of action—the lumenal membrane of the cells of the thick ascending limb—by being secreted in the proximal convoluted tubule by the organic acid transport mechanism; the fraction thus secreted is excreted in the urine.

In nephrotic syndrome,[5] loop diuretics become bound to albumin in the tubular fluid, and consequently are not available to act on the $Na^+/K^+/2Cl^-$ carrier—another cause of diuretic resistance. Molecular variation in the $Na^+/K^+/2Cl^-$ carrier may also be important in some cases of diuretic resistance (Shankar & Brater, 2003).

The fraction not excreted in the urine is metabolised, mainly in liver—**bumetanide** by cytochrome P450 pathways and **furosemide** being glucuronidated. The plasma half-lives of both these drugs are approximately 90 min (longer in renal failure), and the durations of action 3–6 h. The clinical use of loop diuretics is given in the box.

Unwanted effects

Unwanted effects directly related to the renal action of loop diuretics are common.[6] Excessive Na^+ and water loss are common, especially in elderly patients, and can cause hypovolaemia and hypotension. Potassium loss, resulting in low plasma K^+ (hypokalaemia), and metabolic alkalosis are common. Hypokalaemia increases the effects and toxicity of several drugs (e.g. **digoxin** and type III antidysrhythmic drugs, Ch. 21), so this is potentially a clinically important source of drug interaction (Ch. 56). If necessary, hypokalaemia can be averted or treated by concomitant use of K^+-sparing diuretics (see below), sometimes with supplementary potassium replacement. Hypomagnesaemia is less often recognised but can also be clinically important. Hyperuricaemia is common and can precipitate acute gout (see Ch. 26). Excessive diuresis leads to reduced renal perfusion and pre-renal renal impairment (an early warning of this is a rise in serum urea concentration).

Unwanted effects *unrelated to the renal actions* of the drugs are infrequent. Dose-related hearing loss (compounded by concomitant use of other ototoxic drugs such as aminoglycoside antibiotics) can result from impaired ion transport by the basolateral membrane of the stria vascularis in the inner ear. It occurs only at much higher doses than usually needed to produce diuresis. Idiosyncratic allergic reactions (e.g. rashes, bone marrow depression) are uncommon.

Diuretics acting on the distal tubule

Diuretics acting on the distal tubule include thiazides (e.g. **bendroflumethiazide**, **hydrochlorothiazide**) and related drugs (e.g. **chlortalidone**, **indapamide** and **metolazone**; see Fig. 28.5C).

Thiazides are less powerful than loop diuretics but are preferred in treating uncomplicated hypertension (Ch. 22). They are better tolerated than loop diuretics, and in clinical trials have been shown to reduce risks of stroke and heart attack associated with hypertension. In the largest trial

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[5]Several diseases that damage renal glomeruli impair their ability to retain plasma albumin, causing massive loss of albumin in the urine and a reduced concentration of albumin in the plasma, which can in turn cause peripheral oedema. This is referred to as nephrotic syndrome.

[6]Such unwanted effects are re-enacted in extreme form in Bartter syndrome type 1, a rare autosomal recessive single gene disorder of the $Na^+/K^+/2Cl^-$ transporter, whose features include polyhydramnios—caused by fetal polyuria—and, postnatally, renal salt loss, low blood pressure, hypokalaemic metabolic alkalosis and hypercalciuria.

(ALLHAT 2002), chlortalidone performed as well as newer antihypertensive drugs (an angiotensin-converting enzyme [ACE] inhibitor and a calcium antagonist). They bind to the Cl^- site of the distal tubular Na^+/Cl^- co-transport system, inhibiting its action and causing natriuresis with loss of sodium and chloride ions in the urine. The resulting contraction in blood volume stimulates renin secretion, leading to angiotensin formation and aldosterone secretion (Ch. 22, see Figs 22.4 and 22.9). This homeostatic mechanism limits the effect of the diuretic on the blood pressure, resulting in an in vivo dose–hypotensive response relationship with only a gentle gradient during chronic dosing.

Effects of thiazides on Na^+, K^+, H^+ and Mg^{2+} balance are qualitatively similar to those of loop diuretics, but smaller in magnitude. In contrast to loop diuretics, however, thiazides reduce Ca^{2+} excretion, which may be advantageous in older patients at risk of osteoporosis. This could favour thiazides over loop diuretics in terms of bone metabolism during long-term use in older patients (Schoofs et al., 2003).

Although thiazides are milder than loop diuretics when used alone, co-administration with loop diuretics has a synergistic effect, because the loop diuretic delivers a greater fraction of the filtered load of Na^+ to the site of action of the thiazide in the distal tubule.

Thiazide diuretics have a vasodilator action (see Chs 4 and 22). When used in the treatment of hypertension (Ch. 22), the initial fall in blood pressure results from the decreased blood volume caused by diuresis, but vasodilatation contributes to the later phase.

Thiazide diuretics have a paradoxical effect in diabetes insipidus, where they *reduce* the volume of urine by interfering with the production of hypotonic fluid in the distal tubule, and hence reduce the ability of the kidney to excrete hypotonic urine (i.e. they reduce free water clearance).

Pharmacokinetic aspects

Thiazides and related drugs are effective orally. All are excreted in the urine, mainly by tubular secretion, and they compete with uric acid for the organic anion transporter (OAT; see Ch. 9). **Bendroflumethiazide** has its maximum effect at about 4–6 h and duration is 8–12 h. **Chlortalidone** has a longer duration of action.

The clinical use of thiazide diuretics is given in the clinical box.

Unwanted effects

Apart from an increase in *urinary frequency*, the commonest unwanted effect (not obviously related to the main renal actions of the thiazides) is *erectile dysfunction*. This emerged in an analysis of reasons given by patients for withdrawing

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Clinical uses of thiazide diuretics (e.g. bendroflumethiazide)

- *Hypertension*.
- Mild *heart failure* (loop diuretics are usually preferred).
- Severe resistant *oedema* (**metolazone**, especially, is used, together with loop diuretics).
- To prevent recurrent stone formation in *idiopathic hypercalciuria*.
- *Nephrogenic diabetes insipidus*.

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from blinded treatment in the Medical Research Council mild hypertension trial, where (to the surprise of the investigators) erectile dysfunction was substantially more common than in men allocated to a β-adrenoceptor antagonist or to placebo. Thiazide-associated erectile dysfunction is reversible; it is less common with the low doses used in current practice but remains a problem. *Potassium loss* can be important, as can loss of Mg^{2+}. Excretion of uric acid is decreased, and hypochloraemic alkalosis can occur.

Impaired glucose tolerance (see Ch. 30), due to inhibition of insulin secretion, is thought to result from activation of K_{ATP} channels in pancreatic islet cells.[7] **Diazoxide**, a non-diuretic thiazide, also activates K_{ATP} channels, causing vasodilatation and impaired insulin secretion. **Indapamide** is said to lower blood pressure with less metabolic disturbance than related drugs, possibly because it is marketed at a lower equivalent dose.

Hyponatraemia is potentially serious, especially in the elderly. Hypokalaemia can be a cause of adverse drug interaction (see above under Loop diuretics) and can precipitate encephalopathy in patients with severe liver disease.

Idiosyncratic reactions (e.g. rashes, blood dyscrasias) are rare but can be serious.

Aldosterone antagonists

Spironolactone and **eplerenone** (Weinberger, 2004) have very limited diuretic action when used singly, because distal Na^+/K^+ exchange—the site on which they act (Fig. 28.5D)—accounts for reabsorption of only 2% of filtered Na^+. They do, however, have marked antihypertensive effects (Ch. 22), prolong survival in selected patients with heart failure (Ch. 22) and can prevent hypokalaemia when combined with loop diuretics or with thiazides. They compete with aldosterone for its intracellular receptor (see Ch. 32), thereby inhibiting distal Na^+ retention and K^+ secretion (see Fig. 28.5D).

Pharmacokinetic aspects

Spironolactone is well absorbed from the gut. Its plasma half-life is only 10 min, but its active metabolite, **canrenone**, has a plasma half-life of 16 h. The action of spironolactone is largely attributable to canrenone. Consistent with this, its onset of action is slow, taking several days to develop. Eplerenone has a shorter elimination half-life than canrenone and has no active metabolites. It is administered by mouth once daily.

Unwanted effects

Aldosterone antagonists predispose to hyperkalaemia, which is potentially fatal. Potassium supplements should not be co-prescribed, and close monitoring of plasma creatinine and electrolytes is needed if these drugs are used for patients with impaired renal function, especially if other drugs that can increase plasma potassium, such as *ACE inhibitors*, *angiotensin receptor antagonists* (sartans) (Ch. 22) or *β-adrenoceptor antagonists* (Ch. 14) are also prescribed—as they often are for patients with heart failure. Gastrointestinal upset is quite common. Actions of spironolactone/canrenone on progesterone and androgen receptors in tissues other than the kidney can result in

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[7]The chemically related sulfonylurea group of drugs used to treat diabetes mellitus (Ch. 30) act in the opposite way, by closing K_{ATP} channels and enhancing insulin secretion.

> **Clinical uses of potassium-sparing diuretics (e.g. amiloride, spironolactone)**
>
> - With K⁺-losing (i.e. loop or thiazide) diuretics to prevent K⁺ loss, where hypokalaemia is especially hazardous (e.g. patients requiring **digoxin** or **amiodarone**; see Ch. 21).
> - **Spironolactone** or **eplerenone** is used in:
>   - *heart failure*, to improve survival (see Ch. 21)
>   - *primary hyperaldosteronism* (Conn's syndrome)
>   - *resistant essential hypertension* (especially low-renin hypertension)
>   - *secondary hyperaldosteronism* caused by hepatic cirrhosis complicated by ascites.

gynaecomastia, menstrual disorders and testicular atrophy. Eplerenone has lower affinity for these receptors, and such oestrogen-like side effects are less common with licensed doses of this drug.

The clinical use of potassium-sparing diuretics is given in the clinical box.

Triamterene and amiloride

Like aldosterone antagonists, **triamterene** and **amiloride** have only limited diuretic efficacy, because they also act in the distal nephron, where only a small fraction of Na⁺ reabsorption occurs. They act on the collecting tubules and collecting ducts, inhibiting Na⁺ reabsorption by blocking lumenal sodium channels (see Ch. 4) and decreasing K⁺ excretion (see Fig. 28.5D).

They can be given with loop diuretics or thiazides in order to maintain potassium balance.

Pharmacokinetic aspects

Triamterene is well absorbed in the gastrointestinal tract. Its onset of action is within 2 h, and its duration of action 12–16 h. It is partly metabolised in the liver and partly excreted unchanged in the urine. Amiloride is less well absorbed and has a slower onset, with a peak action at 6 h and duration of about 24 h. Most of the drug is excreted unchanged in the urine.

Unwanted effects

The main unwanted effect, hyperkalaemia, is related to the pharmacological action of these drugs and can be dangerous, especially in patients with renal impairment or receiving other drugs that can increase plasma K⁺ (see above). Gastrointestinal disturbances have been reported but are infrequent. Triamterene has been identified in kidney stones, but its aetiological role is uncertain. Idiosyncratic reactions, for example rashes, are uncommon.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (Fig. 28.5A)—for example **acetazolamide**—increase excretion of bicarbonate with accompanying Na⁺, K⁺ and water, resulting in an increased flow of an alkaline urine and metabolic acidosis. These agents, although not now used as diuretics, are still used in the treatment of glaucoma to reduce the formation of aqueous humour (Ch. 13), and also in some types of infantile epilepsy (Ch. 44).

Urinary loss of bicarbonate depletes extracellular bicarbonate, and the diuretic effect of carbonic anhydrase inhibitors is consequently self-limiting.

DIURETICS THAT ACT INDIRECTLY BY MODIFYING THE CONTENT OF THE FILTRATE

Osmotic diuretics

Osmotic diuretics are pharmacologically inert substances (e.g. **mannitol**) that are filtered in the glomerulus but not reabsorbed by the nephron (see Fig. 28.4).[8] To cause a diuresis, they must constitute an appreciable fraction of the osmolarity of tubular fluid. Within the nephron, their main effect is exerted on those parts of the nephron that are freely permeable to water: the proximal tubule, descending limb of the loop and (in the presence of ADH; see above) the collecting tubules. Passive water reabsorption is reduced by the presence of non-reabsorbable solute within the tubule; consequently a larger volume of fluid remains within the proximal tubule. This has the secondary effect of reducing Na⁺ reabsorption.

Therefore the main effect of osmotic diuretics is to increase the amount of water excreted, with a smaller increase in Na⁺ excretion. They are sometimes used in acute renal failure, which can occur as a result of haemorrhage, injury or systemic infections. Glomerular filtration rate is reduced, and absorption of NaCl and water in the proximal tubule becomes almost complete, so that more distal parts of the nephron virtually 'dry up', and urine flow ceases. Protein is deposited in the tubules and may impede the flow of fluid. Osmotic diuretics (e.g. **mannitol** given intravenously in a dose of 12–15 g) can limit these effects, at least if given in the earliest stages, albeit while increasing intravascular volume and risking left ventricular failure.

They are also used for the emergency treatment of acutely raised intracranial or intraocular pressure. Such treatment has nothing to do with the kidney, but relies on the increase in plasma osmolarity by solutes that do not enter the brain or eye, which results in efflux of water from these compartments.

Unwanted effects include transient expansion of the extracellular fluid volume (with a risk of causing left ventricular failure) and hyponatraemia. Headache, nausea and vomiting can occur.

DRUGS THAT ALTER THE pH OF THE URINE

It is possible, by the use of pharmacological agents, to produce urinary pH values ranging from approximately 5 to 8.5.

Carbonic anhydrase inhibitors increase urinary pH by blocking bicarbonate reabsorption (see above). **Citrate** (given by mouth as a mixture of sodium and potassium salts) is metabolised via the Krebs cycle with generation of bicarbonate, which is excreted, alkalinising the urine. This may have some antibacterial effects, as well as improving dysuria (a common symptom of bladder infection, consisting of a burning sensation while passing urine). Additionally, some citrate is excreted in the urine as such and

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[8]In hyperglycaemia, glucose acts as an osmotic diuretic once plasma glucose exceeds the renal reabsorptive threshold (usually approximately 12 mmol/l), accounting for the cardinal symptom of polyuria in diabetes mellitus; see Chapter 30.

Diuretics

- Normally < 1% of filtered Na^+ is excreted.
- Diuretics increase the excretion of salt (NaCl or $NaHCO_3$) and water.
- Loop diuretics, thiazides and K^+-sparing diuretics are the main therapeutic drugs.
- Loop diuretics (e.g. **furosemide**) cause copious urine production. They inhibit the $Na^+/K^+/2Cl^-$ co-transporter in the thick ascending loop of Henle. They are used to treat heart failure and other diseases complicated by salt and water retention. Hypovolaemia and hypokalaemia are important unwanted effects.
- Thiazides (e.g. **bendroflumethiazide**) are less potent than loop diuretics. They inhibit the Na^+/Cl^- co-transporter in the distal convoluted tubule. They are used to treat hypertension. Erectile dysfunction is an important adverse effect. Hypokalaemia and other metabolic effects can occur.
- Potassium-sparing diuretics:
  - act in the distal nephron and collecting tubules; they are very weak diuretics but effective in some forms of hypertension and heart failure, and they can prevent hypokalaemia caused by loop diuretics or thiazides
  - **spironolactone** and **eplerenone** compete with aldosterone for its receptor
  - **amiloride** and **triamterene** act by blocking the sodium channels controlled by aldosterone's protein mediator.

inhibits urinary stone formation. Alkalinisation is important in preventing certain weak acid drugs with limited aqueous solubility, such as *sulfonamides* (see Ch. 50), from crystallising in the urine; it also decreases the formation of uric acid and cystine stones by favouring the charged anionic form that is more water soluble (Ch. 8).

Alkalinising the urine increases the excretion of drugs that are weak acids (e.g. salicylates and some barbiturates). Sodium bicarbonate is sometimes used to treat salicylate overdose (Ch. 9).

Urinary pH can be decreased with **ammonium chloride**, but this is now rarely, if ever, used clinically except in a specialised test to discriminate between different kinds of renal tubular acidosis.

DRUGS THAT ALTER THE EXCRETION OF ORGANIC MOLECULES

Uric acid metabolism and excretion are relevant in the treatment and prevention of gout (Ch. 26), and a few points about its excretion are made here.

Uric acid is derived from the catabolism of purines, and is present in plasma mainly as ionised urate. In humans, it passes freely into the glomerular filtrate, and most is then reabsorbed in the proximal tubule while a small amount is secreted into the tubule by the anion-secreting mechanism. The net result is excretion of approximately 8–12% of filtered urate. The secretory mechanism is generally inhibited by low doses of drugs that affect uric acid transport (see below), whereas higher doses are needed to block reabsorption. Such drugs therefore tend to cause retention of uric acid at low doses, while promoting its excretion at higher doses. Normal plasma urate concentration is approximately 0.24 mmol/l. In some individuals, the plasma concentration is high, predisposing to gout. In this disorder, urate crystals are deposited in joints and soft tissues,[9] resulting in acute arthritis and, if untreated, chronic chalky deposits—'tophi'—characteristic of this condition. Drugs that increase the elimination of urate (*uricosuric agents*, e.g. **probenecid** and **sulfinpyrazone**) may be useful in such patients, although these have largely been supplanted by **allopurinol**, which inhibits urate synthesis (Ch. 26).

Probenecid inhibits the reabsorption of urate in the proximal tubule, increasing its excretion. It has the opposite effect on penicillin, inhibiting its secretion into the tubules and raising its plasma concentration. Given orally, probenecid is well absorbed in the gastrointestinal tract, maximal concentrations in the plasma occurring in about 3 h. Approximately 90% is bound to plasma albumin. Free drug passes into the glomerular filtrate but more is actively secreted into the proximal tubule, whence it may diffuse back because of its high lipid solubility (see also Ch. 9). Sulfinpyrazone acts similarly.

The main effect of uricosuric drugs is to block urate reabsorption and lower plasma urate concentration. Both probenecid and sulfinpyrazone inhibit the secretion as well as the reabsorption of urate and, if given in subtherapeutic doses, can actually increase plasma urate concentrations.

Aspirin (and other salicylates such as **sulfasalazine**), also inhibits urate secretion in normal analgesic doses, increasing blood urate concentration, which may exacerbate gouty arthritis (see Ch. 26). (But salicylates become uricosuric themselves at the very high doses used in the past to treat rheumatoid arthritis.)

Probenicid, as specified above, inhibits penicillin excretion, and at one time was used to enhance the action of penicillin (e.g. in single-dose treatment of gonorrhoea). It is licensed in the UK to prevent nephrotoxicity caused by **cidofovir** (Ch. 51), an antiviral drug used to treat cytomegalovirus retinitis in AIDS patients for whom other antiviral drugs are inappropriate. It is given with probenecid, and intravenous hydration, to prevent its concentration within the tubular lumen, without which it causes tubular toxicity.

DRUGS USED IN RENAL FAILURE

Many congenital and acquired diseases damage the kidneys, leading to common end points of acute or chronic renal failure, which are treated by various forms of artificial dialysis or filtration, or renal transplantation. Where possible, treatment of the underlying cause is indicated. Hypertension is both a cause and a consequence of renal impairment, so its treatment with antihypertensive drugs (Ch. 22) is extremely important in the context of renal

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[9]The distribution is determined by body temperature: crystals come out of solution in cool extremities such as the joints of the big toe—the classic site for acute gout—and the pinna of the ear, a common site for gouty tophi.

disease. *ACE inhibitors* and *angiotensin II antagonists* have a renoprotective effect—over and above their antihypertensive effect—in some situations. Aggressive management of dyslipidaemia (Ch. 23) is also of great importance. **Epoetin** (Ch. 24) is used to treat the anaemia of chronic renal failure. Vitamin D preparations (**calcitriol** or **alphacalcidol**), used to treat the osteodystrophy of chronic renal failure, are covered in Chapter 35. Antibacterial drugs are crucial in treating renal and urinary tract infections, and are dealt with in Chapter 50.

Renal failure often results in *hyperphosphataemia* and *hyperkalaemia*, which may require drug treatment.

HYPERPHOSPHATAEMIA

Phosphate metabolism is closely linked with that of calcium and is discussed in Chapter 35. Phosphate, at concentrations commonly occurring in chronic renal insufficiency, causes vascular smooth muscle cell differentiation into osteoblast-like cells able to sustain mineralisation.

Hyperphosphataemia (plasma phosphate concentration > 1.45 mmol/l) is common in renal failure and may lead calcium phosphate to precipitate in tissues. Large calcium phosphate deposits around joints limit mobility but otherwise cause surprisingly few symptoms. Conjunctival calcification can cause conjunctivitis ('uraemic red eye'). Calcification of the aortic valve can cause stenosis. Abrupt metastatic calcification in subcutaneous tissues and small vessels can result in extensive soft tissue necrosis (*acute calciphylaxis*). Hyperphosphataemia is the major trigger for the onset of hyperparathyroidism in early chronic renal failure, and leads to renal osteodystrophy.

These effects of hyperphosphataemia have led to the widespread use of phosphate-binding preparations in renal failure. The antacid **aluminium hydroxide** (Ch. 29) binds phosphate in the gastrointestinal tract, reducing its absorption, but may increase plasma aluminium in dialysis patients.[10] Calcium-based phosphate-binding agents (e.g. calcium carbonate) are widely used. They are contraindicated in hypercalcaemia or hypercalciuria but until recently have been believed to be otherwise safe. However, calcium salts may predispose to tissue calcification (including of artery walls), and calcium-containing phosphate binders may actually contribute to the very high death rates from cardiovascular disease in dialysis patients (Goldsmith et al., 2004).

An anion exchange resin, **sevelamer**, lowers plasma phosphate, and is less likely than calcium carbonate to cause arterial calcification (Asmus et al., 2005). Sevelamer is not absorbed and has an additional effect in lowering low-density-lipoprotein cholesterol. It is given in gram doses by mouth three times a day with meals. Its adverse effects are gastrointestinal disturbance, and it is contraindicated in bowel obstruction.

HYPERKALAEMIA

Severe hyperkalaemia is life-threatening. It is commonly caused by renal failure, especially if there is concomitant hypoaldosteronism (e.g. in Addison's disease; Ch. 32) and by potassium-sparing diuretics (see above) or drugs that interfere with renin secretion (e.g. β-adrenoceptor antagonists; Ch. 14), or with angiotensin II formation or action (i.e. ACE inhibitors and angiotensin receptor antagonists; Ch. 22).

Prompt treatment is indicated if the plasma K⁺ concentration exceeds 6.5 mmol/l. Cardiac toxicity is counteracted directly by administering calcium gluconate intravenously (Table 21.1), and by measures that shift K⁺ into the intracellular compartment, for example glucose plus insulin (Ch. 30, clinical box). **Salbutamol** (**albuterol**), administered intravenously or by inhalation, also causes cellular K⁺ uptake and is used for this indication (e.g. Murdoch et al., 1991); it acts synergistically with insulin. Intravenous sodium bicarbonate is also often recommended, and moves potassium into cells. Removal of excessive potassium from the body can be achieved by cation exchange resins such as **sodium** or **calcium polystyrene sulfonate** administered by mouth (in combination with **sorbitol** to prevent constipation) or as an enema. Dialysis is often needed.

DRUGS USED IN URINARY TRACT DISORDERS

Bed wetting (enuresis) is normal in very young children and persists in around 5% of children aged 10. Disordered micturition is also extremely common in adults of either sex, and becomes more so with advancing age. Associated structural problems (e.g. prostatic hypertrophy, uterine prolapse) may warrant surgical intervention, and urinary infection—curable with antibiotics—may have been overlooked. However, many cases of incontinence (socially devastating) are functional, and should in principle be amenable to drugs acting on urinary tract smooth muscle or on the nerves controlling this. Currently available treatment is, however, disappointing, perhaps because it is not easy to prevent incontinence without causing urinary retention.

Nocturnal enuresis in children aged 10 or more may warrant **desmopressin** (an analogue of antidiuretic hormone, given by mouth or by nasal spray; Ch. 32) combined with restricting fluid intake, in addition to practical measures such as an enuresis alarm. Tricyclic antidepressants such as **amitriptyline** (Ch. 46) are sometimes used for up to 3 months, but adverse effects including behaviour disturbance can occur, and relapse is common after stopping treatment.

Symptoms from benign prostatic hypertrophy may be improved by α₁-adrenoceptor antagonists, for example **doxazosin** or **tamsulosin** (Ch. 14), or by an inhibitor of androgen synthesis such as **finasteride** (Ch. 34).

Incontinence in adults caused by neurogenic detrusor muscle instability is managed by pelvic floor exercises combined with muscarinic receptor antagonists (Ch. 13) such as **oxybutinin**, **tolterodine**, **propiverine** or **trospium**, but the dose is limited by their adverse effects.

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[10]Before Kerr identified the cause in Newcastle, the use of alum to purify municipal water supplies led to a horrible and untreatable neurodegenerative condition known as 'dialysis dementia', and also to a particularly painful and refractory form of bone disease.

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29

The gastrointestinal tract

OVERVIEW

In addition to its main function of digestion and absorption of food, the gastrointestinal tract is one of the major endocrine systems in the body and has its own integrative neuronal network, the enteric nervous system (see Ch. 12), which contains almost the same number of neurons as the spinal cord. It is also the site of many common pathologies, ranging from simple dyspepsia to complex autoimmune conditions such as Crohn's disease. Medicines for treating these gastrointestinal disorders comprise some 8% of all prescriptions. In this chapter, we briefly review the physiological control of gastrointestinal function and then discuss the pharmacological characteristics of drugs affecting gastric secretion and motility, and those used to treat intestinal inflammation.

THE INNERVATION AND HORMONES OF THE GASTROINTESTINAL TRACT

The blood vessels and the glands (exocrine, endocrine and paracrine) that comprise the gastrointestinal tract are under both neuronal and hormonal control.

NEURONAL CONTROL

There are two principal intramural plexuses in the tract: the *myenteric plexus* (*Auerbach's plexus*) between the outer, longitudinal and the middle, circular muscle layers, and the *submucous plexus* (*Meissner's plexus*) on the lumenal side of the circular muscle layer. These plexuses are interconnected, and their ganglion cells receive preganglionic parasympathetic fibres from the vagus, which are mostly cholinergic and excitatory, although a few are inhibitory. Incoming sympathetic fibres are largely postganglionic. In addition to innervating blood vessels, smooth muscle and some glandular cells directly, some sympathetic fibres may terminate in these plexuses, where they inhibit acetylcholine secretion (see Ch. 12).

The neurons within the plexuses constitute the *enteric nervous system* and secrete not only acetylcholine and noradrenaline (norepinephrine), but also 5-hydroxytryptamine, purines, nitric oxide and a variety of pharmacologically active peptides (see Chs 12–14, 16, 19 and 20). The enteric plexus also contains sensory neurons, which respond to mechanical and chemical stimuli.

HORMONAL CONTROL

The hormones of the gastrointestinal tract include both endocrine and paracrine secretions. The endocrine secretions (i.e. substances released into the bloodstream) are mainly peptides synthesised by endocrine cells in the mucosa. Important examples include *gastrin* and *cholecystokinin*. The paracrine secretions include many regulatory peptides released from special cells found throughout the wall of the tract. These hormones act on nearby cells, and in the stomach the most important of these is *histamine*. Some of these paracrine factors also function as neurotransmitters.

Orally administered drugs are, of course, absorbed in the gastrointestinal tract (Ch. 8). Other functions of the gastrointestinal tract that are important from the viewpoint of pharmacological intervention are:

- gastric secretion
- vomiting (emesis) and nausea
- gut motility and defaecation
- the formation and excretion of bile.
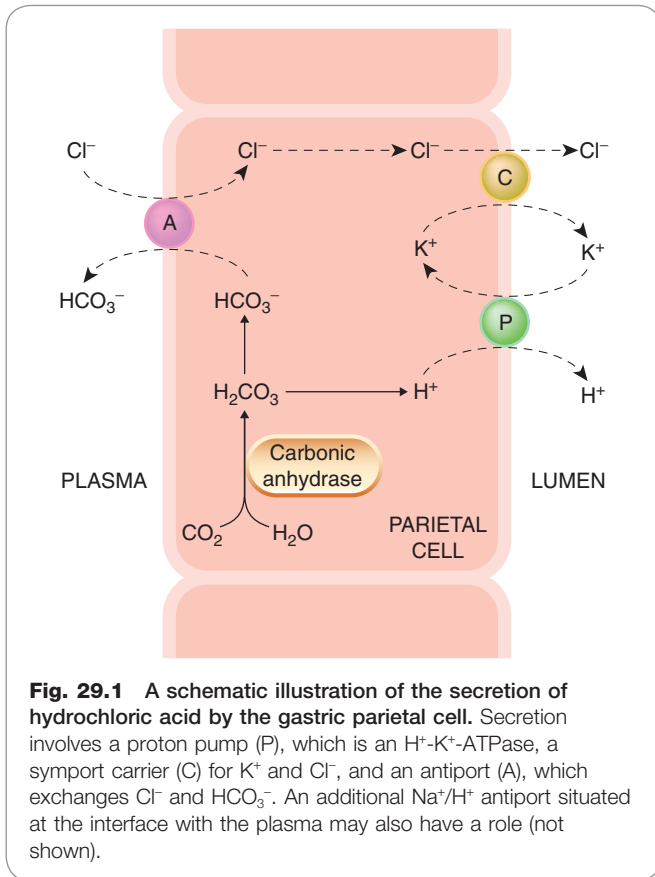
GASTRIC SECRETION

The stomach secretes about 2.5 litres of gastric juice daily. The principal exocrine components are proenzymes such as *prorennin* and *pepsinogen* elaborated by the *chief* or *peptic* cells, and hydrochloric acid (HCl) and *intrinsic factor* (see Ch. 25) secreted by the *parietal* or *oxyntic* cells. The production of acid is important for promoting proteolytic digestion of foodstuffs, iron absorption and killing pathogens. Mucus-secreting cells also abound among the surface cells of the gastric mucosa. Bicarbonate ions are secreted and trapped in the mucus, creating a gel-like protective barrier that maintains the mucosal surface at a pH of 6–7 in the face of a much more acidic environment (pH 1–2) in the lumen. Alcohol and bile can disrupt this layer. Locally produced 'cytoprotective' prostaglandins stimulate the secretion of both mucus and bicarbonate.

Disturbances in these secretory and protective mechanisms are thought to be involved in the pathogenesis of *peptic ulcer*, and indeed in other types of gastric damage such as *gastro-oesophageal reflux disease* (GORD)[1] and injury caused by non-steroidal anti-inflammatory drugs (NSAIDs).

THE REGULATION OF ACID SECRETION BY PARIETAL CELLS

The regulation of acid secretion is important in the pathogenesis of peptic ulcer, and constitutes a particular target for drug action. The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a pH less than 1, the concentration of hydrogen ions being more than a million times higher than that of the plasma. The Cl⁻ is actively transported into canaliculi in the cells that communicate with the lumen of the gastric glands and thus with the stomach itself. This Cl⁻ secretion is accompanied by K⁺, which is then exchanged for H⁺ from within the cell

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[1]Or GERD in the USA, to reflect the different spelling of *esophageal*.

Fig. 29.1 A schematic illustration of the secretion of hydrochloric acid by the gastric parietal cell. Secretion involves a proton pump (P), which is an H^+-K^+-ATPase, a symport carrier (C) for K^+ and Cl^-, and an antiport (A), which exchanges Cl^- and HCO_3^-. An additional Na^+/H^+ antiport situated at the interface with the plasma may also have a role (not shown).

by a K^+-H^+-ATPase (the 'proton pump', Fig. 29.1). Carbonic anhydrase catalyses the combination of carbon dioxide and water to give carbonic acid, which dissociates into H^+ and bicarbonate ions. The latter exchanges across the basal membrane of the parietal cell for Cl^-. The principal mediators that directly—or indirectly—control parietal cell acid output are:
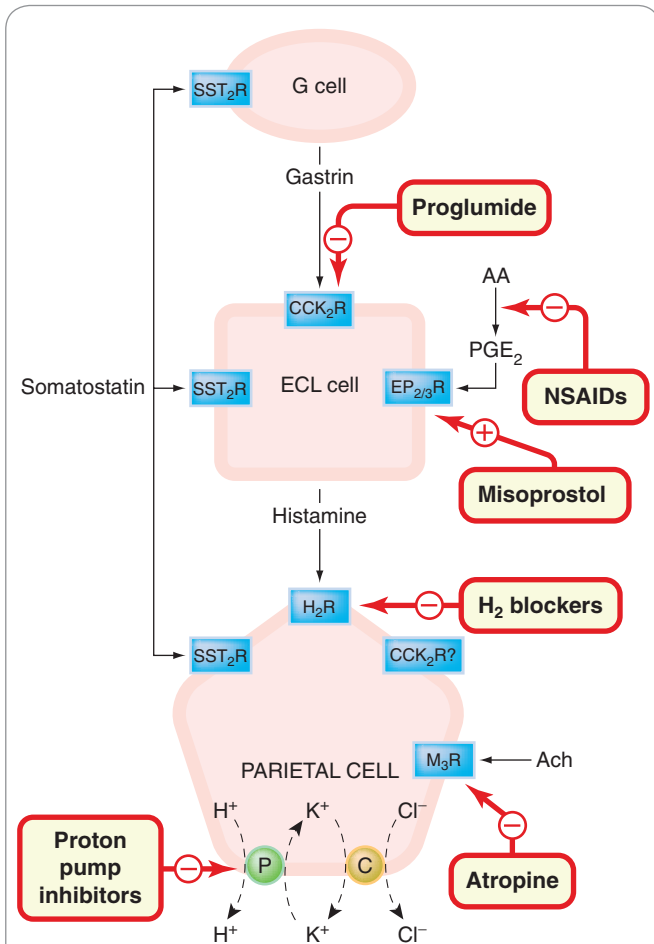
- histamine (a stimulatory local hormone)
- gastrin (a stimulatory peptide hormone)
- acetylcholine (a stimulatory neurotransmitter)
- prostaglandins E_2 and I_2 (local hormones that inhibit acid secretion)
- somatostatin (an inhibitory peptide hormone).

HISTAMINE

Histamine is discussed in Chapter 26, and only those aspects of its pharmacology relevant to gastric secretion will be dealt with here. Neuroendocrine cells abound in the stomach and the dominant type are the *ECL cells* (**e**ntero**c**hromaffin-**l**ike cells; histamine-containing cells similar to mast cells) which lie close to the parietal cells. They sustain a steady basal release of histamine, which is further increased by gastrin and acetylcholine. Histamine acts in a paracrine fashion on parietal cell H_1 receptors, increasing intracellular cAMP. These cells are responsive to histamine concentrations that are below the threshold required for vascular H_2 receptor activation.

GASTRIN

Gastrin is synthesised by *G cells* in the gastric antrum and secreted into the portal blood (i.e. it acts in an endocrine

Fig. 29.2 Schematic diagram showing the regulation of the acid-secreting gastric parietal cell, illustrating the site of action of drugs influencing acid secretion. The initial step in controlling physiological secretion is the release of gastrin from G cells. This acts through its CCK_2 receptor on ECL cells to release histamine and may also have a secondary direct effect on parietal cells themselves, although this is not entirely clear. Histamine acts on parietal cell H_2 receptors to elevate cAMP that activates the secretion of acid by the proton pump. Direct vagal stimulation also provokes acid secretion and released acetylcholine directly stimulates M_3 receptors on parietal cells. Somatostatin probably exerts a tonic inhibitory influence on G cells, ECL cells and parietal cells, while local (or therapeutically administered) prostaglandins exert inhibitory effects predominately on ECL cell function. AA, arachidonic acid; ACh, acetylcholine; C, symport carrier for K^+ and Cl^-; CCK_2, gastrin/cholecystokinin receptor; ECL, mast cell-like histamine-secreting enterochromaffin cell; NSAIDs, non-steroidal anti-inflammatory drugs; P, proton pump (H^+-K^+-ATPase); PGE_2, prostaglandin E_2.

fashion). Its main action is stimulation of acid secretion by ECL cells through its action at gastrin/cholecystokinin (CCK)$_2$ receptors, which elevate intracellular Ca^{2+}. Gastrin receptors also occur on the parietal cells but their significance in the control of physiological secretion is controversial. CCK_2 receptors are blocked by the experimental drug **proglumide** (Fig. 29.2), which weakly inhibits gastrin action.

Gastrin also stimulates histamine synthesis by ECL cells and indirectly increases pepsinogen secretion, stimulates

blood flow and increases gastric motility. Release of this hormone is controlled by both neuronal transmitters and blood-borne mediators, as well as by the chemistry of the stomach contents. Amino acids and small peptides directly stimulate the gastrin-secreting cells, as do milk and solutions of calcium salts, explaining why it is inappropriate to use calcium-containing salts as antacids.

ACETYLCHOLINE

Acetylcholine (together with a battery of other neurotransmitters and peptides), released from postganglionic cholinergic neurons, stimulates specific muscarinic M_3 receptors on the surface of the parietal cells (see Ch. 13), thereby elevating intracellular Ca^{2+} and stimulating the release of protons. It also has complex effects on other cell types; by inhibiting somatostatin release from D cells, it potentiates its action on parietal cell acid secretion.

PROSTAGLANDINS

Most cells of the gastrointestinal tract produce prostaglandins (PGs; see Ch. 6), the most important being PGE_2 and I_2. Prostaglandins exert 'cytoprotective' effects on many aspects of gastric function including increasing bicarbonate secretion ($EP_{1/2}$ receptors), increasing the release of protective mucin (EP_4 receptor), reducing gastric acid output probably by acting on $EP_{2/3}$ receptors on ECL cells and preventing the vasoconstriction (and thus damage to the mucosa) that follows injury or insult. This is probably an action mediated through $EP_{2/4}$ receptors. **Misoprostol** (see below) is a synthetic prostaglandin that probably exploits many of these effects to bring about its therapeutic action.

SOMATOSTATIN

This hormone is released from *D cells* at several locations within the stomach. By acting at its somatostatin $(SST)_2$ receptor, it exerts paracrine inhibitory actions on gastrin release from G cells, histamine release from ECL cells, as well as directly on parietal cell acid output.

THE COORDINATION OF FACTORS REGULATING ACID SECRETION

The regulation of the parietal cell is complex and many local hormones probably play a role in the fine-tuning of the secretory response. The generally accepted model today is that the *gastrin–ECL–parietal cell axis* is the dominant mechanism for controlling acid secretion. According to this idea (see Fig. 29.2), which is supported by the majority of transgenic 'knockout' mouse studies, the initial step in controlling physiological secretion is the release of gastrin from G cells. This acts through its CCK_2 receptor on ECL cells to release histamine and may also have a secondary direct effect on parietal cells themselves, although this has been disputed. Histamine acts on H_2 receptors on parietal cells to elevate cAMP and to activate the secretion of protons as described.

Direct vagal stimulation can also provoke acid secretion (the basis for 'stress ulcers') through a release of acetylcholine, which directly stimulates M_3 receptors on parietal cells. Somatostatin probably exerts a tonic inhibitory influence on G cells, ECL and parietal cells, and local (or therapeutically administered) prostaglandins, acting through $EP_{2/3}$ receptors, exert inhibitory effects predominantly on ECL cell function.

> ### Secretion of gastric acid, mucus and bicarbonate
>
> - The control of the gastrointestinal tract is through nervous and humoral mechanisms:
>   - acid is secreted from gastric parietal cells by a proton pump (K^+-H^+-ATPase)
>   - the three endogenous secretagogues for acid are histamine, acetylcholine and gastrin
>   - prostaglandins E_2 and I_2 inhibit acid, stimulate mucus and bicarbonate secretion, and dilate mucosal blood vessels
>   - somatostatin inhibits all phases of parietal cell activation.
> - The genesis of peptic ulcers involves:
>   - infection of the gastric mucosa with *Helicobacter pylori*
>   - an imbalance between the mucosal-damaging (acid, pepsin) and the mucosal-protecting agents (mucus, bicarbonate, prostaglandins E_2 and I_2, and nitric oxide).

This control system is clearly complex but prolonged exposure of tissues to excess acid secretion is dangerous and must be tightly regulated (see Schubert & Peura, 2008).

DRUGS USED TO INHIBIT OR NEUTRALISE GASTRIC ACID SECRETION

The principal clinical indications for reducing acid secretion are *peptic ulceration* (both duodenal and gastric), *GORD* (in which gastric juice causes damage to the oesophagus) and the *Zollinger–Ellison syndrome* (a rare condition that is caused by a gastrin-producing tumour).

The reasons why peptic ulcers develop are not fully understood, although infection of the stomach mucosa with *Helicobacter pylori*[2]—a Gram-negative bacillus that causes chronic gastritis—is now generally considered to be a major cause (especially of duodenal ulcer) and, while there are some problems with this notion (see Axon, 2007), forms the usual basis for therapy. Treatment of *H. pylori* infection is discussed below.

Many non-specific NSAIDs (see Ch. 26) cause gastric bleeding and erosions by inhibiting cyclo-oxygenase-1, the enzyme responsible for synthesis of protective prostaglandins (see above). More selective cyclo-oxygenase-2 inhibitors such as **celecoxib** appear to cause less stomach damage (but see Ch. 26 for a discussion of this issue).

Therapy of peptic ulcer and reflux oesophagitis aims to decrease the secretion of gastric acid with H_2 receptor antagonists or proton pump inhibitors, and/or to neutralise secreted acid with antacids (see Huang & Hunt, 2001). These treatments are often coupled with measures to eradicate *H. pylori* (see Horn, 2000).

HISTAMINE H_2 RECEPTOR ANTAGONISTS

The discovery and development of histamine H_2-blocking drugs by Black and his colleagues was a major

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[2]*Helicobacter pylori* infection in the stomach has been classified as a class 1 (definite) carcinogen for gastric cancer.

Table 29.1 Details of some antagonist drugs used to define the three types of histamine receptor

Drug	Binding constant (K_B; mol/l)		
	H_1	H_2	H_3
Mepyramine	0.4×10^9	–	$> 3 \times 10^6$
Cimetidine	4.5×10^4	0.8×10^6	3.3×10^5
Thioperamide	$> 10^4$	$> 10^5$	4.3×10^9

Data derived from Black J W et al. 1972 Nature 236: 385–390; Ganellin C R 1982 In: Ganellin C R, Parson M E (eds) Pharmacology of histamine receptors. Wright, Bristol, pp 11–102; Arrang J M et al. 1987 Nature 327: 117–123; van der Werf J F, Timmerman H 1989 Trends Pharmacol Sci 10: 159–162.

breakthrough in the treatment of gastric ulcers—a condition that could hitherto only be treated by (sometimes rather heroic) surgery.[3] The ability to distinguish between histamine receptor subtypes using pharmacological agents was, in itself, a major intellectual advance (see Table 29.1). H_2 receptor antagonists competitively inhibit histamine actions at all H_2 receptors, but their main clinical use is as inhibitors of gastric acid secretion. They can inhibit histamine- and gastrin-stimulated acid secretion; pepsin secretion also falls with the reduction in volume of gastric juice. These agents not only decrease both basal and food-stimulated acid secretion by 90% or more, but numerous clinical trials indicate that they also promote healing of gastric and duodenal ulcers. However, relapses are likely to follow after cessation of treatment.

The drugs used are **cimetidine**, **ranitidine** (sometimes in combination with bismuth; see below), **nizatidine** and **famotidine**. There is little difference between them. The effect of cimetidine on gastric secretion in human subjects is shown in Figure 29.3. The clinical use of H_2 receptor antagonists is given in the clinical box.

Pharmacokinetic aspects and unwanted effects
The drugs are generally given orally and are well absorbed, although preparations for intramuscular and intravenous use are also available (except famotidine). Dosage regimens vary depending on the condition under treatment. Low-dosage over-the-counter formulations of cimetidine, ranitidine and famotidine are available for short-term uses, without prescription, from pharmacies.

Unwanted effects are rare. Diarrhoea, dizziness, muscle pains, alopecia, transient rashes, confusion in the elderly and hypergastrinaemia have been reported. Cimetidine sometimes causes *gynaecomastia* in men and, rarely, a decrease in sexual function. This is probably caused by a modest affinity for androgen receptors. Cimetidine (but not other H_2 receptor antagonists) also inhibits cytochrome P450, and can retard the metabolism (and thus potentiate the action) of a range of drugs including oral anticoagulants and tricyclic antidepressants.
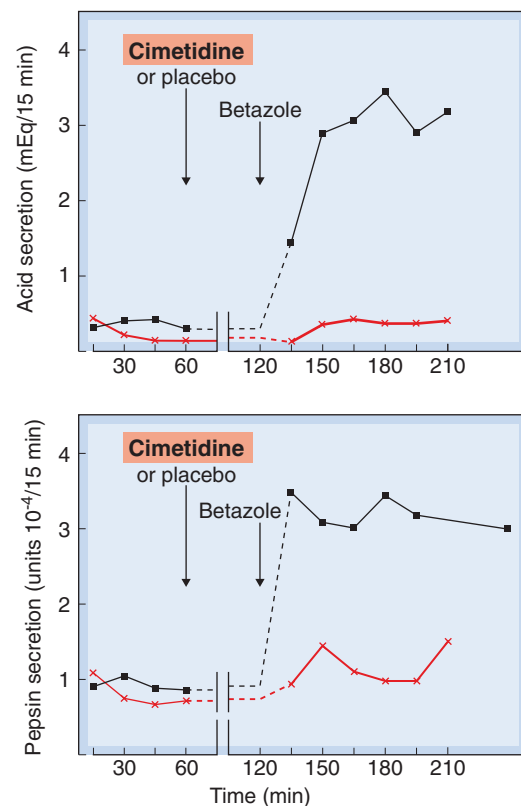
[3]This era has been referred to as the 'BC'—before cimetidine—era of gastroenterology (Schubert & Peura 2008)! It is an indication of the clinical importance of the development of this drug.


Fig. 29.3 The effect of cimetidine on betazole-stimulated gastric acid and pepsin secretion in humans. Either cimetidine or a placebo was given orally 60 min prior to a subcutaneous injection (1.5 mg/kg) of betazole, a relatively specific histamine H_2-receptor agonist that stimulates gastric acid secretion. (Modified from Binder H J, Donaldson R M 1978 Gastroenterology 74: 371–375.)

PROTON PUMP INHIBITORS
The first proton pump inhibitor was **omeprazole**, which irreversibly inhibits the H^+-K^+-ATPase (the proton pump), the terminal step in the acid secretory pathway (see Figs 29.1 and 29.2). Both basal and stimulated gastric acid secretion (Fig. 29.4) are reduced. The drug is a weak base, and accumulates in the acid environment of the canaliculi of the stimulated parietal cell where it is activated. This preferential accumulation means that it has a specific effect on these cells. Other proton pump inhibitors (all of which are very similar) include **esomeprazole** (the [S] isomer of omeprazole), **lansoprazole**, **pantoprazole** and **rabeprazole**. The clinical use of these inhibitors is given in the clinical box.

Pharmacokinetic aspects and unwanted effects
Oral administration is the most common route of administration, although some injectable preparations are available. Omeprazole is given orally, but as it degrades rapidly at low pH, it is administered as capsules containing enteric-coated granules. It is absorbed and, from the blood, passes into the parietal cells and then into the canaliculi. Increased doses give disproportionately higher increases in plasma concentration (possibly because its inhibitory effect on acid secretion improves its own bioavailability). Although its half-life is about 1 h, a single daily dose affects acid
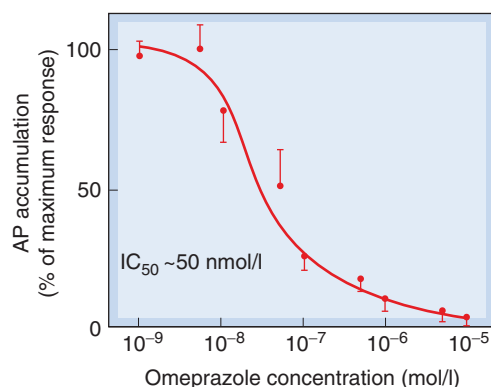
Fig. 29.4 The inhibitory action of omeprazole on acid secretion from isolated human gastric glands stimulated by 50 μmol/l histamine. Acid secretion was measured by the accumulation of a radiolabelled weak base, aminopyrine (AP), in the secretory channels. The data represent the mean and standard error of measurements from eight patients. (Adapted from Lindberg P et al. 1987 Trends Pharmacol Sci 8: 399–402.)

> **Clinical use of agents affecting gastric acidity**
>
> - Histamine H_2 receptor antagonists (e.g. **ranitidine**):
>   – *peptic ulcer*
>   – *reflux oesophagitis.*
> - Proton pump inhibitors (e.g. **omeprazole**, **lansoprasole**):
>   – *peptic ulcer*
>   – *reflux oesophagitis*
>   – as one component of therapy for *Helicobacter pylori* infection
>   – *Zollinger–Ellison syndrome* (a rare condition caused by gastrin-secreting tumours).
> - Antacids (e.g. **magnesium trisilicate**, **aluminium hydroxide**, **alginates**):
>   – *dyspepsia*
>   – symptomatic relief in *peptic ulcer* or (alginate) *oesophageal reflux*.
> - **Bismuth chelate**:
>   – as one component of therapy for *H. pylori* infection.

secretion for 2–3 days, because it accumulates in the canaliculi and inhibits H^+-K^+-ATPase irreversibly. With daily dosage, there is an increasing antisecretory effect for up to 5 days, after which a plateau is reached.

Unwanted effects of this class of drugs are uncommon. They may include headache, diarrhoea (both sometimes severe) and rashes. Dizziness, somnolence, mental confusion, impotence, gynaecomastia, and pain in muscles and joints have been reported. Proton pump inhibitors should be used with caution in patients with liver disease, or in women who are pregnant or breastfeeding. The use of these drugs may 'mask' the symptoms of gastric cancer.

ANTACIDS

Antacids are the simplest way to treat the symptoms of excessive gastric acid secretion. They directly neutralise acid, which also has the effect of inhibiting the activity of peptic enzymes, which practically ceases at pH 5. Given in sufficient quantity for long enough, they can produce healing of duodenal ulcers but are less effective for gastric ulcers.

Most antacids in common use are salts of magnesium and aluminium. Magnesium salts cause diarrhoea and aluminium salts constipation, so mixtures of these two can, happily, be used to preserve normal bowel function. Some preparations of these substances (e.g. magnesium trisilicate mixtures and some proprietary aluminium preparations) contain high concentrations of sodium and should not be given to patients on a sodium-restricted diet. Numerous antacid preparations are available; a few of the more significant are given below.

Magnesium hydroxide is an insoluble powder that forms magnesium chloride in the stomach. It does not produce systemic alkalosis, because Mg^{2+} is poorly absorbed from the gut. Another salt, **magnesium trisilicate**, is an insoluble powder that reacts slowly with the gastric juice, forming magnesium chloride and colloidal silica. This agent has a prolonged antacid effect, and it also adsorbs pepsin.

Aluminium hydroxide gel forms aluminium chloride in the stomach; when this reaches the intestine, the chloride is released and is reabsorbed. Aluminium hydroxide raises the pH of the gastric juice to about 4, and also adsorbs pepsin. Its action is gradual, and its effect continues for several hours.[4] Colloidal aluminium hydroxide combines with phosphates in the gastrointestinal tract, and the increased excretion of phosphate in the faeces that occurs results in decreased excretion of phosphate via the kidney. This effect has been used in treating patients with chronic renal failure (see Ch. 28).

Alginates or **simeticone** are sometimes combined with antacids. Alginates are believed to increase the viscosity and adherence of mucus to the oesophageal mucosa, forming a protective barrier (see also below), whereas simeticone is an anti-foaming agent, intended to relieve bloating and flatulence.

The clinical use of antacids is given in the clinical box.

TREATMENT OF *HELICOBACTER PYLORI* INFECTION

H. pylori infection has been implicated as a causative factor in the production of gastric and, more particularly, duodenal ulcers, as well as a risk factor for gastric cancer. Indeed, some would argue that infectious gastroduodenitis is actually the chief clinical entity associated with ulcers, and gastric cancer its prominent sequela. Certainly, eradication of *H. pylori* infection promotes rapid and long-term healing of ulcers, and it is routine practice to test for the organism in patients presenting with suggestive symptoms. If the test is positive, then the organism can generally be

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[4]There was a suggestion—no longer widely believed—that aluminium could trigger Alzheimer's disease. In fact, aluminium is not absorbed to any significant extent following oral administration of aluminium hydroxide, although when introduced by other routes (e.g. during renal dialysis with aluminium-contaminated solutions) it is extremely toxic.

eradicated with a 1- or 2-week regimen of 'triple therapy', comprising a proton pump inhibitor in combination with the antibacterials **amoxicillin** and **metronidazole** or **clarithromycin** (see Ch. 50); other combinations are also used. Bismuth-containing preparations (see below) are sometimes added. While elimination of the bacillus can produce long-term remission of ulcers, reinfection with the organism can occur.

DRUGS THAT PROTECT THE MUCOSA

Some agents, termed *cytoprotective*, are said to enhance endogenous mucosal protection mechanisms (see above) and/or to provide a physical barrier over the surface of the ulcer.

Bismuth chelate
Bismuth chelate (colloidal bismuth subcitrate, tripotassium dicitratobismuthate) is used in combination regimens to treat *H. pylori*. It has toxic effects on the bacillus, and may also prevent its adherence to the mucosa or inhibit its bacterial proteolytic enzymes. It is also believed to have other mucosa-protecting actions, by mechanisms that are unclear, and is widely used as an over-the-counter remedy for mild gastrointestinal symptoms.Very little is absorbed, but if renal excretion is impaired, the raised plasma concentrations of bismuth can result in encephalopathy.

Unwanted effects include nausea and vomiting, and blackening of the tongue and faeces.

Sucralfate
Sucralfate is a complex of aluminium hydroxide and sulfated sucrose, which releases aluminium in the presence of acid. The residual complex carries a strong negative charge and binds to cationic groups in proteins, glycoproteins, etc. It can form complex gels with mucus, an action that is thought to decrease the degradation of mucus by pepsin and to limit the diffusion of H^+. Sucralfate can also inhibit the action of pepsin and stimulate secretion of mucus, bicarbonate and prostaglandins from the gastric mucosa. All these actions contribute to its mucosa-protecting action.

Sucralfate is given orally, and in the acid environment of the stomach the polymerised product forms a tenacious paste, which can produce an obstructive lump (known as a *bezoar*[5]) that gets stuck in the stomach; about 30% is still present in the stomach 3 h after administration. It reduces the absorption of a number of other drugs, including fluoroquinolone antibiotics, **theophylline**, **tetracycline**, **digoxin** and **amitriptyline**. Because it requires an acid environment for activation, antacids given concurrently or prior to its administration will reduce its efficacy.

Unwanted effects are few, the most common being constipation. Less common effects include dry mouth, nausea, vomiting, headache, bezoar formation and rashes.

Misoprostol
Prostaglandins of the E and I series have a generally protective action in the gastrointestinal tract, and a deficiency in endogenous production (after ingestion of a NSAID, for example) may contribute to ulcer formation. Misoprostol is a stable analogue of prostaglandin E_1. It is given orally and is used to promote the healing of ulcers or to prevent the gastric damage that can occur with chronic use of NSAIDs. It exerts a direct action on the ECL cell (and possibly parietal cell also; Fig. 29.2), inhibiting the basal secretion of gastric acid as well as the stimulation of production seen in response to food, pentagastrin and caffeine. It also increases mucosal blood flow and augments the secretion of mucus and bicarbonate.

Unwanted effects include diarrhoea and abdominal cramps; uterine contractions can also occur, so the drug should not be given during pregnancy (unless deliberately to induce a therapeutic abortion; see Ch. 34). Prostaglandins and NSAIDs are discussed more fully in Chs 6 and 26.

VOMITING

Nausea and vomiting are unwanted side effects of many clinically used drugs, notably those used for cancer chemotherapy as well as opioids, general anaesthetics and **digoxin**. They also occur in motion sickness,[6] during early pregnancy and in numerous disease states (e.g. migraine) as well as bacterial and viral infections.

THE REFLEX MECHANISM OF VOMITING

Vomiting is regulated centrally by the *vomiting centre* and the *chemoreceptor trigger zone* (CTZ), both of which lie in the medulla. The CTZ is sensitive to chemical stimuli and is the main site of action of many emetic and antiemetic drugs. The blood–brain barrier in the neighbourhood of the CTZ is relatively permeable, allowing circulating mediators to act directly on this centre. The CTZ also regulates motion sickness. Impulses from the CTZ pass to those areas of the brain stem—known collectively as the vomiting centre—that control and integrate the visceral and somatic functions involved in vomiting.

An outline of the pathways involved in the control of vomiting is given in Figure 29.5 and reviewed in detail by Hornby (2001). The main neurotransmitters are acetylcholine, histamine, 5-hydroxytryptamine (5-HT), dopamine and substance P, and receptors for these transmitters have been demonstrated in the relevant areas (see Chs 12–14 and 38). It has been hypothesised that enkephalins (see Chs 19 and 41) are also implicated in the mediation of vomiting, acting possibly at δ (CTZ) or µ (vomiting centre) opioid receptors. Substance P (see Ch. 19) acting at neurokinin-1 receptors in the CTZ, and endocannabinoids (Ch. 18), may also be involved.

The neurobiology of nausea is much less well understood. Nausea and vomiting may occur together or separately and may subserve different physiological functions (see Andrews & Horn, 2006). From the pharmacologist's viewpoint, it is easier to control vomiting than nausea, and many effective antiemetics (e.g. 5-HT$_3$ antagonists) are much less successful in this regard.

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[5]From the Persian word meaning 'a cure for poisoning'. It refers to the belief that a concoction made from lumps of impacted rubbish retrieved from the stomach of goats would protect against poisoning by one's enemies.

[6]In fact, the word *nausea* is derived from the Greek word meaning 'boat', with the obvious implication of associated motion sickness. *Vomiting* is derived from the Latin and a *vomitorium* was the 'fast exit' passageway in ancient theatres. It has a certain resonance, as we think you will agree!
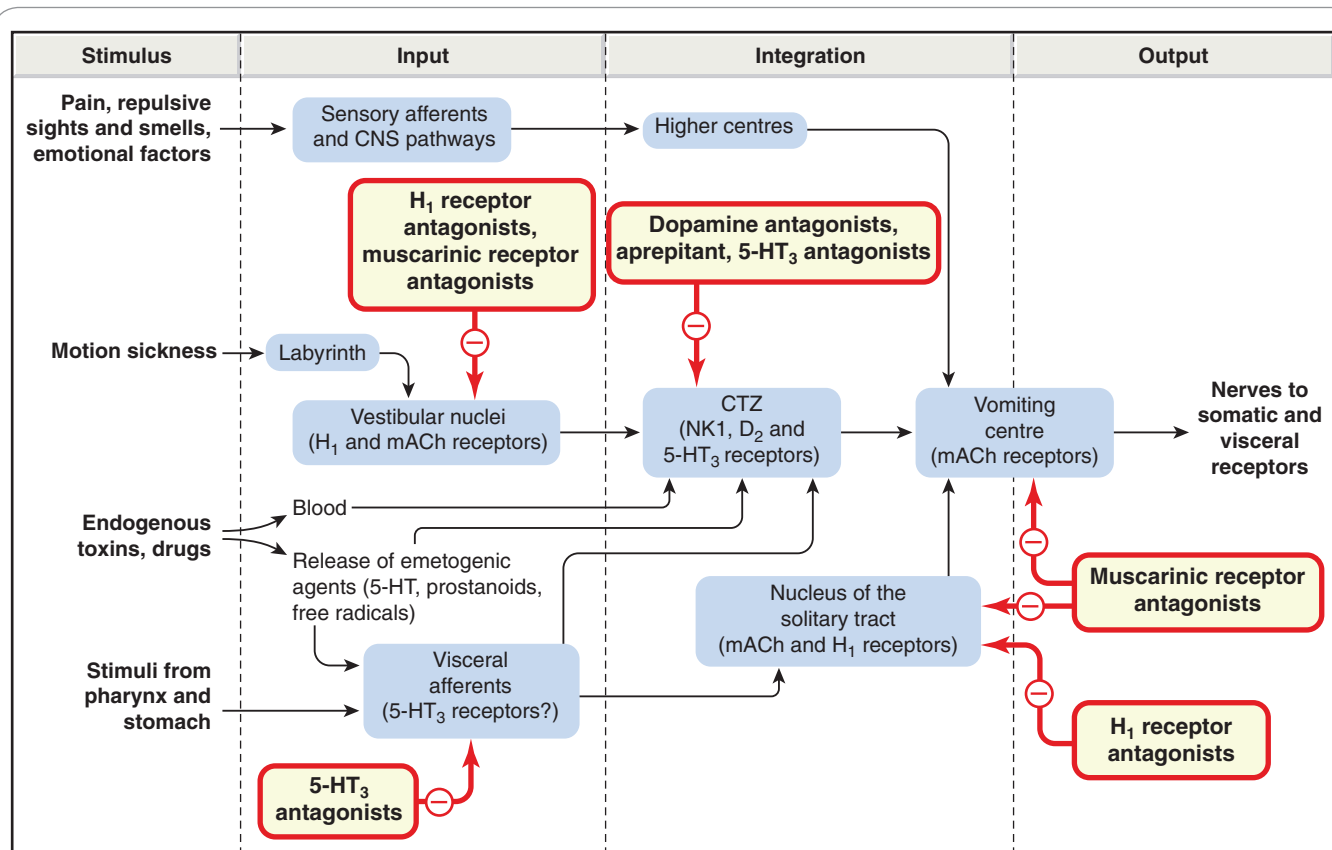
Fig. 29.5 Schematic diagram of the factors involved in the control of vomiting, with the probable sites of action of antiemetic drugs. The cerebellum may function as a second relay or gating mechanism in the link between the labyrinth and chemoreceptor trigger zone (CTZ; not shown). 5-HT$_3$, 5-hydroxytryptamine type 3; D$_2$, dopamine D$_2$; H$_1$, histamine H$_1$; mACh, muscarinic acetylcholine; NK$_1$, neurokinin 1. (Based partly on a diagram from Borison H L et al. 1981 J Clin Pharmacol 21: 235–295.)

ANTIEMETIC DRUGS

Several antiemetic agents are available, and these are generally used for specific conditions, although there may be some overlap. Such drugs are of particular importance as an adjunct to cancer chemotherapy, where the nausea and vomiting produced by many cytotoxic drug (see Ch. 55) can be almost unendurable.[7] In using drugs to treat the morning sickness of pregnancy, the problem of potential damage to the fetus has always to be borne in mind. In general, all drugs should be avoided during the first 3 months of pregnancy, if possible. Details of the main categories of antiemetics are given below, and their main clinical uses are summarised in the box.

RECEPTOR ANTAGONISTS

Many H$_1$ (see Ch. 26), muscarinic (see Ch. 13), 5-HT$_3$ (see Ch. 15) and dopamine (Ch. 45) receptor antagonists exhibit clinically useful antiemetic activity.

H$_1$ receptor antagonists
Cinnarizine, **cyclizine** and **promethazine** are the most commonly employed; they are effective against nausea and

vomiting arising from many causes, including motion sickness and the presence of irritants in the stomach. None is very effective against substances that act directly on the CTZ. Promethazine is used for morning sickness of pregnancy (on the rare occasions when this is so severe that drug treatment is justified), and has been used by NASA to treat space motion sickness. Drowsiness and sedation, while possibly contributing to their clinical efficacy, are the chief unwanted effects.

Muscarinic receptor antagonists
Hyoscine (**scopolamine**) is employed principally for prophylaxis and treatment of motion sickness, and may be administered orally or as a transdermal patch. Dry mouth and blurred vision are the most common unwanted effects. Drowsiness also occurs, but the drug has less sedative action than the antihistamines because of poor central nervous system penetration.

5-HT$_3$ receptor antagonists
Dolasetron, **granisetron**, **ondansetron**, **palonosteron** and **tropisetron** (see Ch. 15), are of particular value in preventing and treating the vomiting and, to a lesser extent the nausea, commonly encountered postoperatively or that caused by radiation therapy or administration of cytotoxic drugs such as **cisplatin**. The primary site of action of these drugs is the CTZ. They may be given orally or by injection

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[7]It was reported that a young, medically qualified patient being treated by combination chemotherapy for sarcoma stated that 'the severity of vomiting at times made the thought of death seem like a welcome relief'.

- Emetic stimuli include:
  - chemicals or drugs in the blood or intestine
  - neuronal input from the gastrointestinal tract, labyrinth and central nervous system (CNS).
- Pathways and mediators include:
  - impulses from the chemoreceptor trigger zone and various other CNS centres relayed to the vomiting centre
  - chemical transmitters such as histamine, acetylcholine, dopamine, 5-hydroxytryptamine and substance P, acting on H_1, muscarinic, D_2, 5-HT_3 and NK_1 receptors, respectively.
- Antiemetic drugs include:
  - H_1 receptor antagonists (e.g. **cinnarizine**)
  - muscarinic antagonists (e.g. **hyoscine**)
  - 5-HT_3 receptor antagonists (e.g. **ondansetron**)
  - D_2 receptor antagonists (e.g. **metoclopramide**)
  - cannabinoids (e.g. **nabilone**)
  - neurokinin-1 antagonists (e.g. **aprepitant, fosaprepitant**).
- Main side effects of principal antiemetics include:
  - drowsiness and antiparasympathetic effects (hyoscine, nabilone > cinnarizine)
  - dystonic reactions (metoclopramide)
  - general CNS disturbances (nabilone)
  - headache, gastrointestinal tract upsets (ondansetron).

(sometimes helpful if nausea is already present). Unwanted effects such as headache and gastrointestinal upsets are relatively uncommon.

Dopamine antagonists

Antipsychotic phenothiazines (see Ch. 45), such as **chlorpromazine**, **perphenazine**, **prochlorperazine** and **trifluoperazine**, are effective antiemetics commonly used for treating the more severe nausea and vomiting associated with cancer, radiation therapy, cytotoxic drugs, opioids, anaesthetics and other drugs. They can be administered orally, intravenously or by suppository. They act mainly as antagonists of the dopamine D_2 receptors in the CTZ (see Fig. 29.5) but they also block histamine and muscarinic receptors.

Unwanted effects are common and include sedation (especially chlorpromazine), hypotension and extrapyramidal symptoms including dystonias and tardive dyskinesia (Ch. 45).

Other antipsychotics, such as **haloperidol** and **levomepromazine** (Ch. 45), also act as D_2 antagonists in the CTZ and can be used for acute chemotherapy-induced emesis.

Metoclopramide and domperidone

Metoclopramide is a D_2 receptor antagonist (Fig. 29.5), closely related to the phenothiazine group, that acts centrally on the CTZ and also has a peripheral action on the gastrointestinal tract itself, increasing the motility of the oesophagus, stomach and intestine. This not only adds to the antiemetic effect, but explains its use in the treatment

of gastro-oesophageal reflux (see below) and hepatic and biliary disorders. As metoclopramide also blocks dopamine receptors (see Ch. 43) elsewhere in the central nervous system, it produces a number of unwanted effects including disorders of movement (more common in children and young adults), fatigue, motor restlessness, spasmodic torticollis (involuntary twisting of the neck) and occulogyric crises (involuntary upward eye movements). It stimulates prolactin release (see Ch. 32), causing galactorrhoea and disorders of menstruation.

Domperidone is a similar drug often used to treat vomiting due to cytotoxic therapy as well as gastrointestinal symptoms. Unlike metoclopramide, it does not readily penetrate the blood–brain barrier and is consequently less prone to producing central side effects. Both drugs are given orally, have plasma half-lives of 4–5 h and are excreted in the urine.

NK₁ receptor antagonists

Aprepitant blocks substance P (NK_1) receptors (see Ch. 19) in the CTZ and vomiting centre. Substance P causes vomiting when injected intravenously and is released by gastrointestinal vagal afferent nerves as well as in the vomiting centre itself. Aprepitant is given orally, and is effective in controlling the late phase of emesis caused by cytotoxic drugs, with few significant unwanted effects. **Fosaprepitant** is a prodrug of aprepitant, given intravenously.

OTHER ANTIEMETIC DRUGS

Anecdotal evidence originally suggested the possibility of using cannabinoids (see Ch. 18) as antiemetics (see Pertwee, 2001). The synthetic cannabinol **nabilone** has been found to decrease vomiting caused by agents that stimulate the CTZ, and is sometimes effective where other drugs have failed (see Ch. 18). The antiemetic effect is antagonised by **naloxone**, which implies that opioid receptors may be important in the mechanism of action. Nabilone is given orally; it is well absorbed from the gastrointestinal tract and is metabolised in many tissues. Its plasma half-life is approximately 120 min, and its metabolites are excreted in the urine and faeces.

Unwanted effects are common, especially drowsiness, dizziness and dry mouth. Mood changes and postural hypotension are also fairly frequent. Some patients experience hallucinations and psychotic reactions, resembling the effect of other cannabinoids (see Ch. 18).

High-dose glucocorticoids (particularly **dexamethasone**; see Chs 26 and 32) can also control emesis, especially when this is caused by cytotoxic drugs. The mechanism of action is not clear. Dexamethasone can be used alone but is frequently deployed in combination with a phenothiazine, ondansetron or aprepitant.

THE MOTILITY OF THE GASTROINTESTINAL TRACT

Drugs that alter the motility of the gastrointestinal tract include:

- purgatives, which accelerate the passage of food through the intestine
- agents that increase the motility of the gastrointestinal smooth muscle without causing purgation
- antidiarrhoeal drugs, which decrease motility

> **Clinical use of antiemetic drugs**
>
> - Histamine H_1 receptor antagonists (see also clinical box in Ch. 26):
>   - **cyclizine**: motion sickness
>   - **cinnarizine**: motion sickness, vestibular disorders (e.g. Ménière's disease)
>   - **promethazine**: severe morning sickness of pregnancy.
> - Muscarinic receptor antagonists:
>   - **hyoscine**: motion sickness.
> - Dopamine D_2 receptor antagonists:
>   - phenothiazines (e.g. **prochlorperazine**): vomiting caused by uraemia, radiation, viral gastroenteritis, severe morning sickness of pregnancy
>   - **metoclopramide**: vomiting caused by uraemia, radiation, gastrointestinal disorders, cytotoxic drugs.
>   - **Domperidone** is less liable to cause CNS side effects as it penetrates the blood-brain barrier poorly.
> - 5-Hydroxytryptamine 5-HT_3 receptor antagonists (e.g. **ondansetron**): cytotoxic drugs or radiation, postoperative vomiting.
> - Cannabinoids (e.g. **nabilone**): cytotoxic drugs (see Ch. 18).

- antispasmodic drugs, which decrease smooth muscle tone.

PURGATIVES

The transit of food through the intestine may be hastened by several different types of drugs, including laxatives, faecal softeners and stimulant purgatives. The latter agents may be used to relieve constipation or to clear the bowel prior to surgery or examination.

BULK AND OSMOTIC LAXATIVES

The *bulk laxatives* include **methylcellulose** and certain plant extracts such as **sterculia**, **agar**, **bran** and **ispaghula husk**. These agents are polysaccharide polymers that are not digested in the upper part of the gastrointestinal tract. They form a bulky hydrated mass in the gut lumen promoting peristalsis and improving faecal consistency. They may take several days to work but have no serious unwanted effects.

The *osmotic laxatives* consist of poorly absorbed solutes — the saline purgatives — and **lactulose**. The main salts in use are magnesium sulfate and magnesium hydroxide. By producing an osmotic load, these agents trap increased volumes of fluid in the lumen of the bowel, accelerating the transfer of the gut contents through the small intestine. This results in an abnormally large volume entering the colon, causing distension and purgation within about an hour. Abdominal cramps can occur. The amount of magnesium absorbed after an oral dose is usually too small to have adverse systemic effects, but these salts should be avoided in small children and in patients with poor renal function, in whom they can cause heart block, neuromuscular block or central nervous system depression. While isotonic or hypotonic solutions of saline purgatives cause purgation, hypertonic solutions can cause vomiting. Sometimes, other sodium salts of **phosphate** and **citrate** are given rectally, by suppository, to relieve constipation.

Lactulose is a semisynthetic disaccharide of fructose and galactose. It is poorly absorbed and produces an effect similar to that of the other osmotic laxatives. It takes 2–3 days to act. Unwanted effects, seen with high doses, include flatulence, cramps, diarrhoea and electrolyte disturbance. Tolerance can develop. Another agent, **macrogols**, which consists of inert ethylene glycol polymers, acts in the same way.

FAECAL SOFTENERS

Docusate sodium is a surface-active compound that acts in the gastrointestinal tract in a manner similar to a detergent and produces softer faeces. It is also a weak stimulant laxative. Other agents that achieve the same effect include **arachis oil**, which is given as an enema, and **liquid paraffin**, although this is now seldom used.

STIMULANT LAXATIVES

The stimulant laxative drugs act mainly by increasing electrolyte and hence water secretion by the mucosa, and also by increasing peristalsis — possibly by stimulating enteric nerves. Abdominal cramping may be experienced as a side effect with almost any of these drugs.

Bisacodyl may be given by mouth but is often given by suppository. In the latter case, it stimulates the rectal mucosa, inducing defaecation in 15–30 min. **Glycerol** suppositories act in the same manner. **Sodium picosulfate** and docusate sodium have similar actions. The former is given orally and is often used in preparation for intestinal surgery or colonoscopy.

Senna and **dantron** are *anthroquinone* laxatives. The active principle (after hydrolysis of glycosidic linkages in the case of the plant extract, senna) directly stimulates the myenteric plexus, resulting in increased peristalsis and thus defaecation. Dantron is similar. As this drug is a skin irritant and may be carcinogenic, it is generally used only in the terminally ill.

Laxatives of any type should not be used when there is obstruction of the bowel. Overuse can lead to an atonic colon where the natural propulsive activity is diminished. In these circumstances, the only way to achieve defaecation is to take further amounts of laxatives, so a sort of dependency arises.

DRUGS THAT INCREASE GASTROINTESTINAL MOTILITY

Domperidone is primarily used as an antiemetic (as described above), but it also increases gastrointestinal motility (although the mechanism is unknown). Clinically, it increases lower oesophageal sphincter pressure (thus inhibiting gastro-oesophageal reflux), increases gastric emptying and enhances duodenal peristalsis. It is useful in disorders of gastric emptying and in chronic gastric reflux.

Metoclopramide (also an antiemetic; see above) stimulates gastric motility, causing a marked acceleration of gastric emptying. It is useful in gastro-oesophageal reflux and in disorders of gastric emptying, but is ineffective in paralytic ileus.

Now withdrawn (because it precipitated fatal cardiac arrhythmias), **cisapride** stimulates acetylcholine release in

the myenteric plexus in the upper gastrointestinal tract through a 5-HT$_4$ receptor-mediated effect. **Tegaserod** (also recently withdrawn on account of suspected increase in heart attacks and strokes) acts similarly. These drugs raise oesophageal sphincter pressure and increase gut motility. They were used for treating reflux oesophagitis and in disorders of gastric emptying.

ANTIDIARRHOEAL AGENTS

There are numerous causes of diarrhoea, including underlying disease, infection, toxins and even anxiety. It may also arise as a side effect of drug or radiation therapy. Repercussions range from mild discomfort and inconvenience to a medical emergency requiring hospitalisation and parenteral fluid and electrolyte replacement therapy. Globally, acute diarrhoeal disease is one of the principal causes of death in malnourished infants, especially in developing countries where medical care is less accessible and 1–2 million children die each year for want of simple counter-measures.

During an episode of diarrhoea, there is an increase in the motility of the gastrointestinal tract, accompanied by an increased secretion coupled with a decreased absorption of fluid, which leads to a loss of electrolytes (particularly Na$^+$) and water. Cholera toxins and some other bacterial toxins produce a profound increase in electrolyte and fluid secretion by irreversibly activating the G-proteins that couple the surface receptors of the mucosal cells to adenylyl cyclase (see Ch. 3).

There are three approaches to the treatment of severe acute diarrhoea:

1. Maintenance of fluid and electrolyte balance.
2. Use of anti-infective agents.
3. Use of spasmolytic or other antidiarrhoeal agents.

The maintenance of fluid and electrolyte balance by means of oral rehydration is the first priority, and wider application of this cheap and simple remedy could save the lives of many infants in the developing world. Many patients require no other treatment. In the ileum, as in parts of the nephron, there is co-transport of Na$^+$ and glucose across the epithelial cell. The presence of glucose (and some amino acids) therefore enhances Na$^+$ absorption and thus water uptake. Preparations of sodium chloride and glucose for oral rehydration are available in powder form, ready to be dissolved in water before use.

Many gastrointestinal infections are viral in origin, and because those that are bacterial generally resolve fairly rapidly, the use of anti-infective agents is usually neither necessary nor useful. Other cases may require more aggressive therapy, however. *Campylobacter* sp. is the commonest cause of bacterial gastroenteritis in the UK, and severe infections may require **ciprofloxacin** (Ch. 50). The most common bacterial organisms encountered by travellers include *Escherichia coli*, *Salmonella* and *Shigella*, as well as protozoa such as *Giardia* and *Cryptosporidium* spp. Drug treatment (Chs 50 and 53) may be necessary in these and other more serious infections.

TRAVELLER'S DIARRHOEA

More than 3 million people cross international borders each year. Many travel hopefully, but some 20–50% come back ill, having encountered enterotoxin-producing *E. coli* (the most common cause) or other organisms. Most infections are mild and self-limiting, requiring only oral replacement of fluid and salt, as detailed above. General principles for the drug treatment of traveller's diarrhoea are detailed by Gorbach (1987).[8] Up-to-date information on the condition, including the prevalence of infectious organisms around the globe as well as recommended treatment guidelines, is issued in the UK by the National Travel Health Network and Centre (see Web links in the reference list).

ANTIMOTILITY AND SPASMOLYTIC AGENTS

The main pharmacological agents that decrease motility are opiates (Ch. 41) and muscarinic receptor antagonists (Ch. 13). Agents in this latter group are seldom employed as primary therapy for diarrhoea because of their actions on other systems, but small doses of **atropine** are sometimes used, combined with **diphenoxylate** (see below). The action of **morphine**, the archetypal opiate, on the alimentary tract is complex; it increases the tone and rhythmic contractions of the intestine but diminishes propulsive activity. The pyloric, ileocolic and anal sphincters are contracted, and the tone of the large intestine is markedly increased. Its overall effect is constipating.

The main opiates used for the symptomatic relief of diarrhoea are **codeine** (a morphine congener), diphenoxylate and **loperamide** (both **pethidine** congeners that do not readily penetrate the blood–brain barrier and are used only for their actions in the gut). All may have unwanted effects including constipation, abdominal cramps, drowsiness and dizziness. Paralytic ileus can also occur. They should not be used in young (< 4 years of age) children.

Loperamide is the drug of first choice for traveller's diarrhoea and is a component of several proprietary antidiarrhoeal medicines. It has a relatively selective action on the gastrointestinal tract and undergoes significant enterohepatic cycling. It reduces the frequency of abdominal cramps, decreases the passage of faeces and shortens the duration of the illness.

Diphenoxylate also lacks morphine-like activity in the central nervous system, although large doses (25-fold higher) produce typical opioid effects. Preparations of diphenoxylate usually contain atropine as well. Codeine and loperamide have antisecretory actions in addition to their effects on intestinal motility. Cannabinoid receptor agonists also reduce gut motility in animals, most probably by decreasing acetylcholine release from enteric nerves. There have been anecdotal reports of a beneficial effect of cannabis against dysentery and cholera.

Drugs that reduce spasm in the gut are also of value in irritable bowel syndrome and diverticular disease. Muscarinic receptor antagonists (Ch. 13) used for this purpose include atropine, hyoscine, **propantheline** and **dicycloverine**. The last named is thought to have some additional direct relaxant action on smooth muscle. All produce antimuscarinic side effects such as dry mouth, blurred vision and urinary retention. **Mebeverine**, a derivative of **reserpine**, has a direct relaxant action on gastrointestinal smooth muscle. Unwanted effects are few.

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[8]Who flippantly (although accurately) observed that 'travel broadens the mind and loosens the bowels'.

> ### Drugs and gastrointestinal tract motility
>
> - Purgatives include:
>   - bulk laxatives (e.g. **ispaghula** husk, first choice for slow action)
>   - osmotic laxatives (e.g. **lactulose**)
>   - faecal softeners (e.g. **docusate**)
>   - stimulant purgatives (e.g. **senna**).
> - Drugs that can increase motility without purgation:
>   - **domperidone**, used in disorders of gastric emptying.
> - Drugs used to treat diarrhea:
>   - oral rehydration with isotonic solutions of NaCl plus glucose and starch-based cereal (important in infants)
>   - antimotility agents, for example **loperamide** (unwanted effects: drowsiness and nausea).

ADSORBENTS

Adsorbent agents are used extensively in the symptomatic treatment of diarrhoea, although properly controlled trials proving efficacy have not been carried out. The main preparations used contain kaolin, pectin, chalk, charcoal, methylcellulose and activated attapulgite (magnesium aluminium silicate). It has been suggested that these agents may act by adsorbing microorganisms or toxins, by altering the intestinal flora or by coating and protecting the intestinal mucosa, but there is no hard evidence for this. They are often given as mixtures with other drugs (e.g. **kaolin** and **morphine** mixture BP).

DRUGS FOR CHRONIC BOWEL DISEASE

This category comprises *irritable bowel syndrome* (IBS) and *inflammatory bowel disease* (IBD). IBS is characterised by bouts of diarrhoea, constipation or abdominal pain. The aetiology of the disease is uncertain, but psychological factors may play a part. Treatment is symptomatic, with a high-residue diet plus loperamide or a laxative if needed.

Ulcerative colitis and *Crohn's disease* are forms of IBD, affecting the colon or ileum. They are autoimmune inflammatory disorders, which can be severe and progressive, requiring long-term drug treatment with anti-inflammatory and immunosuppressant drugs (see Ch. 26), and occasionally surgical resection. The following agents are used.

GLUCOCORTICOIDS

Glucocorticoids are potent anti-inflammatory agents and are dealt with fully in Chapters 26 and 32. The drugs of choice are generally **prednisolone** or **budesonide** (although others can be used), given orally or locally into the bowel by suppository or enema.

AMINOSALICYLATES

While glucocorticoids are useful for the acute attacks of inflammatory bowel diseases, they are not the ideal for the long-term treatment (because of their side effects). Mainte-

nance of remission in both ulcerative colitis and Crohn's disease is generally achieved with aminosalicylates, although they are less useful in the latter condition.

Sulfasalazine consists of the sulfonamide **sulfapyridine** linked to **5-aminosalicylic acid** (5-ASA). The latter forms the active moiety when it is released in the colon. Its mechanism of action is obscure. It may reduce inflammation by scavenging free radicals, by inhibiting prostaglandin and leukotriene production, and/or by decreasing neutrophil chemotaxis and superoxide generation. Its unwanted effects are diarrhoea, salicylate sensitivity and interstitial nephritis. 5-ASA is not absorbed, but the sulfapyridine moiety, which seems to be therapeutically inert in this instance, is absorbed, and its unwanted effects are those associated with the sulfonamides (see Ch. 50).

Newer compounds in this class, which presumably share a similar mechanism of action, include **mesalazine** (5-ASA itself), **olsalazine** (a 5-ASA dimer linked by a bond that is hydrolysed by colonic bacteria) and **balsalazide** (a prodrug from which 5-ASA is also released following hydrolysis of a diazo linkage).

OTHER DRUGS

The immunosuppressants **azathioprine** and **6-mercaptopurine** (see Ch. 26) are also sometimes used in patients with severe disease. Recently, **infliximab** and **adalimumab**, monoclonal antibodies directed against tumour necrosis factor (TNF)-α, (see Ch. 26) have been used with success for the treatment of inflammatory bowel diseases. These drugs are expensive, and in the UK their use is restricted to moderate/severe Crohn's disease that is unresponsive to glucocorticoids or immunomodulators. The antiallergy drug **sodium cromoglicate** (see Ch. 27) is sometimes used for treating gastrointestinal symptoms associated with food allergies.

DRUGS AFFECTING THE BILIARY SYSTEM

The commonest pathological condition of the biliary tract is cholesterol *cholelithiasis*, i.e. the formation of gallstones with high cholesterol content. Surgery is generally the preferred option, but there are orally active drugs that dissolve non-calcified 'radiolucent' cholesterol gallstones. The principal agent is **ursodeoxycholic acid**, a minor constituent of human bile (but the main bile acid in the bear, hence *urso-*). Diarrhoea is the main unwanted effect.

Biliary colic, the pain produced by the passage of gallstones through the bile duct, can be very intense, and immediate relief may be required. **Morphine** relieves the pain effectively, but it may have an undesirable local effect because it constricts the sphincter of Oddi and raises the pressure in the bile duct. **Buprenorphine** may be preferable. **Pethidine** has similar actions, although it relaxes other smooth muscle, for example that of the ureter. Atropine is commonly employed to relieve biliary spasm because it has antispasmodic action and may be used in conjunction with morphine. **Glyceryl trinitrate** (see Ch. 21) can produce a marked fall of intrabiliary pressure and may be used to relieve biliary spasm.

FUTURE DIRECTIONS

It might be thought that the widespread availability of several different types of safe antisecretory drug would

have satisfied the medical need for antiulcer therapies, but this is not so. Although the incidence of ulcers has dropped, thanks to these drugs, other diseases associated with excess acid production (GORD, NSAID-induced damage) are on the increase, at least in the 'developed' countries. The prospects for new types of histamine antagonist (e.g. H_3 antagonists) are being explored as are antagonists at gastrin receptors. The most interesting new candidates though are the *potassium competitive acid blocker*, several of which are in various stages of clinical development. Potassium ions are exchanged for protons by the proton pump (see Fig. 29.1) and so potassium antagonists would represent an alternative modality for inhibiting the secretion of acid. This novel field, as well as other projects, are discussed by Mossner & Caca (2005).

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Useful Web resources

http://www.nathnac.org. (*This is the site for the UK Health Protection Agency's National Travel Health Network and Centre. There are two components to the site, one for lay people and one for health professionals. Click on the latter and enter 'Travellers' diarrhoea' as a search term to retrieve current information and advice*)

30 The control of blood glucose and drug treatment of diabetes mellitus

OVERVIEW

In this chapter, we describe the endocrine control of blood glucose by pancreatic hormones, especially *insulin* but also *glucagon*, *somatostatin* and *amylin*, and gut hormones (*incretins*), especially *glucagon-like peptide-1* (GLP-1) and *gastric inhibitory peptide* (GIP, which is also known as glucose-dependent insulinotropic peptide). The second part of the chapter is devoted to diabetes mellitus and its treatment with insulin preparations (including insulin analogues), and other hypoglycaemic agents—*metformin*, *sulfonylureas*, *α-glucosidase inhibitors*, *glitazones*, long-acting incretin mimetics such as *exenatide*, and *gliptins* which potentiate incretins by blocking their degradation.

INTRODUCTION

Insulin is the main hormone controlling intermediary metabolism. Its most striking acute effect is to lower blood glucose. Reduced (or absent) secretion of insulin often coupled with reduced sensitivity to its action, 'insulin resistance' which is closely related to obesity, causes *diabetes mellitus*. This disease, recognised since ancient times, is named for the production of copious volumes of sugary urine. Diabetes is rapidly increasing to epidemic proportions (in step with obesity, Ch. 31), and its consequences are dire—especially atherosclerosis (myocardial and cerebral infarction, amputation), kidney failure, neuropathy and blindness.

In this chapter, we first describe the control of blood sugar. The second part of the chapter is devoted to diabetes mellitus and its treatment with drugs.

CONTROL OF BLOOD GLUCOSE

Glucose is the obligatory source of energy for the adult brain, and physiological control of blood glucose reflects the need to maintain adequate fuel supplies in the face of intermittent food intake and variable metabolic demands. More fuel is made available by feeding than is required immediately, and excess calories are stored as glycogen or fat. During fasting, these energy stores need to be mobilised in a regulated manner. The most important regulatory hormone is *insulin*, the actions of which are described below. Increased blood glucose stimulates insulin secretion (Fig. 30.1), whereas reduced blood glucose reduces insulin secretion. The effect of glucose on insulin secretion depends on whether the glucose load is administered intravenously or by mouth. Glucose administered by mouth is more effective in stimulating insulin secretion because it stimulates the release of incretin hormones from the gut, which promote insulin secretion (Fig. 30.1). The effect of glucose

on insulin secretion is abnormal in patients with diabetes (Fig. 30.2). *Hypoglycaemia*, caused by excessive insulin, not only reduces insulin secretion but also elicits secretion of an array of 'counter-regulatory' hormones, including *glucagon*, *adrenaline* (Ch. 14), *glucocorticoids* (Ch. 32) and *growth hormone* (Ch. 32), all of which increase blood glucose. Their main effects on glucose uptake and carbohydrate metabolism are summarised and contrasted with those of insulin in Table 30.1.

PANCREATIC ISLET HORMONES

The islets of Langerhans, the endocrine part of the pancreas, contain four main types of peptide-secreting cells: B (or β) cells secrete *insulin*, A cells secrete *glucagon*, D cells secrete *somatostatin* and PP cells secrete *pancreatic polypeptide* (the function of which is unknown). The core of each islet contains mainly the predominant B cells surrounded by a mantle of A cells interspersed with D cells or PP cells (see Fig. 30.1). In addition to insulin, B cells secrete a peptide known as *islet amyloid polypeptide* or *amylin*, which delays gastric emptying and opposes insulin by stimulating glycogen breakdown in striated muscle, and C-peptide (see below). Glucagon opposes insulin, increasing blood glucose and stimulating protein breakdown in muscle. Somatostatin inhibits secretion of insulin and of glucagon. It is widely distributed outside the pancreas and is also released from the hypothalamus, inhibiting the release of growth hormone from the pituitary gland (Ch. 32).

INSULIN

Insulin was the first protein for which the amino acid sequence was determined (by Sanger's group in Cambridge in 1955). It consists of two peptide chains (of 21 and 30 amino acid residues) linked by disulfide bonds.

SYNTHESIS AND SECRETION

Like other peptide hormones (see Ch. 19), insulin is synthesised as a precursor (preproinsulin) in the rough endoplasmic reticulum. Preproinsulin is transported to the Golgi apparatus, where it undergoes proteolytic cleavage to proinsulin and then to insulin plus a fragment of uncertain function called C-peptide.[1] Insulin and C-peptide are stored in granules in B cells, and are normally co-secreted by exocytosis in equimolar amounts together with smaller and variable amounts of proinsulin.

The main factor controlling the synthesis and secretion of insulin is the blood glucose concentration (Fig. 30.1). B cells respond both to the absolute glucose concentration and to

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[1]Not to be confused with C-reactive peptide, which is an acute-phase reactant used clinically as a marker of inflammation (Ch. 6).
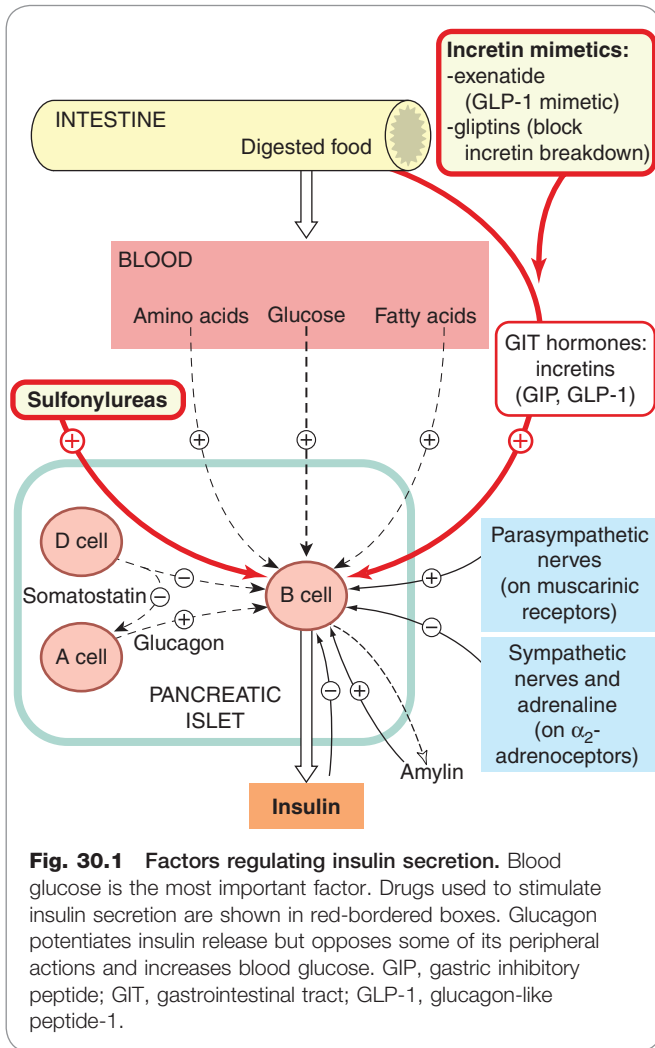
Fig. 30.1 Factors regulating insulin secretion. Blood glucose is the most important factor. Drugs used to stimulate insulin secretion are shown in red-bordered boxes. Glucagon potentiates insulin release but opposes some of its peripheral actions and increases blood glucose. GIP, gastric inhibitory peptide; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1.

the rate of change of blood glucose. Other physiological stimuli to insulin release include amino acids (particularly arginine and leucine), fatty acids, the parasympathetic nervous system and *incretins* (see below). The main incretins are *GLP-1* and *GIP*. Pharmacologically, sulfonylurea drugs (see below) act by releasing insulin.

There is a steady basal release of insulin and also a response to an increase in blood glucose. This response has
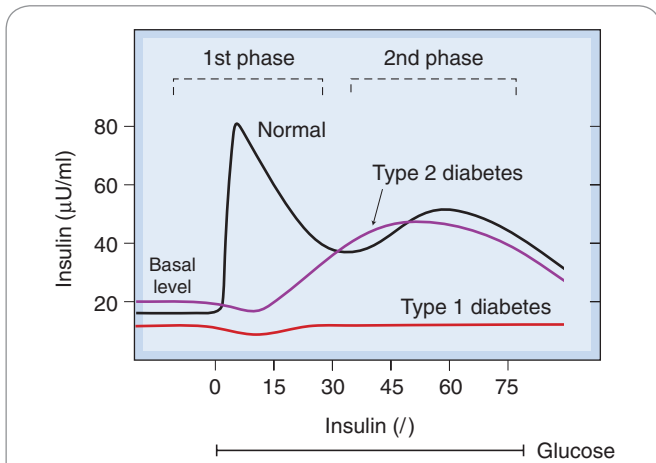

Fig. 30.2 Schematic diagram of the two-phase release of insulin in response to a constant glucose infusion. The first phase is missing in type 2 (non-insulin-dependent) diabetes mellitus, and both are missing in type 1 (insulin-dependent) diabetes mellitus. The first phase is also produced by amino acids, sulfonylureas, glucagon and gastrointestinal tract hormones. (Data from Pfeifer et al. 1981 Am J Med 70: 579–588.)

Table 30.1	The effect of hormones on blood glucose		
Hormone	**Main actions**	**Main stimuli for secretion**	**Main effect**
Main regulatory hormone			
Insulin	↑ Glucose uptake ↑ Glycogen synthesis ↓ Glycogenolysis ↓ Gluconeogenesis	Acute rise in blood glucose Incretins (GIP and GLP-1)	↓ Blood glucose
Main counter-regulatory hormones			
Glucagon	↑ Glycogenolysis ↑ Glyconeogenesis		
Adrenaline (epinephrine)	↑ Glycogenolysis	Hypoglycaemia (i.e. blood glucose <3 mmol/l), (e.g. with exercise, stress, high protein meals), etc.	↑ Blood glucose
Glucocorticoids	↓ Glucose uptake ↑ Gluconeogenesis ↓ Glucose uptake and utilisation		
Growth hormone	↓ Glucose uptake		

Table 30.2 Effects of insulin on carbohydrate, fat and protein metabolism

Type of metabolism	Liver cells	Fat cells	Muscle
Carbohydrate metabolism	↓ Gluconeogenesis ↓ Glycogenolysis ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis
Fat metabolism	↑ Lipogenesis ↓ Lipolysis	↑ Synthesis of triglycerides ↑ Fatty acid synthesis ↓ Lipolysis	–
Protein metabolism	↓ Protein breakdown	–	↑ Amino acid uptake ↑ Protein synthesis

two phases: an initial rapid phase reflecting release of stored hormone, and a slower, delayed phase reflecting continued release of stored hormone and new synthesis (Fig. 30.2). The response is abnormal in diabetes mellitus, as discussed later.

ATP-sensitive potassium channels (K_{ATP}; Ch. 4) determine the resting membrane potential in B cells. Glucose enters B cells via a membrane transporter called Glut-2, and its subsequent metabolism via glucokinase (the rate-limiting enzyme that acts as the 'glucose sensor' linking insulin secretion to extracellular glucose) and glycolysis increases intracellular ATP. This blocks K_{ATP} channels, causing membrane depolarisation and opening of voltage-dependent calcium channels, leading to Ca^{2+} influx. The resulting increase in cytoplasmic Ca^{2+} triggers insulin secretion, but only in the presence of amplifying messengers including diacylglycerol, non-esterified arachidonic acid (which facilitates further Ca^{2+} entry), and 12-lipoxygenase products of arachidonic acid (mainly *12-S-hydroxyeicosatetraenoic acid* or 12-*S*-HETE; see Ch. 17). Phospholipases are commonly activated by Ca^{2+}, but free arachidonic acid is liberated in B cells by an ATP-sensitive Ca^{2+}-insensitive (ASCI) phospholipase A_2. Consequently, in B cells, Ca^{2+} entry and arachidonic acid production are both driven by ATP, linking cellular energy status to insulin secretion.

Insulin release is inhibited by the sympathetic nervous system (Fig. 30.1). Adrenaline (epinephrine) increases blood glucose by inhibiting insulin release (via α_2 adrenoceptors) and by promoting glycogenolysis via β_2-adrenoceptors in striated muscle and liver. Several peptides, including somatostatin, galanin (an endogenous K_{ATP} activator) and amylin, also inhibit insulin release.

About one-fifth of the insulin stored in the pancreas of the human adult is secreted daily. Circulating insulin is measured by immunoassay, but this may give an overestimate because many insulin antibodies cross-react with proinsulin and its less active degradation products. The plasma insulin concentration after an overnight fast is 20–50 pmol/l. Plasma insulin concentration is reduced in patients with type 1 (insulin-dependent) diabetes mellitus (see below), and markedly increased in patients with

insulinomas (uncommon functioning tumours of B cells), as is C-peptide, with which it is co-released.[2] It is also raised in obesity and other normoglycaemic insulin-resistant states.

ACTIONS

Insulin is the main hormone controlling intermediary metabolism, having actions on liver, fat and muscle (Table 30.2). It is an *anabolic hormone*: its overall effect is to conserve fuel by facilitating the uptake and storage of glucose, amino acids and fats after a meal. Acutely, it reduces blood glucose. Consequently, a fall in plasma insulin increases blood glucose. The biochemical pathways through which insulin exerts its effects are summarised in Figure 30.3, and molecular aspects of its mechanism are discussed below.

Insulin influences glucose metabolism in most tissues, especially the liver, where it inhibits glycogenolysis (glycogen breakdown) and gluconeogenesis (synthesis of glucose from non-carbohydrate sources) while stimulating glycogen synthesis. It also increases glucose utilisation (glycolysis), but the overall effect is to increase hepatic glycogen stores.

In muscle, unlike liver, uptake of glucose is slow and is the rate-limiting step in carbohydrate metabolism. The main effects of insulin are to increase facilitated transport of glucose via a transporter called Glut-4, and to stimulate glycogen synthesis and glycolysis.

Insulin increases glucose uptake by Glut-4 in adipose tissue as well as in muscle, enhancing glucose metabolism. One of the main end products of glucose metabolism in adipose tissue is glycerol, which is esterified with

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[2]Insulin for injection does not contain C-peptide, which therefore provides a means of distinguishing endogenous from exogenous insulin. This is used to differentiate insulinoma (an insulin-secreting tumour causing high circulating insulin with high C-peptide) from surreptitious injection of insulin (high insulin, normal or low C-peptide). Deliberate induction of hypoglycaemia by self-injection with insulin is a well-recognised, if unusual, manifestation of psychiatric disorder, especially in health professionals—it has also been used in murder.
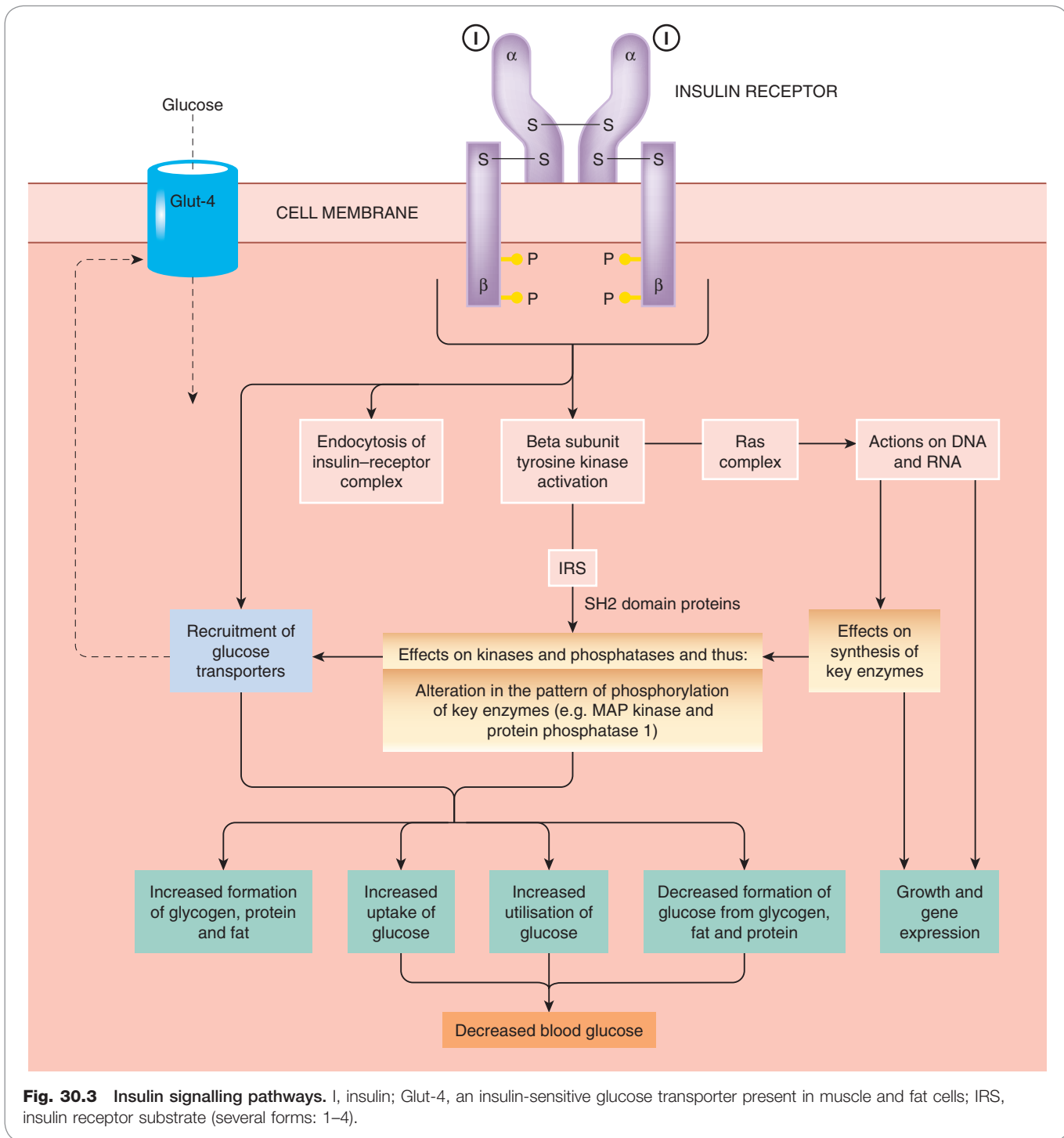
Fig. 30.3 Insulin signalling pathways. I, insulin; Glut-4, an insulin-sensitive glucose transporter present in muscle and fat cells; IRS, insulin receptor substrate (several forms: 1–4).

fatty acids to form triglycerides, thereby affecting fat metabolism (see below and Table 30.2).

Insulin increases synthesis of fatty acid and triglyceride in adipose tissue and in liver. It inhibits lipolysis, partly via dephosphorylation—and hence inactivation—of lipases (Table 30.2). It also inhibits the lipolytic actions of adrena-line, growth hormone and glucagon by opposing their actions on adenylyl cyclase.

Insulin stimulates uptake of amino acids into muscle and increases protein synthesis. It also decreases protein catabolism and inhibits oxidation of amino acids in the liver.

Other metabolic effects of insulin include transport into cells of K^+, Ca^{2+}, nucleosides and inorganic phosphate.[3]

Long-term effects of insulin

In addition to its rapid effects on metabolism, exerted via altered activity of enzymes and transport proteins, insulin has long-term actions via altered enzyme synthesis. It is an important anabolic hormone during fetal development. It stimulates cell proliferation and is implicated in somatic and visceral growth and development.

Mitogenic actions of insulin are of great concern in the development of insulin analogues, because these are intended for long-term use; **insulin glargine** (one widely used analogue; see below) is 6–8-fold more mitogenic than human insulin, and cultured breast cancer cells proliferate in response to near-therapeutic concentrations of this analogue in vitro, but it is not known if there is any clinically significant parallel in vivo. Mammary tumours developed in rats given one long-acting insulin analogue.

MECHANISM OF ACTION

Insulin binds to a specific receptor on the surface of its target cells. The receptor is a large transmembrane glycoprotein complex belonging to the tyrosine kinase-linked type 3 receptor superfamily (Ch. 3) and consisting of two α and two β subunits (Fig. 30.3). Occupied receptors aggregate into clusters, which are subsequently internalised in vesicles, resulting in downregulation. Internalised insulin is degraded in lysosomes, but the receptors are recycled to the plasma membrane.

▼ The signal transduction mechanisms that link receptor binding to the biological effects of insulin are complex. Receptor autophosphorylation—the first step in signal transduction—is a consequence of dimerisation, allowing each receptor to phosphorylate the other, as explained in Chapter 3.

Insulin receptor substrate (IRS) proteins undergo rapid tyrosine phosphorylation specifically in response to insulin and insulin-like growth factor-1 but not to other growth factors. The best-characterised substrate is IRS-1, which contains 22 tyrosine residues that are potential phosphorylation sites. It interacts with proteins that contain a so-called SH2 domain (see Ch. 3, Fig. 3.15), thereby passing on the insulin signal. Knockout mice lacking IRS-1 are hyporesponsive to insulin (insulin resistant) but do not become diabetic, because of robust B-cell compensation with increased insulin secretion. By contrast, mice lacking IRS-2 fail to compensate and develop overt diabetes, implicating the IRS-2 gene as a candidate for human type 2 diabetes (IRS proteins are reviewed by Lee & White, 2004). Activation of phosphatidylinositol 3-kinase by interaction of its SH2 domain with phosphorylated IRS has several important effects, including recruitment of insulin-sensitive glucose transporters (Glut-4) from the Golgi apparatus to the plasma membrane in muscle and fat cells.

The longer-term actions of insulin entail effects on DNA and RNA, mediated partly at least by the Ras signalling complex. Ras is a protein that regulates cell growth and cycles between an active GTP-bound form and an inactive GDP-bound form (see Chs 3 and 55). Insulin shifts the equilibrium in favour of the active form, and initiates a phosphorylation cascade that results in activation of mitogen-activated protein kinase (MAP-kinase), which in turn activates several nuclear transcription factors, leading to the expression of genes that are involved both with cell growth and with intermediary metabolism. Regulation of the rate of mRNA transcription by insulin provides an important means of modulating enzyme activity.

Insulin for treatment of diabetes mellitus is considered below.

GLUCAGON

SYNTHESIS AND SECRETION

Glucagon is a single-chain polypeptide of 21 amino acid residues synthesised mainly in the A cell of the islets, but also in the upper gastrointestinal tract. It has considerable structural homology with other gastrointestinal tract hormones, including secretin, vasoactive intestinal peptide and GIP (see Ch. 29).

One of the main physiological stimuli to glucagon secretion is the concentration of amino acids, in particular L-arginine, in plasma. Therefore an increase in secretion follows ingestion of a high-protein meal, but compared with insulin there is relatively little change in plasma glucagon concentrations throughout the day. Glucagon secretion is stimulated by low and inhibited by high concentrations of glucose and fatty acids in the plasma. Sympathetic nerve activity and circulating adrenaline stimulate glucagon release via β-adrenoceptors. Parasympathetic nerve activity also increases secretion, whereas somatostatin, released from D cells adjacent to the glucagon-secreting A cells in the periphery of the islets, inhibits glucagon release.

ACTIONS

Glucagon increases blood glucose and causes breakdown of fat and protein. It acts on specific G-protein-coupled receptors to stimulate adenylyl cyclase, and consequently its actions are somewhat similar to β-adrenoceptor-mediated actions of adrenaline. Unlike adrenaline, however, its metabolic effects are more pronounced than

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> ### Endocrine pancreas and blood glucose
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> - Islets of Langerhans secrete insulin from B (or β) cells, glucagon from A cells and somatostatin from D cells.
> - Many factors stimulate insulin secretion, but the main one is blood glucose. Incretins, especially GIP and GLP-1 secreted, respectively, by K and L cells in the gut are also important.
> - Insulin has essential metabolic actions as a fuel storage hormone and also affects cell growth and differentiation. It decreases blood glucose by:
>   - increasing glucose uptake into muscle and fat via Glut-4
>   - increasing glycogen synthesis
>   - decreasing gluconeogenesis
>   - decreasing glycogen breakdown.
> - Glucagon is a fuel-mobilising hormone, stimulating gluconeogenesis and glycogenolysis, also lipolysis and proteolysis. It increases blood sugar and also increases the force of contraction of the heart.
> - Diabetes mellitus is a chronic metabolic disorder in which there is hyperglycaemia. There are two main types:
>   - type 1 (insulin-dependent) diabetes, with an absolute deficiency of insulin
>   - type 2 (non-insulin-dependent) diabetes, with a relative deficiency of insulin associated with reduced sensitivity to its action (insulin resistance).

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[3]The action on K^+ is exploited in the emergency treatment of hyperkalaemia by intravenous glucose with insulin (see Ch. 28).

Clinical uses of glucagon

- **Glucagon** can be given intramuscularly or subcutaneously as well as intravenously.
- Treatment of *hypoglycaemia* in unconscious patients (who cannot drink); unlike intravenous glucose, it can be administered by non-medical personnel (e.g. spouses or ambulance crew). It is useful if obtaining intravenous access is difficult.
- Treatment of *acute cardiac failure* precipitated by β-adrenoceptor antagonists.

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its cardiovascular actions. Glucagon is proportionately more active on liver, while the metabolic actions of adrenaline are more pronounced on muscle and fat. Glucagon stimulates glycogen breakdown and gluconeogenesis, and inhibits glycogen synthesis and glucose oxidation. Its metabolic actions on target tissues are thus the opposite of those of insulin. Glucagon increases the rate and force of contraction of the heart, although less markedly than adrenaline.

Clinical uses of glucagon are summarised in the clinical box.

SOMATOSTATIN

Somatostatin is secreted by the D cells of the islets. It is also generated in the hypothalamus, where it acts to inhibit the release of growth hormone (see Ch. 32). In the islet, it inhibits release of insulin and of glucagon. **Octreotide** is a long-acting analogue of somatostatin. It inhibits release of a number of hormones, and is used clinically to relieve symptoms from several uncommon gastroenteropancreatic endocrine tumours, and for treatment of acromegaly[4] (the endocrine disorder caused by a functioning tumour of cells that secrete growth hormone from the anterior pituitary; see Ch. 32).

AMYLIN (ISLET AMYLOID POLYPEPTIDE)

▼ The term *amyloid* refers to amorphous protein deposits in different tissues that occur in a variety of diseases, including several neurodegenerative conditions (see Ch. 39). Amyloid deposits occur in the pancreas of patients with diabetes mellitus, although it is not known if this is functionally important. The major component of pancreatic amyloid is a 37-amino acid residue peptide known as islet amyloid polypeptide or amylin. This is stored with insulin in secretory granules in B cells and is co-secreted with insulin. Amylin delays gastric emptying. Supraphysiological concentrations stimulate the breakdown of glycogen to lactate in striated muscle. Amylin also inhibits insulin secretion (Fig. 30.1). It is structurally related to calcitonin (see Ch. 35) and has weak calcitonin-like actions on calcium metabolism and osteoclast activity. It is also about 50% identical with calcitonin gene-related peptide (CGRP; see Ch. 19), and large intravenous doses cause vasodilatation, presumably by an action on CGRP receptors. Whether amylin has a role in the physiological control of glucose metabolism is controversial, but there is interest in the therapeutic potential of amylin agonists (such as **pramlintide**, an analogue with three proline substitutions that reduce its tendency to aggregate into insoluble fibrils)—see Schmitz et al. (2004) for a review.

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[4]Octreotide is used either short term before surgery on the pituitary tumour, or while waiting for radiotherapy of the tumour to take effect, or if other treatments have been ineffective.

INCRETINS

La Barre suggested in the 1930s that crude secretin contained two active principles: 'excretin', which stimulates the exocrine pancreas and 'incretin', which stimulates insulin release. He proposed that incretin presented possibilities for the treatment of diabetes. 'Excretin' did not catch on (perhaps not helped by an unfortunate association with other bodily functions—at least to an Anglo-Saxon ear), but 'incretin' has gone from strength to strength, and some 80 years later several incretin-based drugs are now licensed for clinical use (see below). Incretin action proved to be due to peptide hormones released from the gut, mainly *glucagon-like insulinotropic peptide* (GIP) and *glucagon-like peptide-1* (GLP-1). These are both members of the glucagon peptide superfamily (Ch. 19). GIP is a 42-amino acid peptide stored in and secreted by enteroendocrine K cells in the duodenum and proximal jejunum. GLP-1 is secreted by L cells which are more widely distributed in the gut, including in the ileum and colon as well as more proximally. Two forms of GLP-1 are secreted after a meal: GLP-1(7-37) and GLP-1(7-36) amide; these are similarly potent. Most of the circulating activity is due to GLP-1(7-36) amide. Release of GIP and GLP-1 by ingested food provides an early stimulus to insulin secretion before absorbed glucose or other products of digestion reach the islet cells in the portal blood (Fig. 30.1). As well as stimulating insulin secretion, both these hormones inhibit pancreatic glucagon secretion and slow the rate of absorption of digested food by reducing gastric emptying. They are also implicated in control of food intake via appetite and satiety (see Ch. 31). The actions of GIP and GLP-1 are terminated rapidly by dipeptidyl peptidase-4 (DPP-4). This enzyme is a membrane glycoprotein with rather wide substrate specificity—it has been implicated in suppression of malignancy (e.g. Wesley et al., 2005).

DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic disorder characterised by a high blood glucose concentration—hyperglycaemia (fasting plasma glucose > 7.0 mmol/l, or plasma glucose > 11.1 mmol/l, 2 h after a meal)—caused by insulin deficiency, often combined with insulin resistance. Hyperglycaemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. When the renal threshold for glucose reabsorption is exceeded, glucose spills over into the urine (glycosuria) and causes an osmotic diuresis (polyuria) which, in turn, results in dehydration, thirst and increased drinking (polydipsia). Insulin deficiency causes wasting through increased breakdown and reduced synthesis of proteins. Diabetic ketoacidosis is an acute emergency. It develops in the absence of insulin because of accelerated breakdown of fat to acetyl-CoA, which, in the absence of aerobic carbohydrate metabolism, is converted to acetoacetate and β-hydroxybutyrate (which cause acidosis) and acetone (a ketone).

Various complications develop as a consequence of the metabolic derangements in diabetes, often over many years. Many of these are the result of disease of blood vessels, either large (macrovascular disease) or small (microangiopathy). Dysfunction of vascular endothelium (see Ch. 22) is an early and critical event in the

development of vascular complications. Oxygen-derived free radicals, protein kinase C and non-enzymic products of glucose and albumin called *advanced glycation end products* (AGE) have been implicated. Macrovascular disease consists of accelerated atheroma (Ch. 23) and its thrombotic complications (Ch. 24), which are commoner and more severe in diabetic patients. Microangiopathy is a distinctive feature of diabetes mellitus and particularly affects the retina, kidney and peripheral nerves. Diabetes mellitus is the commonest cause of chronic renal failure, which itself represents a huge and rapidly increasing problem, the costs of which to society as well as to individual patients are staggering. Coexistent hypertension promotes progressive renal damage, and treatment of hypertension slows the progression of diabetic nephropathy and reduces the risk of myocardial infarction. Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists (Ch. 22) are more effective in preventing diabetic nephropathy than other antihypertensive drugs, perhaps because they prevent fibroproliferative actions of angiotensin II and aldosterone.

Diabetic neuropathy[5] is associated with accumulation of osmotically active metabolites of glucose, produced by the action of aldose reductase, but *aldose reductase inhibitors* have been disappointing as therapeutic drugs (see Chung & Chung, 2005, for a review).

There are two main types of diabetes mellitus:

1. **Type 1 diabetes** (previously known as insulin-dependent diabetes mellitus—IDDM—or juvenile-onset diabetes).
2. **Type 2 diabetes** (previously known as non-insulin-dependent diabetes mellitus—NIDDM—or maturity-onset diabetes).

In type 1 diabetes, there is an absolute deficiency of insulin resulting from autoimmune destruction of pancreatic B cells. Without insulin treatment, such patients will ultimately die with diabetic ketoacidosis.

▼ Type 1 diabetic patients are usually young (children or adolescents) and not obese when they first develop symptoms. There is an inherited predisposition, with a 10-fold increased incidence in first-degree relatives of an index case, and strong associations with particular histocompatibility antigens (HLA types). Studies of identical twins have shown that genetically predisposed individuals must additionally be exposed to an environmental factor such as viral infection (e.g. with coxsackievirus or echovirus). Viral infection may damage pancreatic B cells and expose antigens that initiate a self-perpetuating autoimmune process. The patient becomes overtly diabetic only when more than 90% of the B cells have been destroyed. This natural history provides a tantalising prospect of intervening in the prediabetic stage, and a variety of strategies have been mooted, including immunosuppression, early insulin therapy, antioxidants, nicotinamide and many others; so far these have disappointed, but this remains a very active field.

Type 2 diabetes is accompanied both by insulin resistance (which precedes overt disease) and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as B-cell function declines. Treatment is initially dietary, although

oral hypoglycaemic drugs usually become necessary, and about one-third of patients ultimately require insulin. Prospective studies have demonstrated a relentless deterioration in diabetic control[6] over the years.

Insulin secretion in the two main forms of diabetes is shown schematically in Figure 30.2, contrasted with the normal response.

There are many other less common forms of diabetes mellitus in addition to the two main ones described above, and hyperglycaemia can also be a clinically important adverse effect of several drugs, including glucocorticoids (Ch. 32), high doses of thiazide diuretics (Ch. 28) and several of the protease inhibitors used to treat HIV infection (Ch. 51).

TREATMENT OF DIABETES MELLITUS

Insulin is essential for the treatment of type 1 diabetes, and a valuable component of the treatment of many patients with type 2 disease.

▼ For many years, it was assumed, as an act of faith, that normalising plasma glucose would prevent diabetic complications. The Diabetes Control and Complications Trial (American Diabetes Association, 1993) showed that this faith was well placed: type 1 diabetic patients were randomly allocated to intensive or conventional management. Mean fasting blood glucose concentration was 2.8 mmol/l lower in the intensively treated group, who had a substantial reduction in the occurrence and progression of retinopathy, nephropathy and neuropathy over a period of 4–9 years. These benefits outweighed a three-fold increase in severe hypoglycaemic attacks and modest excess weight gain.

The UK Prospective Diabetes Study showed that *lowering blood pressure* markedly improves outcome in type 2 diabetes. Normalisation of blood glucose was not achieved even in intensively treated patients. Better metabolic control did improve outcome, but (in contrast to lowering blood pressure) the magnitude of the benefit was disappointing and statistically significant only for microvascular complications. In long-term follow-up, patients from this study who had been allocated to intensive treatment continued to have better outcomes than patients treated with diet alone (despite diabetic control becoming similar in the two groups after the blinded treatment period had finished), suggesting that early diabetic control (within the first 12 years from diagnosis) is important (Holman et al., 2008). By contrast, studies of intensive control later in the course of the disease have been disappointing with harm from hypoglycaemia outweighing any benefit of intensive treatment.

Realistic goals in type 2 diabetic patients are usually less ambitious than in younger type 1 patients. Diet is the cornerstone (albeit one with a tendency to crumble), combined with increased exercise. Oral agents are used to control symptoms from hyperglycaemia, as well as to limit microvascular complications, and are introduced early. Dietary measures and statins to prevent atheromatous disease (Ch. 24) are crucial. Details of dietary management and treatment for specific diabetic complications are beyond the scope of this book. Newer drugs (glitazones and drugs that mimic or potentiate incretins) have been shown to reduce glycated haemoglobin (typically by 0.5–1 percentage points) but their effects (if any) on clinical outcomes such as diabetic complications are unproven.

INSULIN TREATMENT

The effects of insulin and its mechanism of action are described above. Here we describe pharmacokinetic aspects and adverse effects, both of which are central to its

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[5]Neuropathy ('disease of the nerves') causes dysfunction of peripheral nerve fibres, which can be motor, sensory or autonomic. Diabetic neuropathy often causes numbness in a 'stocking' distribution caused by damage to sensory fibres, and postural hypotension and erectile dysfunction due to autonomic neuropathy.

[6]Diabetic control is not easily estimated by determination of blood glucose, because this is so variable. Instead, glycated haemoglobin (haemoglobin A_{1C}) is measured. This provides an integrated measure of control over the lifespan of the red cell: approximately 120 days.

therapeutic use. Insulin for clinical use was once either porcine or bovine but is now almost entirely human (made by recombinant DNA technology). Animal insulins are liable to elicit an immune response, a problem that is avoided by the use of recombinant human insulin. Although recombinant insulin is more consistent in quality than insulins extracted from pancreases of freshly slaughtered animals, doses are still quantified in terms of units of activity, with which doctors and patients are familiar, rather than of mass.

Pharmacokinetic aspects and insulin preparations

Insulin is destroyed in the gastrointestinal tract, and must be given parenterally—usually subcutaneously, but intravenously or occasionally intramuscularly in emergencies. Intraperitoneal insulin is used in diabetic patients with end-stage renal failure treated by ambulatory peritoneal dialysis. Pulmonary absorption of insulin occurs, but an aerosol formulation was withdrawn from therapeutic use. Other potential approaches include incorporation of insulin into biodegradable polymer microspheres as a slow-release formulation, and its encapsulation with a lectin in a glucose-permeable membrane.[7] Once absorbed, insulin has an elimination half-life of approximately 10 min. It is inactivated enzymically in the liver and kidney, and 10% is excreted in the urine. Renal impairment reduces insulin requirement.

One of the main problems in using insulin is to avoid wide fluctuations in plasma concentration and thus in blood glucose. Different formulations vary in the timing of their peak effect and duration of action. *Soluble insulin* produces a rapid and short-lived effect. Longer-acting preparations are made by precipitating insulin with protamine or zinc, thus forming finely divided amorphous solid or relatively insoluble crystals, which are injected as a suspension from which insulin is slowly absorbed. These preparations include *isophane insulin* and amorphous or crystalline *insulin zinc suspensions*. Mixtures of different forms in fixed proportions are available. **Insulin lispro** is an insulin analogue in which a lysine and a proline residue are 'switched'. It acts more rapidly but for a shorter time than natural insulin, enabling patients to inject themselves immediately before the start of a meal. **Insulin glargine** is another modified insulin analogue, designed with the opposite intention, namely to provide a constant basal insulin supply and mimic physiological postabsorptive basal insulin secretion. Insulin glargine, which is a clear solution, forms a microprecipitate at the physiological pH of subcutaneous tissue, and absorption from the subcutaneous site of injection is prolonged. Used in conjunction with short-acting insulin, it lowers postabsorptive plasma glucose.

Various dosage regimens are used. Some type 1 patients inject a combination of short- and intermediate-acting insulins twice daily, before breakfast and before the evening meal. Improved control of blood glucose can be achieved with multiple daily injections of short-acting insulins with meals, and a longer-acting insulin at night. Insulin pumps are used in hospital and sometimes, by specialists, in outpatients. The most sophisticated forms of pump regulate the dose by means of a sensor that continuously measures blood glucose, but these are not routinely available.

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[7]This could, in theory, provide variable release of insulin controlled by the prevailing glucose concentration, because glucose and glycated insulin compete for binding sites on the lectin.

> ### Clinical uses of insulin and other hypoglycaemic drugs for injection
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> - Patients with *type 1 diabetes* require long-term **insulin**:
>   - an intermediate-acting preparation (e.g. **isophane insulin**) or a long-acting analogue (e.g. **glargine**) is often combined with soluble insulin or a short-acting analogue (e.g. **lispro**) taken before meals.
> - **Soluble insulin** is used (intravenously) in emergency treatment of hyperglycaemic emergencies (e.g. *diabetic ketoacidosis*).
> - Approximately one-third of patients with *type 2 diabetes* ultimately benefit from insulin.
> - Short-term treatment of patients with type 2 diabetes or impaired glucose tolerance during intercurrent events (e.g. *operations*, *infections*, *myocardial infarction*).
> - During pregnancy, for *gestational diabetes* not controlled by diet alone.
> - Emergency treatment of *hyperkalaemia*: insulin is given with glucose to lower extracellular K^+ via redistribution into cells.
> - **Exenatide** for type 2 diabetes in addition to oral agents to improve control and lose weight.

Unwanted effects

The main undesirable effect of insulin is hypoglycaemia. This is common and, if very severe, can cause brain damage. In one large clinical trial, intensive insulin therapy resulted in a three-fold increase in severe hypoglycaemia compared with usual care. The treatment of hypoglycaemia is to take a sweet drink or snack or, if the patient is unconscious, to give intravenous glucose or intramuscular glucagon (see above). Rebound hyperglycaemia ('Somogyi effect') can follow insulin-induced hypoglycaemia, because of the release of counter-regulatory hormones (see above). This can cause hyperglycaemia before breakfast following an unrecognised hypoglycaemic attack during sleep in the early hours of the morning. It is essential to appreciate this possibility to avoid the mistake of increasing (rather than reducing) the evening dose of insulin in this situation.

Allergy to human insulin is unusual but can occur. It may take the form of local or systemic reactions. Insulin resistance as a consequence of antibody formation is rare. Theoretical concerns regarding mitogenic effects of insulin analogues are mentioned above.

OTHER HYPOGLYCAEMIC AGENTS

Biguanides

Metformin is the only drug of the biguanide class (originally found in French lilac, *Galega officinalis*) that is used clinically.

Actions and mechanism

Biguanides have several biochemical actions. They:

- reduce hepatic glucose production (gluconeogenesis), which is markedly increased in type 2 diabetes
- increase glucose uptake and utilisation in skeletal muscle (i.e. they reduce insulin resistance)
- reduce carbohydrate absorption
- increase fatty acid oxidation

Table 30.3 Oral hypoglycaemic sulfonylurea drugs

Drug	Relative potency[a]	Duration of action and (half-life) (hours)	Pharmacokinetic aspects[b]	General comments
Tolbutamide	1	6–12 (4)	Some converted in liver to weakly active hydroxytolbutamide; some carboxylated to inactive compound Renal excretion	A safe drug; least likely to cause hypoglycaemia May decrease iodide uptake by thyroid Contraindicated in liver failure
Glibenclamide[c]	150	18–24 (10)	Some is oxidised in the liver to moderately active products and is excreted in urine; 50% is excreted unchanged in the faeces	May cause hypoglycaemia The active metabolite accumulates in renal failure
Glipizide	100	16–24 (7)	Peak plasma levels in 1 h Most is metabolised in the liver to inactive products, which are excreted in urine; 12% is excreted in faeces	May cause hypoglycaemia Has diuretic action Only inactive products accumulate in renal failure

[a] Relative to tolbutamide.
[b] All are highly protein bound (90–95%).
[c] Termed gliburide in USA.

- reduce circulating low-density and very-low-density lipoprotein (LDL and VLDL, respectively, see Ch. 23).

Reduced hepatic gluconeogenesis is especially important. The mechanism involves activation in hepatocytes of AMP-activated protein kinase (AMPK), an important enzyme in metabolic control (Towler & Hardie, 2007). Activation of AMPK increases expression of a nuclear receptor that inhibits expression of genes that are important for gluconeogenesis in the liver (see Kim et al., 2008 for details).

Metformin has a half-life of about 3 h and is excreted unchanged in the urine.

Unwanted effects
Metformin, while preventing hyperglycaemia, does *not* cause hypoglycaemia, and the commonest unwanted effects are dose-related gastrointestinal disturbances (e.g. anorexia, diarrhoea, nausea), which are usually but not always transient. Lactic acidosis is a rare but potentially fatal toxic effect, and metformin should not be given routinely to patients with renal or hepatic disease, hypoxic pulmonary disease or shock. Such patients are predisposed to lactic acidosis because of reduced drug elimination or reduced tissue oxygenation. Compensated heart failure is not a contraindication, and indeed metformin is associated with improved outcome in patients with diabetes and heart failure (Eurich et al., 2007). It should be avoided in other situations that predispose to lactic acidosis including some forms of mitochondrial myopathy that are associated with diabetes. Long-term use may interfere with absorption of vitamin B$_{12}$.

Clinical use
Metformin is used to treat patients with type 2 diabetes. It does not stimulate appetite (rather the reverse; see above!) and is consequently the drug of first choice in the majority of type 2 patients who are obese, provided they have unimpaired renal and hepatic function. It can be combined with sulfonylureas, glitazones or insulin. Potential uses outside diabetes include other syndromes with accompanying insulin resistance including polycystic ovary syndrome, non-alcoholic fatty liver disease and some forms of premature puberty, but these indications remain experimental.

Sulfonylureas
The sulfonylureas were developed following the chance observation that a sulfonamide derivative (used to treat typhoid) caused hypoglycaemia. Numerous sulfonylureas are available. The first used therapeutically were **tolbutamide** and **chlorpropamide**. Chlorpropamide has a long duration of action and a substantial fraction is excreted in the urine. Consequently, it can cause severe hypoglycaemia, especially in elderly patients in whom renal function declines inevitably but insidiously (Ch. 28). It causes flushing after alcohol because of a disulfiram-like effect (Ch. 48), and has an action like that of antidiuretic hormone on the distal nephron, giving rise to hyponatraemia and water intoxication. Williams (1994) comments that 'time honoured but idiosyncratic chlorpropamide should now be laid to rest'—a sentiment with which we concur. Tolbutamide, however, remains useful. So-called second-generation sulfonylureas (e.g. **glibenclamide**, **glipizide**; see Table 30.3) are more potent (on a milligram basis), but their maximum hypoglycaemic effect is no greater and control of blood glucose no better than with tolbutamide. These drugs all contain the sulfonylurea moiety and act in the same way, but different substitutions result in differences in pharmacokinetics and hence in duration of action (see Table 30.3).

Mechanism of action
The principal action of sulfonylureas is on B cells (Fig. 30.1), stimulating insulin secretion and thus reducing plasma glucose. High-affinity receptors for sulfonylureas are present on the K$_{ATP}$ channels (Ch. 4) in B-cell plasma membranes, and the binding of various sulfonylureas parallels their potency in stimulating insulin release. Block by sulfonylurea drugs of K$_{ATP}$ channel activation causes depolarisation, Ca^{2+} entry and insulin secretion. (Compare this with the physiological control of insulin secretion, see above.)

Pharmacokinetic aspects

Sulfonylureas are well absorbed after oral administration, and most reach peak plasma concentrations within 2–4 h. The duration of action varies (Table 30.3). All bind strongly to plasma albumin and are implicated in interactions with other drugs (e.g. salicylates and sulfonamides) that compete for these binding sites (see below and Ch. 56). Most sulfonylureas (or their active metabolites) are excreted in the urine, so their action is increased in the elderly and in patients with renal disease.

Most sulfonylureas cross the placenta and enter breast milk and their use is contraindicated in pregnancy and in breastfeeding.

Unwanted effects

The sulfonylureas are usually well tolerated. Unwanted effects are specified in Table 30.3. The commonest adverse effect is hypoglycaemia, which can be severe and prolonged. Its incidence is related to the potency and duration of action of the agent, the highest incidence occurring with long-acting chlorpropamide and glibenclamide and the lowest with tolbutamide. Long-acting sulfonylureas are best avoided in the elderly and in patients with even mild renal impairment because of the risk of hypoglycaemia. Sulfonylureas stimulate appetite and often cause weight gain. This is a major concern in obese diabetic patients. About 3% of patients experience gastrointestinal upsets. Allergic skin rashes can occur, and bone marrow toxicity (Ch. 57), although rare, can be severe.

During and for a few days after acute myocardial infarction, insulin must be substituted for sulfonylurea treatment. This is associated with a substantial reduction in short-term mortality, although it remains unclear if this is due to a beneficial effect specific to insulin or to a detrimental effect of sulfonylurea drugs in this setting, or both. Another vexing question is whether prolonged therapy with oral hypoglycaemic drugs has adverse effects on the cardiovascular system. A study in the USA in the 1970s found that after 4–5 years of treatment, there was an increase in cardiovascular deaths in the group treated with oral drugs compared with the groups treated with insulin or placebo. Blockade of K_{ATP} in heart and vascular tissue could theoretically have adverse effects, but evidence for an adverse cardiovascular effect is inconclusive.

Drug interactions

Several drugs augment the hypoglycaemic effect of sulfonylureas. Non-steroidal anti-inflammatory drugs, coumarins, some uricosuric drugs (e.g. **sulfinpyrazone**), alcohol, monoamine oxidase inhibitors, some antibacterial drugs (including *sulfonamides*, **trimethoprim** and **chloramphenicol**) and some imidazole antifungal drugs have all been reported to produce severe hypoglycaemia when given with a sulfonylurea. The probable basis of most of these interactions is competition for metabolising enzymes, but interference with plasma protein binding or with transport mechanisms facilitating excretion may play some part.

Agents that decrease the action of sulfonylureas on blood glucose include high doses of thiazide diuretics and corticosteroids.

Clinical use

Sulfonylureas are used to treat type 2 diabetes in its early stages, but because they require functional B cells, they are not useful in type 1 or late-stage type 2 diabetes. They can be combined with metformin or with thiazolidinediones.

OTHER DRUGS THAT STIMULATE INSULIN SECRETION

Several drugs that act, like the sulfonylureas, by blocking the sulfonylurea receptor on K_{ATP} channels in pancreatic B cells but lack the sulfonylurea moiety have recently been developed. These include **repaglinide** and **nateglinide** which, though much less potent than most sulfonylureas, have rapid onset and offset kinetics leading to short duration of action and a low risk of hypoglycaemia.[8] These drugs are administered shortly before a meal to reduce the postprandial rise in blood glucose in type 2 diabetic patients inadequately controlled with diet and exercise. They may cause less weight gain than conventional sulfonylureas. Later in the course of the disease, they can be combined with metformin or thiazolidinediones. Unlike glibenclamide, these drugs are relatively selective for K_{ATP} channels on B cells versus K_{ATP} channels in vascular smooth muscle.

Thiazolidinediones (glitazones)

The thiazolidinediones (or *glitazones*) were developed following the chance observation that a **clofibrate** analogue, **ciglitazone**, which was being screened for effects on lipids, unexpectedly lowered blood glucose. Ciglitazone caused liver toxicity, as did **troglitazone**, but there are only rare reports of hepatotoxicity with (**rosiglitazone** and **pioglitazone** which is the only drug of this class in clinical use.)

Effects

The effect of thiazolidinediones on blood glucose is slow in onset, the maximum effect being achieved only after 1–2 months of treatment. Thiazolidinediones:

- reduce hepatic glucose output
- increase glucose uptake into muscle, by enhancing the effectiveness of endogenous insulin.

They reduce the amount of exogenous insulin needed to maintain a given level of blood glucose by approximately 30%. Reduced blood glucose concentration is accompanied by reduced insulin and free fatty acid concentrations. Triglycerides decline, while LDL and high-density lipoprotein (HDL) are unchanged or slightly increased. The proportion of small dense LDL particles (believed to be the most atherogenic; Ch. 23) is reduced. Weight gain of 1–4 kg is common, usually stabilising in 6–12 months. Some of this is attributable to fluid retention: there is an increase in plasma volume of up to 500 ml, with a concomitant reduction in haemoglobin concentration caused by haemodilution; there is also an increase in extravascular fluid, and increased deposition of subcutaneous (as opposed to visceral) fat.

Mechanism of action

Thiazolidinediones bind to a nuclear receptor called the *peroxisome proliferator-activated receptor-γ* (PPARγ), which is complexed with retinoid X receptor (RXR; see Ch. 3).[9]

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[8]It is ironic that these aggressively marketed drugs share many of the properties of tolbutamide, the oldest, least expensive and least fashionable of the sulfonylureas. Perhaps diabetologists should turn some of their investigative effort to studying how best to use this Cinderella drug!

[9]Compare with fibrates (to which thiazolidinediones are structurally related), which bind to PPARα (see Ch. 23).

PPARγ occurs mainly in adipose tissue, but also in muscle and liver. It causes differentiation of adipocytes (this contributes to the unwanted effect of weight gain), increases lipogenesis and enhances uptake of fatty acids and glucose. It also promotes amiloride-sensitive sodium ion reabsorption in renal collecting ducts, explaining the adverse effect of fluid retention (Guan et al., 2005). Endogenous agonists of PPARγ include unsaturated fatty acids and various derivatives of these, including prostaglandin J_2. Thiazolidinediones are exogenous agonists, which cause the PPARγ–RXR complex to bind to DNA, promoting transcription of several genes with products that are important in insulin signalling. These include lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid-binding protein, Glut-4, phosphoenolpyruvate carboxykinase, malic enzyme and others. It remains something of a mystery that glucose homeostasis should be so responsive to drugs that bind to receptors found mainly in fat cells; it has been suggested that the explanation may lie in resetting of the glucose–fatty acid (Randle) cycle by the reduction in circulating free fatty acids.

Pharmacokinetic aspects

Pioglitazone is rapidly and nearly completely absorbed, with time to peak plasma concentration of less than 2 h. It is highly (> 99%) bound to plasma proteins, and is subject to hepatic metabolism and has a short (< 7 h) elimination half-life for the parent drug, but substantially longer (up to 24 h) for the metabolite. Pioglitazone is metabolised mainly by a CYP2C isozyme and CYP3A4 to active metabolites, which are eliminated mainly in bile.

Unwanted effects

The serious hepatotoxicity of ciglitazone and troglitazone was not encountered during clinical trials of pioglitazone, and reports of liver dysfunction since general release have been rare. Regular blood tests of liver function are currently recommended. One (unproven) hypothesis is that the hepatotoxicity of troglitazone is caused by quinone metabolites of its α-tocopherol side chain. The commonest unwanted effects of pioglitazone are weight gain and fluid retention (see above). Fluid retention is a substantial concern, because it can precipitate or worsen heart failure, which contraindicates their use. In addition to increased cardiovascular risk, both observational studies and meta-analysis of randomised controlled trials (Loke et al., 2009) indicate an increased risk (approximately a doubling of risk) of fractures with chronic use. Symptoms of uncertain cause, including headache, fatigue and gastrointestinal disturbances, have also been reported. Thiazolidinediones are contraindicated in pregnant or breastfeeding women and in children. It is theoretically possible that these drugs could cause ovulation to resume in women who are anovulatory because of insulin resistance (e.g. with polycystic ovary syndrome). Another glitazone (rosiglitazone) was withdrawn from clinical use recently because of concerns over excess cardiovascular risks.

Clinical use

Because insulin resistance is one important component of the pathogenesis of type 2 diabetes, and has been implicated in the excess cardiovascular mortality that accompanies the common 'metabolic syndrome' (visceral obesity, hypertension, dyslipidaemia, insulin resistance, etc.), there is a good rationale for pioglitazone in type 2 diabetes.

There is, however, as yet no evidence that this optimism is justified in terms of improved clinical outcomes (see, for example, Gale, 2001)—cardiovascular clinical end-point trials to rebut this view are still awaited. Pioglitazone is additive with other oral hypoglycaemic drugs in terms of effect on blood glucose, and short-term studies support their use in combination with metformin or with a sulfonylurea in patients whose blood glucose is inadequately controlled on one of these drugs and are unsuited to addition of the other.

α-Glucosidase inhibitors

Acarbose, an inhibitor of intestinal α-glucosidase, is used in type 2 patients whose diabetes is inadequately controlled by diet with or without other agents. It delays carbohydrate absorption, reducing the postprandial increase in blood glucose. The commonest adverse effects are related to its main action and consist of flatulence, loose stools or diarrhoea, and abdominal pain and bloating. Like metformin, it may be particularly helpful in obese type 2 patients, and it can be co-administered with metformin.

Incretin mimetics and related drugs

Exenatide is a synthetic version of *exendin-4*, a peptide found in the saliva of the Gila monster (a lizard, which presumably evolved this as means to disable its prey by rendering them hypoglycaemic).

Exenatide mimics the effects of GLP-1 (see above), but is longer acting. It lowers blood glucose after a meal by increasing insulin secretion, suppressing glucagon secretion and slowing gastric emptying (see above). It reduces food intake (by an effect on satiety) and is associated with modest weight loss. It reduces hepatic fat accumulation.

Exenatide is not absorbed by the gut and is administered subcutaneously. It is much more stable than GLP-1, and is administered twice daily before the first and last meal of the day. A long-acting preparation (for once-weekly administration) is under investigation (Drucker et al., 2008). It can cause hypoglycaemia and a range of gastrointestinal effects. Pancreatitis is a rare but sometimes severe problem.

Exenatide is used in patients with type 2 diabetes in combination with metformin with or without a sulfonylurea when these have been inadequate.

Gliptins

Gliptins (e.g. **sitagliptin**, **vildagliptin**) are synthetic drugs that competitively inhibit dipeptidylpeptidase-4 (DPP-4), thereby lowering blood glucose by potentiating endogenous incretins (GLP-1 and GIP, see above). Sitagliptin does not cause weight loss or weight gain.

Sitagliptin is well absorbed from the gut and is administered once daily by mouth. It is mainly eliminated by renal excretion and is also metabolised by hepatic CYP enzymes. It is well tolerated with an adverse effect profile in clinical trials similar to placebo, and similar occurrence of hypoglycaemia between placebo and sitagliptin. Vildagliptin is not available in the USA, where the Food and Drug Administration has required further investigation to exclude skin and renal toxicity.

Sitagliptin is used for type 2 diabetes, usually in addition to other oral hypoglycaemic drugs (see clinical box on uses of oral hypoglycaemic drugs).

Drugs used in diabetes mellitus

Insulin and other injectable drugs

- Human **insulin** is made by recombinant DNA technology. For routine use, it is given subcutaneously (by intravenous infusion in emergencies).
- Different formulations of insulin differ in their duration of action:
  - fast- and short-acting soluble insulin: peak action after subcutaneous dose 2–4 h and duration 6–8 h; it is the only formulation that can be given intravenously
  - intermediate-acting insulin (e.g. isophane insulin)
  - long-acting forms (e.g. insulin zinc suspension).
- The main unwanted effect is hypoglycaemia.
- Altering the amino acid sequence ('designer' insulins, e.g. **lispro** and **glargine**) can usefully alter insulin kinetics.
- Insulins are used for all type 1 diabetic patients and approximately one-third of patients with type 2 diabetes.
- **Exenatide** is an incretin mimetic which is injected twice daily in some type 2 diabetic patients inadequately controlled by oral drugs. Unlike insulin it causes weight loss.

Oral hypoglycaemic drugs

- These are used in type 2 diabetes.
- Biguanides (e.g. **metformin**):
  - have complex peripheral actions in the presence of residual insulin, increasing glucose uptake in striated muscle and inhibiting hepatic glucose output and intestinal glucose absorption
  - cause anorexia and encourage weight loss
  - can be combined with sulfonylureas.
- Sulfonylureas and other drugs that stimulate insulin secretion (e.g. **tolbutamide**, **glibenclamide**, **nateglinide**):
  - can cause hypoglycaemia (which stimulates appetite and leads to weight gain)
  - are effective only if B cells are functional
  - block ATP-sensitive potassium channels in B cells
  - are well tolerated but promote weight gain.
- Thiazolidinediones (e.g. **pioglitazone**):
  - increase insulin sensitivity and lower blood glucose in type 2 diabetes
  - can cause weight gain and oedema
  - increase osteoporotic fractures
  - are peroxisome proliferator-activated receptor-γ (a nuclear receptor) agonists.
- Gliptins (e.g. **sitagliptin**):
  - potentiate endogenous incretins by blocking DPP-4
  - are added to other orally active drugs to improve control in patients with type 2 diabetes
  - are well tolerated and weight neutral.
- α-Glucosidase inhibitor, **acarbose**:
  - reduces carbohydrate absorption
  - causes flatulence and diarrhoea.

Clinical uses of oral hypoglycaemic drugs

- *Type 2 diabetes mellitus*, to reduce symptoms from hyperglycaemia (e.g. thirst, excessive urination). ('Tight' control of blood glucose has only a small effect on vascular complications in this setting.)
- **Metformin** is preferred for obese patients unless contraindicated by factors that predispose to lactic acidosis (renal or liver failure, heart failure, hypoxaemia).
- **Acarbose** (α-glucosidase inhibitor) reduces carbohydrate absorption; it causes flatulence and diarrhoea.
- Drugs that act on the sulfonylurea receptor (e.g. **tolbutamide**, **glibenclamide**) are well tolerated but often promote weight gain.
- Glitazones (e.g. **pioglitazone**) improve control (reduce haemoglobin A_{1C}) but increase weight, cause fluid retention and increase risk of fractures.
- Gliptins (e.g. **sitagliptin**) improve control, are well tolerated and weight neutral, but long-term experience is lacking.

POTENTIAL NEW ANTIDIABETIC DRUGS

Several agents are currently being studied, including α_2 adrenoceptor antagonists, inhibitors of fatty acid oxidation and activators of glucokinase. Lipolysis in fat cells is controlled by adrenoceptors of the β_3 subtype (see Ch. 14). The possibility of using selective β_3 agonists, currently in development, in the treatment of obese patients with type 2 diabetes is being investigated (see Ch. 31). There is interest in inhibitors of protein kinase C, for example **ruboxistaurin**, an inhibitor specific for the β isoform of protein kinase C, because of evidence implicating activation of this pathway in the development of vascular diabetic complications (Aiello, 2005)—a clinical trial is ongoing.

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