26 Anti-inflammatory and immunosuppressant drugs

OVERVIEW

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

The chief drugs used to treat inflammation may be divided into five major groups:

- **Drugs that inhibit the cyclo-oxygenase (COX) enzyme – the non-steroidal anti-inflammatory drugs (NSAIDs) and the coxibs.**
- **Antirheumatoid drugs – the disease-modifying antirheumatic drugs (DMARDs), including some immunosuppressants.**
- **The glucocorticoids.**
- **Anticytokines and other biological agents.**
- **Other drugs that do not fit into these groups, including antihistamines and drugs used to control gout.**

We first describe the therapeutic effects, mechanism of action and unwanted effects common to all NSAIDs, and then deal in a little more detail with aspirin, paracetamol and drugs that are selective for COX-2. The antirheumatoid drugs comprise a rather heterogeneous group and include immunosuppressant drugs that are also used to treat other autoimmune diseases, and prevent rejection of organ transplants. The glucocorticoids are covered in Chapter 33, but are briefly discussed in this chapter. We then consider the biopharmaceutical 'revolution' which has changed the therapeutic landscape 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 coxibs, which are more selective for COX-2. NSAIDs, 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 examples on the global market; common examples are listed in Table 26.1 and some NSAID structures depicted in Figure 26.1.

These drugs provide symptomatic relief from fever, 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, as well as headaches and migraine. Several NSAIDs are available over the counter and they are widely used to treat minor aches and pains and other ailments. There are also 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 provoke 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 thromboxane. As explained in Chapter 17, there are two common isoforms of this enzyme, COX-1 and COX-2, but there may be other isoforms as yet uncharacterised. While COX-1 and COX-2 are closely related (>60% sequence identity) and catalyse the same reaction, 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 principally in tissue homeostasis. It is, for example, responsible for the production of prostaglandins involved in gastric cytoprotection (see Ch. 30), platelet aggregation (Ch. 24), renal blood flow autoregulation (Ch. 29) and the initiation of parturition (Ch. 35).

In contrast, COX-2 is induced mainly in inflammatory cells when they are activated by, for example, the inflammatory cytokines – interleukin (IL)-1 and tumour necrosis factor (TNF)-α (see Ch. 18). Thus the COX-2 isoform is considered to be mainly responsible for the production of prostanoid mediators of inflammation (Vane & Botting, 2001). There are, however, some significant exceptions. COX-2 is constitutively expressed in the kidney, generating prostacyclin, which plays a part in renal homeostasis (see Ch 29), and in the central nervous system (CNS), where its function is not clear.

Most 'traditional' NSAIDs inhibit both COX-1 and COX-2, although their relative potency against the two isoforms differs. 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 have already been exposed to less selective drugs and have already suffered some

[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 selectivity	Comments
Aceclofenac	Phenylacetate	RA, OA, AS	–	–
Acemetacin	Indole ester	RD, OA, MS, PO	–	Ester of indometacin
Aspirin	Salicylate	Mainly CV usage	Weakly COX-1 selective	Component of many OTC preparations
Celecoxib	Coxib	RA, OA, AS	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, H&M	Weakly COX-2 selective	Moderate potency. Various salts
Etodolac	Pyranocarboxylate	RA, OA	Moderately COX-2 selective	Possibly fewer gastrointestinal effects
Etoricoxib	Coxib	RA, OA, G, AS	Very COX-2 selective	–
Fenoprofen	Propionate	RA, OA, MS, PO	Non-selective	Pro-drug; 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, D	Weakly COX-1 selective	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	Moderately COX-2 selective	Possibly fewer gastrointestinal effects
Nabumetone	Naphthylalkenone	RA, OA	–	Prodrug activated in liver
Naproxen	Propionate	RA, OA, G, MS, PO, D	Weakly COX-1 selective	Possibly CV safe?
Parecoxib	Coxib	PO	–	Prodrug activated in liver
Piroxicam	Oxicam	RA, OA, AS	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; CV, cardiovascular; 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 2013 and COX selectivity data, where tested, from Warner & Mitchell, 2004 and 2008.)

gastrointestinal damage. As COX-2 also seems to be important in healing and resolution, one can see how problems might still occur. There is also a concern about the cardiovascular effects of all NSAIDs when these are taken chronically. Some notes on the relative selectivity of some NSAIDs and coxibs are given in Table 26.1.

▼ Though NSAIDs differ in toxicity and degree of patient acceptability and tolerance, their pharmacological actions are broadly similar, with certain important 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 (see Ch. 42) 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. in the CNS during fever) but not in others (see also Ch. 42).

MECHANISM OF ACTION

In 1971 Vane and his colleagues demonstrated that the NSAIDs inhibit prostaglandin biosynthesis by a direct

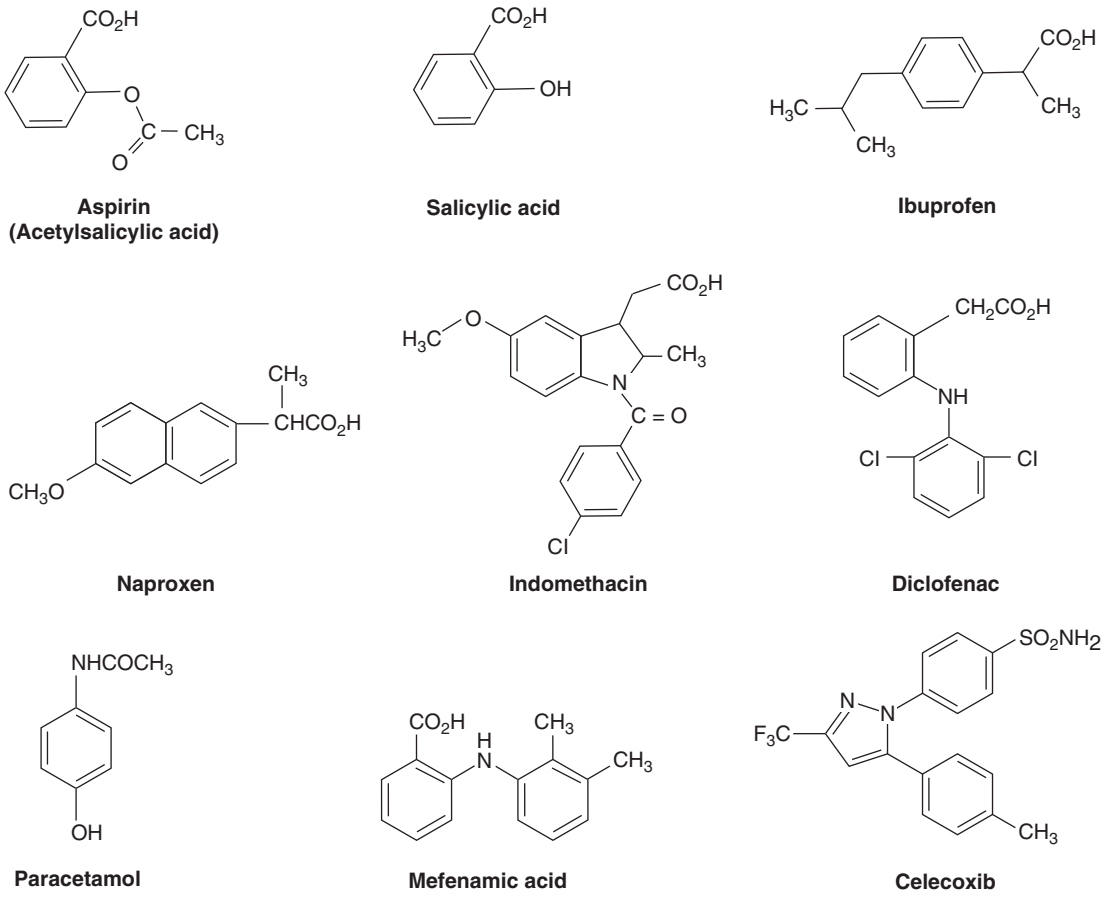

Fig. 26.1 **Significant structural features of some non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs.** Aspirin contains an acetyl group that is responsible for the inactivation of the COX enzyme. Salicylic acid is the end product when aspirin is de-acetylated. Oddly it has anti-inflammatory 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 thought to be important in determining 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 mainly through inhibition of the COX-2 isoform. 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**.

action on the COX enzyme and established the hypothesis that this single action explained their therapeutic actions and most side effects (see Fig. 26.2). This has since been confirmed by numerous studies.

▼ COX enzymes are bifunctional, having two distinct catalytic activities. The first, dioxygenase step incorporates two molecules of oxygen into the arachidonic (or other fatty acid substrate) chain at C11 and C15, giving rise to the highly unstable *endoperoxide intermediate* PGG_2 with a hydroperoxy group at C15. A second, peroxidase 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

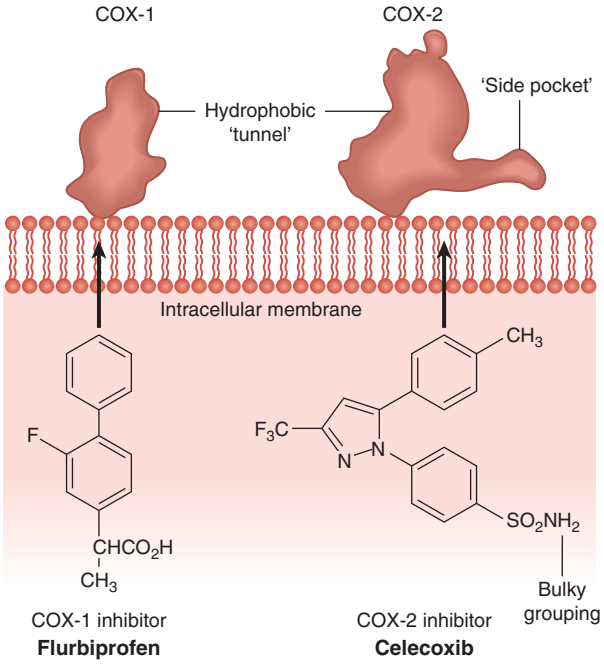

Fig. 26.2 Schematic diagram comparing the binding sites of cyclo-oxygenase (COX)-1 and COX-2. The illustration shows the differences in NSAID binding sites in the two isoforms. Note that the COX-2 binding site is characterised by a 'side pocket' that can accommodate the realtively 'bulky' groups, such 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.)*

enzymes that exist as homodimers attached to intracellular membranes. Interestingly, only one monomer is catalytically active at one time. Structurally, COX-1 and COX-2 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 rapid 'competitive reversible' inhibitors of COX-1, but there are differences in their kinetics. 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 'bulge' in the channel that is not found in COX-1. This is important in understanding why some drugs, especially those with large sulfur-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. Interestingly, aspirin-inactivated COX can still generate some hydroxyacids, but cannot produce PGG_2. Binding of NSAIDs to one COX monomer can inhibit the catalytic activity of the entire dimeric complex.

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 pharmacological profile is listed in the box.

THERAPEUTIC ACTIONS

ANTI-INFLAMMATORY EFFECTS

As described in Chapters 17 and 18, many mediators coordinate inflammatory and allergic reactions. The NSAIDs reduce those components in which prostaglandins, mainly derived from COX-2, play a significant part. These include the vasodilatation (by reducing the synthesis of vasodilator prostaglandins) and the oedema of inflammation because vasodilatation facilitates and potentiates the action of mediators that increase the permeability of postcapillary venules, such as histamine; Ch. 17).

▼ While 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 EFFECTS

A centre in the hypothalamus controls the balance between heat production and heat loss thereby regulating normal body temperature. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', which raises body temperature. 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 healthy humans is not affected by NSAIDs.[2]

▼ The NSAIDs exert their antipyretic action largely through inhibition of prostaglandin production in the hypothalamus. During infection, bacterial endotoxins cause the release from macrophages of IL-1 (Ch. 17). In the hypothalamus this cytokine stimulates the generation of E-type prostaglandins that elevate the temperature set point. COX-2 may have a role here, because IL-1 induces this enzyme in the hypothalamic vascular endothelium. 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 EFFECTS

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

Peripherally, NSAIDs decrease production of prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin (see Chs 18 and 42) and they are therefore effective in arthritis, bursitis, pain of muscular

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

and vascular origin, toothache, dysmenorrhoea, the pain of postpartum states and the pain of cancer metastases in 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. Peripheral inflammatory lesions increase COX-2 expression and prostaglandin release within the cord, facilitating transmission from afferent pain fibres to relay neurons in the dorsal horn (see Ch. 42).

UNWANTED EFFECTS

Overall, the burden of unwanted side effects amongst NSAIDs is high, probably reflecting the fact that they 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 sustained treatment), 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, all NSAIDs share a broadly similar profile of unwanted mechanism-dependent side effects on these processes, 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.

Gastrointestinal disturbances

Adverse gastrointestinal (GI) events are the commonest unwanted effects of the NSAIDs. They are believed to result mainly from inhibition of gastric COX-1, which synthesises prostaglandins that normally inhibit acid secretion and protect the mucosa (see Ch. 30, Fig. 30.2).

Symptoms typically include gastric discomfort ('dyspepsia'), 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 which, while it may be asymptomatic, can carry a risk of serious haemorrhage and/or perforation. These severe GI effects are said to result in the hospitalisation of over 100 000 people per year in the USA, some 15% of whom 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. Oral administration of 'replacement' prostaglandin analogues such as **misoprostol** (see Ch. 30) diminishes the gastric damage produced by these agents and is often co-prescribed or combined in a single pill.

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. Indeed, some older drugs that were better tolerated in the clinic (e.g. **meloxicam**) turned out to have some COX-2 selectivity. Two large prospective studies compared the gastrointestinal side effects of two highly selective COX-2 inhibitors, **celecoxib** and **rofecoxib,** with those of standard comparator NSAIDs in patients with arthritis. The coxibs showed some benefit, although the results were not as clear-cut as had been hoped. The actual situation following therapy is complex because the degree to which the two COX isoforms are inhibited depends not only upon the intrinsic activity of the drug but also the inhibitory kinetics and the pharmacokinetics. Warner and Mitchell (2008) have suggested that the degree to which NSAIDs inhibit COX-1 when they inhibit COX-2 by 80% is the best measure of 'selectivity'.

Damage to the small intestine may also occur following NSAID treatment. It is not clear if a COX-dependent mechanism is involved.

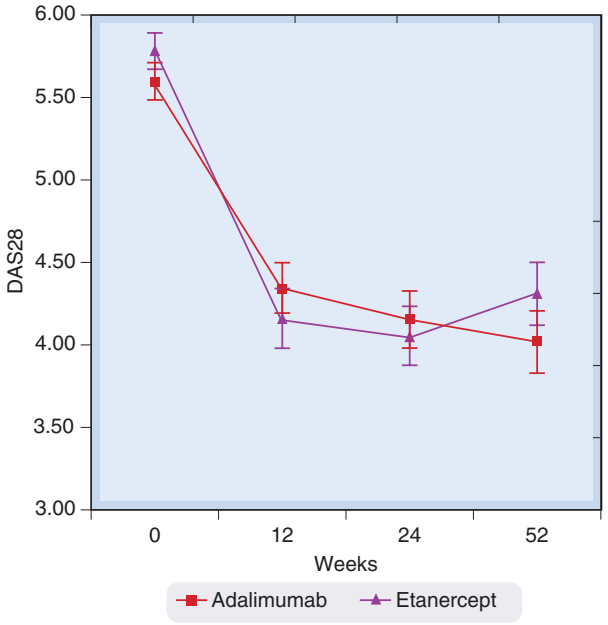

Fig. 26.3 The effect of anticytokine biologics on rheumatoid arthritis. In this figure, adalimumab (a humanised monoclonal antibody that neutralises TNF) and etanercept (a fusion protein decoy receptor that binds to TNF) were used to treat patients with active rheumatoid arthritis. The Y-axis measures a composite disease activity scores obtained from clinical assessment of 28 joints (DAS28: the lower the score, the less swollen and painful the joints). *(From Jobanputra et al. 2012.)*

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, see Ch. 57), and *toxic epidermal necrolysis*[3] (fortunately very 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

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

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. 29). Neonates and the elderly are especially at risk, 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. 29). **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.

Cardiovascular side effects

Though aspirin is widely for its beneficial antiplatelet action (see below) other NSAIDs generally lack this action, and produce various adverse cardiovascular side effects. As well as opposing the effects of some antihypertensive drugs, NSAIDs also raise blood pressure in patients not taking antihypertensive drugs, and therefore predispose to adverse cardiovascular events such as stroke and myocardial infarction.

▼ This was first recognised 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 by its manufacturer in 2004.

With the exception of low-dose aspirin, adverse cardiovascular effects may be common to all NSAIDs, especially following prolonged (months–years) use or in patients with pre-existing cardiovascular risk. Some drugs (e.g. **naproxen**) appear to be better tolerated in this respect than others (see Ray et al., 2009).

The reasons for the adverse cardiovascular effects are unclear and controversial. Since prostaglandins are important in the control of renal function, including the regulation by cells of the *macula densa* region, of renin release and hence blood pressure, inhibition of COX-2 at this site may be the culprit. The hypertensive effect is dose- and time-dependent and rarely occurs with short-term (i.e. days) administration.

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. 28) 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 other NSAIDs, except possibly COX-2 inhibitors (see Ch. 28). 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. All NSAIDs (except COX-2 inhibitors) prevent platelet aggregation and therefore may prolong bleeding. Again, aspirin is the main problem in this regard.

General unwanted effects of cyclo-oxygenase inhibitors

Unwanted effects, many stemming from inhibition of the constitutive housekeeping enzyme COX-1 isoform, 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, ulceration and perforation 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 I_2/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* or elsewhere leading to hypertension.
- '*Analgesic-associated nephropathy*'. This can occur following long-term high-dose regimes of NSAIDs 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. We now look at some of the more significant drugs in a little more detail.

ASPIRIN

Aspirin (acetylsalicylic acid) was among the earliest drugs synthesised, and is still one of the most commonly consumed drugs worldwide.[6] It is also a common ingredient in many over-the-counter proprietary medicines. The drug itself is relatively insoluble, but its sodium and calcium salts dissolve readily in aqueous solutions.

While aspirin was originally an old anti-inflammatory workhorse, it is seldom used for this purpose now, having been supplanted by other, better tolerated NSAIDs.

[4]So called because the availability of NSAIDs (often in combination with other substances, such as caffeine) in over-the-counter proprietary medicines, has tempted some people to consume them in prodigious quantities, for every conceivable malady. Swiss workers manufacturing watches used to share analgesics in the same way as sweets or cigarettes!

[5]An odd side effect of the NSAID diclofenac came to light when a team of scientists investigated the curious decline in the vulture population of 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.

[6]Indeed, many people do not seem to regard it as a 'drug' at all. Many studies of platelet aggregation have been ruined by the failure of volunteers to declare their consumption of aspirin.

Clinical uses of NSAIDs

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. 42)
  - to reduce the requirement for narcotic analgesics (the NSAID **ketorolac** is sometimes given postoperatively for this purpose).
- *Anti-inflammatory*: e.g. **ibuprofen**, **naproxen** for symptomatic relief in rheumatoid arthritis, gout, soft tissue disorders.
- *Antipyretic*: **paracetamol**.

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 (see Ch. 24).

▼ 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, platelets, lacking a nucleus, are not able to accomplish *de novo* protein synthesis, and remain inactivated 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 of aspirin (e.g. 75 mg/day) 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 benefit from taking the drug prophylactically (primary prevention) was challenged in a meta-analysis (Baigent et al., 2009) suggesting that in the normal population, the risk from gastrointestinal bleeding just outweighs the protective action. In cases where there is a previous history of cardiovascular episodes the case for prophylactic aspirin (secondary prevention) seems unassailable.

The use of aspirin has also been canvassed for other conditions. These include:

- colonic and rectal cancer: aspirin (and some COX-2 inhibitors) may reduce some types of colorectal and other cancers although one always has to be aware of the GI risk (Schror, 2011)
- Alzheimer's disease (Ch. 40): epidemiological evidence suggested aspirin might be beneficial but so far, clinical trial results have been disappointing (see Heneka et al., 2011)
- 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 (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 may depend upon inhibition of the NFκB system (Ch. 3) and only secondarily on COX inhibition. 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.

Aspirin

Aspirin (acetylsalicylic acid) is the oldest non-steroidal anti-inflammatory drug. It acts by irreversibly inactivating COX-1 and COX-2.

- In addition to its anti-inflammatory actions, **aspirin** inhibits platelet aggregation, and its main clinical use 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 larger 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.

Unwanted effects

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

▼ Acute salicylate poisoning (a medical emergency that occurs mainly in children and attempted suicides) causes major disturbance of acid–base and electrolyte balance. Salicylates 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 actually cause a depression of the respiratory centre, less CO_2 is exhaled and therefore increases in the blood. 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 uncoupled oxidative phosphorylation). Hyperthermia 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 protein binding sites (Ch. 56) thereby increasing its effective concentration and partly because its effect on platelets further interferes with haemostasis (see Ch. 24). Aspirin also antagonises the effect of some antihypertensive and uricosuric agents such as probenecid and sulfinpyrazone. Because low doses of aspirin may, on their own, reduce urate excretion (Ch. 29), 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 prostaglandin synthesis in the CNS, it has very weak anti-inflammatory activity 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.

▼ One potential solution to this puzzle was suggested by the discovery of a further COX isoform, COX-3 (an alternate splice product of COX-1) in the CNS of some species. 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). However, alternative explanations have also been proposed based upon consideration of the local redox environment in the CNS or the effect of paracetamol metabolites on Trp channels (see reading list and Ch. 42).

Pharmacokinetic aspects

Paracetamol is well absorbed when given orally, 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.

Paracetamol

Paracetamol is a commonly used drug that is available over the counter. It has potent analgesic and antipyretic actions but rather weaker anti-inflammatory effects than other NSAIDs. Its COX inhibitory action seems to be specific to the CNS enzyme.

- 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.

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

▼ 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 are given in Chapter 57. If the patient is seen sufficiently soon after ingestion, the liver damage can be prevented by administering 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 following claims of cardiovascular and other toxicity. Coxibs are generally offered to patients for whom treatment with conventional NSAIDs would pose a high probability of serious gastrointestinal side effects. However, gastrointestinal disturbances may still occur with coxibs, perhaps because COX-2 has been implicated in the healing of pre-existing ulcers, so inhibition could delay recovery from earlier lesions. As is the case with all NSAID treatment, cardiovascular risk should be assessed prior to long-term treatment.

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. 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 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

Rheumatoid arthritis is one of the commonest chronic inflammatory conditions in developed countries, and a common cause of disability. Affected joints become swollen, painful, deformed and immobile. One in three patients with rheumatoid arthritis is likely to become severely disabled. The disease also has cardiovascular and other systemic manifestations and carries an increased risk of mortality. The degenerative joint changes, which are driven by an autoimmune reaction, are characterised by 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 the disease (Ch. 17). A simplified scheme showing the development of rheumatoid arthritis and the sites of action of therapeutic drugs, is given in Figure 26.4.

The drugs most frequently used in initial therapy are the 'disease-modifying antirheumatic drugs' (DMARDs

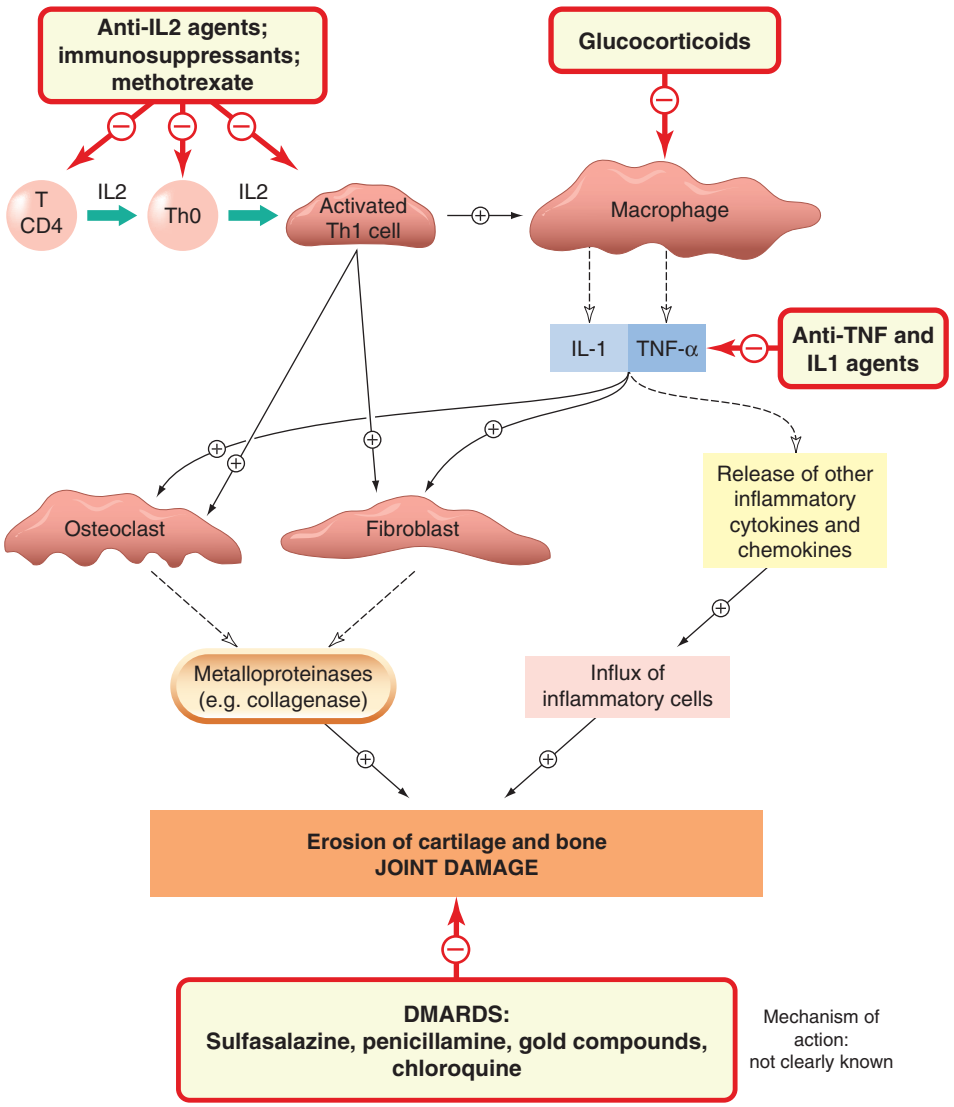

Fig. 26.4 A schematic diagram of the cells and mediators involved in the pathogenesis of rheumatoid joint damage, indicating the sites of action of antirheumatoid drugs. DMARD, disease-modifying antirheumatic drug. For details of the anti-TNF, IL-1 and IL-2 receptor agents, see Chapter 6 and Table 26.3.

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	–	Many side effects. Long latency of action
Antimalarials	Chloroquine	RA, SLE	Moderate	Used when other therapies fail
	Hydroxy-chloroquine sulfate	RA, SLE	Moderate	Also useful for some skin disorders
Immunomodulators	Methotrexate	RA, PS, JRA	Moderate to severe	A 'first-choice' drug. Also used in Crohn's disease and cancer treatment. Often used in combination with other drugs
	Azathioprine	RA, IBS	–	Used when other therapies fail. Also used in transplant rejection, IBS and eczema
	Ciclosporin	RA, AD, PA	Severe	Used when other therapies fail, in some skin diseases and transplant rejection
	Cyclophosphamide	RA	Severe	Used when other therapies fail
	Leflunomide	RA, PA	Moderate to severe	Also used in psoriatic arthritis
NSAID	Sulfasalazine	RA, PA, JRA	–	A 'first-choice' drug. Also used in ulcerative colitis
Penicillin metabolite	Penicillamine	RA	Severe	Many side effects. Long latency of action

AD, atopic dermatitis; IBS, inflammatory bowel disease; JRA, juvenile rheumatoid arthritis; NSAID, non-steroidal anti-inflammatory drug; PA, psoriatic arthritis; PS, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
Data from various sources, including the British National Formulary, 2013.

– especially **methotrexate**) and the NSAIDs. Unlike the NSAIDs, which only reduce the symptoms, DMARDs may halt or reverse the underlying disease itself. Although such claims are often over-optimistic, these drugs are nevertheless useful in the treatment of discrete groups of patients, and Rau (2005) has argued for their continuing use despite the availability of the newer anticytokine agents (see below). Some immunosuppressants (e.g. **azathioprine**, **ciclosporin**) are also used, as are the glucocorticoids (covered in Chs 3 and 33).

Davis and Matteson (2012) have reviewed the question of how to classify and treat this miserable and disabling disease.

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**, **chloroquine** and other anti-malarials (see Table 26.2) and various immunosuppressant drugs.

▼ The antirheumatoid action of most of these agents was discovered through a mixture of serendipity and clinical intuition. When they 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 IgM antibody against host IgG).

The DMARDs are often referred to as *second-line drugs*, with the implication that they are only resorted to when other therapies (e.g. NSAIDs) failed, but 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 variable), concomitant NSAID (or glucocorticoid) therapy can be reduced. Some DMARDs (e.g. methotrexate) 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 (Ch. 56). It has a useful and reliable antirheumatoid action and 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 patient tolerance, and is often given in conjunction with the anticytokine drugs.

Its mechanism of action is unrelated to its effect on folic acid (which is routinely co-administered to prevent blood dyscrasia) but may well be connected with its ability to block adenosine uptake (see Ch. 16 and Chan & Cronstein, 2010).

SULFASALAZINE

Sulfasalazine, another common first-choice DMARD in the UK, produces remission in active rheumatoid arthritis and is also used for chronic inflammatory bowel disease

(see Ch. 30). 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 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 drug is generally well tolerated but common side effects include gastrointestinal disturbances, malaise and headache. Skin reactions and leukopenia 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. Haematological 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. 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 and IL-1 generation, and/or partly by 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 and liver disease) and heavy metal poisoning.

▼ Penicillamine is given orally, but only half the dose 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 the unwanted effects, which occur in about 40% of patients 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. Haematological monitoring is also required when treatment is initiated. Thrombocytopenia may require lowering the dose. Leukopenia or aplastic anaemia are absolute contraindications, as are autoimmune conditions (e.g. thyroiditis, myasthenia gravis). Because penicillamine is a metal chelator, it should not be given with gold compounds.

GOLD COMPOUNDS

Gold is administered as an organic complex, **sodium aurothiomalate**. The anti-inflammatory effect 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. Sodium aurothiomalate is given by deep intramuscular injection. Gold complexes gradually accumulate in synovial cells in joints as well as other tissues, such as liver cells, kidney tubules, the adrenal cortex and macrophages, and remain 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. Important unwanted effects include skin rashes (which can be severe), mouth ulcers, non-specific flu-like symptoms, proteinuria, thrombocytopenia and blood dyscrasias. Anaphylactic reactions 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. 54), 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 exacerbate the skin lesions. The related antimalarial, **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 administration, pharmacokinetic aspects and unwanted effects of chloroquine are dealt with in Ch. 54; 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 the immune response, 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 immunosuppresants is summarised in the clinical box.

Most of these drugs act during the induction phase of the immunological response, reducing lymphocyte proliferation (see Ch. 6), although others also inhibit aspects of the effector phase. There are three main groups:

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

CICLOSPORIN

Ciclosporin is a naturally occurring compound first identified in a 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, see Borel et al., 1996). The drug has numerous actions but those 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 responsible for cell-mediated responses (e.g. decreased delayed-type hypersensitivity)
- some reduction of T cell-dependent B cell responses.

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, sirolimus** and **pimecrolimus** 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.

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 expression. Ciclosporin binds to cyclophilin, a cytosolic protein member of the immunophilin family (a group of proteins that act as intracellular receptors for such drugs). The drug–immunophilin complex binds to, and inhibits, calcineurin which 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 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 not used for arthritis but mainly in organ transplantation and severe atopic eczema. **Pimecrolimus** (used to treat atopic eczema) acts in a similar way. **Sirolimus** (used to prevent organ rejection after transplantation, and also in coating on cardiac 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

mercaptopurine, an analogue that inhibits DNA synthesis (see Ch. 56). Because it inhibits clonal proliferation during the induction phase of the immune response (see Ch. 6) through a cytotoxic action on dividing cells, both cell-mediated and antibody-mediated immune reactions are depressed by this drug. 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.

CYCLOPHOSPHAMIDE

Cyclophosphamide is a potent immunosuppressant that is mainly used to treat cancer. Its mechanism of action is explained in Chapter 56. It has substantial toxicity and is therefore generally reserved for serious cases of rheumatoid arthritis in which all other therapies have failed.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil is a semisynthetic derivative of a fungal antibiotic, and is 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. This enzyme is 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.

▼ 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, used mainly to treat rheumatoid arthritis and occasionally to prevent transplant rejection, 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

The therapeutic action of the glucocorticoids involves both their inhibitory effects on the immune response and their anti-inflammatory actions. These are described in Chapter 33, and their sites of action 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) is also increased. These effects are mediated through inhibition of the action of transcription factors, such as activator protein-1 and NFκB (Ch. 3).

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. These 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 (in the National Health Service), they are generally restricted to patients who do not respond adequately to other DMARD therapy and they are usually administered under specialist supervision only. Some of these drugs are administered in combination with methotrexate, which apparently provides a synergistic anti-inflammatory action.

The characteristics and indications of some current biopharmaceuticals are shown in Table 26.3. The effect of two of these agents on rheumatoid arthritis is shown in Figure 26.3 (see p. 321). Many neutralise soluble cytokines. **Adalimumab**, **certolizumab pegol**, **golimumab**, **etanercept** and **infliximab** target TNF-α; anakinra targets IL-1 and **toclizumab**, IL-6. **Abatacept** and **natalizumab** target T cells, either disrupting activation, proliferation or emigration. **Rituximab** and **belimumab** target B cells. While they are not used for treating arthritis, **basiliximab**, **belatacept** and **daclizumab** are included in the table as they act to prevent the rejection of transplanted organs in a similar way – by suppressing T cell proliferation.

There is debate over the precise nature of the 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 (e.g. 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, certolizumab pegol, infliximab and rituximab every 2 weeks, and abatacept, belimumab, golimumab, natalizumab and toclizumab every month. Sometimes a loading dose of these drugs is given as a preliminary to regular administration.

A proportion of patients (about 30%) do not respond to many of these anticytokine drugs for reasons that are not entirely clear and therapy is generally discontinued if no therapeutic benefit is evident within 2–4 weeks.

Cytokines are crucial to the regulation of host defence systems (see Ch. 18), and leukocytes are key players in their 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

Table 26.3 Biologics used in the treatment of inflammatory disease

Target	Drug	Type	Mode of action	Indication
Soluble TNF	Adalimumab	Humanised monoclonal ab	Imuno-neutralisation	RA (moderate–severe), PA, AS, PP, CD
	Certolizumab pegol	Pegylated ab fragment		RA[a] (moderate–severe)
	Golimumab	Humanised monoclonal ab		RA (moderate–severe), PA, PS
	Infliximab	Chimeric neutralising ab		RA[a] (moderate–severe), PA, AS, PP
	Etanercept	Fusion protein decoy receptor	Neutralisation	RA[a] (moderate–severe), PA, AS, PP
Soluble IL-1	Anakinra	Recombinant version of IL-1 ra	Neutralisation	RA[a] (moderate–severe)
Soluble IL-6	Tocilizumab	Humanised monoclonal ab	Neutralisation	RA[a] (moderate–severe)
T cells	Abatacept	Fusion protein	Prevents co-stimulation of T cells	RA[a] (moderate–severe)
	Basiliximab	Chimeric monoclonal ab	IL-2 receptor antagonist	Immunosuppression for transplantation surgery
	Belatacept	Fusion protein	Prevents activation of T cells	
	Daclizumab	Humanised monoclonal ab	IL-2 receptor antagonist	
	Natalizumab	Humanised monoclonal ab	VLA-4 on lymphocytes (neutralises)	Severe multiple sclerosis
B cells	Belimumab	Humanised monoclonal ab	Immuno-neutralises B-cell-activating factor	SLE
	Rituximab	Chimeric monoclonal ab	Causes B cells lysis	RA[a] (moderate–severe), some malignancies

[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; SLE, systemic lupus erythematosus.

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 urate crystals are deposited in tissues, usually because plasma urate concentration is raised. Sometimes this is linked to over-indulgence in alcoholic beverages, especially beer, or purine-rich foods such as offal (urate is a product of purine metabolism). Increased cell turnover in haematological malignancies, particularly after treatment with cytotoxic drugs (see Ch. 56), or impaired excretion of uric acid are other causes. It is characterised by extremely painful intermittent attacks of acute arthritis produced by the deposition of the crystals in the synovial tissue of distal joints, such as the big toe, and elsewhere, such as the external ear – the common theme is that these are cool, favouring crystal deposition. An inflammatory response is evoked, involving activation of the kinin, complement and plasmin systems (see Ch. 18 and Ch. 6, Fig. 6.1), generation of prostaglandins, lipoxygenase products such as leukotriene B4 (Ch. 17, 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 decreasing uric acid synthesis (**allopurinol**, the main prophylactic drug)
- by increasing uric acid excretion (*uricosuric agents*: **probenecid**, **sulfinpyrazone**; see Ch 29)
- 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 (see below).

ALLOPURINOL

Allopurinol is an analogue of hypoxanthine that reduces the synthesis of uric acid by competitive inhibition of xanthine oxidase (Fig. 26.5). The drug is first converted by xanthine oxidase to alloxanthine, which persists in the tissue for a considerable time, and 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,

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**, **sulfinpyrazone**), 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.

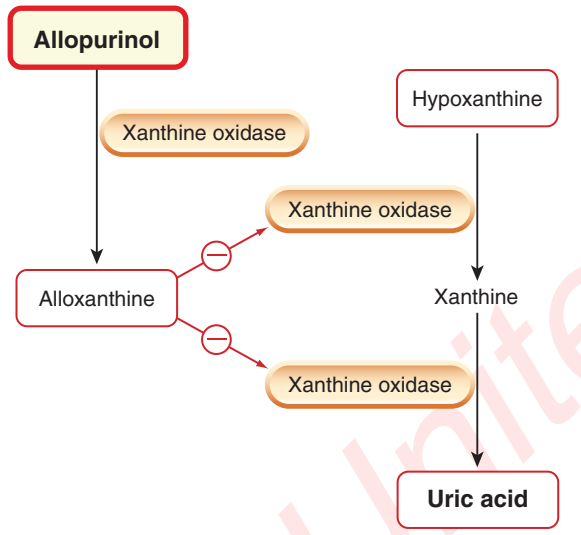

Fig. 26.5 Inhibition of uric acid synthesis by allopurinol. See text for details.

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 actually exacerbates inflammation and pain in an acute attack (see below). **Febuxostat** has a similar pharmacology.

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 otherwise 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 toxic epidermal necrolysis and 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. 56), and also that of azathioprine (Table 26.2), which is metabolised to mercaptopurine. Allopurinol also enhances the effect of another anticancer drug, cyclophosphamide (Ch. 56). 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. 29). They remain useful as prophylaxis for patients with severe recurrent gout who have severe adverse reactions to allopurinol. Common drugs include probenecid and sulfinpyrazone (which also has NSAID activity). **Benzbromarone** is also available on a named patient basis for treatment of patients with renal impairment. Treatment with uricosuric drugs is initiated together with an NSAID, as in the case of 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 of gout. 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 beneficial effect in gouty arthritis and can be used both to prevent and to relieve acute attacks. It prevents migration of neutrophils into the joint apparently 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, by neutrophils that have phagocytosed urate crystals, of a putative inflammatory glycoprotein. Other mechanisms may also be important in bringing about its effects. At higher doses than are used to treat gout, colchicine inhibits mitosis, carrying a risk of serious bone marrow depression.

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

The acute unwanted effects of colchicine during therapy are largely gastrointestinal and include nausea, vomiting and abdominal pain. Severe diarrhoea[7] may be a problem and with large doses, or prolonged treatment, its antimitotic action may cause serious side effects, including gastrointestinal haemorrhage, kidney damage, bone marrow depression and peripheral neuropathy.

ANTAGONISTS OF HISTAMINE

Antihistamines were introduced by Bovet and his colleagues in the 1930s, before the discovery of the four

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

histamine receptor subtypes described in Ch. 17. 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

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**, **olapatadine** and **emadastine**. In addition to their H_1 antagonist activities, some antihistamines (e.g. **ketotifen**) may also have 'mast cell stabilising' and other anti-inflammatory properties unrelated to histamine antagonism (see Assanasen & Naclerio, 2002).

Table 26.4 Comparison of some commonly used systemic H_1 antagonists

Drug	Common use	Comments
Sedating		
Alimemazine	U	Strong sedative action. Used for anaesthetic premedication
Chlorphenamine	AE, H, U	–
Cinnarizine	–	Used to treat nausea, vomiting, motion sickness
Clemastine	H, U	–
Cyclizine	–	Used to treat nausea, vomiting, motion sickness
Cyproheptadine	H, U	Also used for migraine
Hydroxyzine	U	May cause QT interval prolongation
Ketotifen	H	–
Promethazine	H, U, AE	Strong sedative action. Also used to control nausea and vomiting
Non-sedating		
Acrivastine	H, U	–
Bilastine	H, U	–
Cetirizine	H, U	–
Desloratidine	H, U	Metabolite of loratadine. Long-lasting action
Fexofenadine	H, U	'Cardio-safe' metabolite of terfenidine
Levocetirizine	H, U	Isomer of cetirizine
Loratidine	H, U	–
Mizolastine	H, U	May cause QT interval prolongation
Rupatidine	H, U	Also antagonises PAF (see Ch. 17)

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

PHARMACOLOGICAL ACTIONS

Conventionally, the antihistamines are divided into 'first-generation' drugs, which cross the blood–brain barrier and often have sedating actions, and 'second-generation' drugs, which do not. Some of the original 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 57). These drugs were therefore 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 Chapter 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.

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. **chlorphenamine**; see Table 26.4). Several are antiemetic and are used to prevent motion sickness (e.g. **promethazine**; see Ch. 30).

Several H_1-receptor antagonists show weak blockade of α_1 adrenoceptors (e.g. promethazine). Cyproheptadine is a 5-HT antagonist as well as an H_1-receptor antagonist and **rupatadine** is also a PAF 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. 30):
  - prevention of motion sickness (e.g. **cyclizine**, **cinnarizine**)
  - other causes of nausea, especially labyrinthine disorders.
- For sedation (see Ch. 44, e.g. **promethazine**).

PHARMACOKINETIC ASPECTS

Most orally active H_1-receptor antagonists are well absorbed and remain effective for 3–6 h, although there are some prominent exceptions (e.g. **loratidine**, which is converted to a long-acting metabolite). Most appear to be

widely distributed throughout the body, but some do not penetrate the blood–brain barrier, for example the non-sedating 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 anti-muscarinic 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. The main problem with this sector is not so much the efficacy of the drugs (although a proportion of patients, mysteriously, fail to respond) but rather their cost and lack of oral availability. This 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; at least two forms) 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 effective in animal models but have not transferred well to the clinic (see Moss et al., 2008 and Sharma et al., 2013 for a review).

The emerging evidence that all NSAIDs (and coxibs) may have cardiovascular side effects has raised further questions about our existing therapeutic arsenal.[8] One of the few real 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. 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) have been tested in man but have not yet received regulatory approval. Yedgar et al. (2007) discuss some alternative approaches to manipulating the production or action of eicosanoid mediators of inflammation.

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

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27 Skin

OVERVIEW

With a surface area of about 1.6–1.8 m² and a weight of about 4.5 kg in the average adult, skin qualifies as the largest and heaviest organ in the body. It is also an important target for drug therapy as well as cosmetic and other agents. Here, we look at the structure of human skin and briefly review some common skin disorders. We then discuss some of the many types of drugs that act upon, or through, this organ.

INTRODUCTION

Skin is a complex organ with many roles.[1] Firstly, it acts as a barrier. Being impermeable to water it prevents the loss of moisture from the body as well as the ingress of water and many other substances into the body. It also cushions the underlying tissue against thermal and mechanical damage and shields it from ultraviolet radiation and infection. Even if they can thrive in the slightly acidic environment of the skin's surface, microorganisms cannot easily cross the outer barrier of the skin, but should they do so, skin is well endowed with specialised immunological surveillance systems comprising *Langerhans cells*, a type of dendritic cell, as well as mast cells and other immunocompetent cell types.

A second function is thermoregulation. Approximately 10% of the total blood volume is contained within the dense capillary networks of the skin. Skin arterioles, controlled by the sympathetic nervous system, regulate blood flow and heat loss from the skin. Sweat glands (*eccrine glands*) in the skin secrete an aqueous fluid under cholinergic control which, upon evaporation, increases heat loss.

In the presence of sunlight, vitamin D_3 (cholecalciferol) is synthesised in the *stratum basale* and *stratum spinosum* of skin. Absence of this vitamin through lack of exposure to the ultraviolet (UV B) component of sunlight can lead to deficiency symptoms (see Ch. 36). Melanin, produced by melanocytes in the basal dermal layer, gives skin its characteristic colour. The production of melanin granules is stimulated by sunlight.

Skin is also a profoundly sensory organ. It is densely innervated with sensory neurons, including specific sensory nerve endings that signal itch (a sensation unique to skin with an interesting pharmacology), pain, heat and cold as well as specialised receptors that detect touch (*Meissner's corpuscles*) and pressure (*Pacinian corpuscles*). The cell bodies of cutaneous nerves reside in the dorsal root ganglia.

[1]As the American humourist and songwriter Alan Sherman so succinctly put it, 'Skin's the thing that if you've got it outside/It keeps your insides in'.

Being highly visible, skin and its specialised appendages such as hair and nails play an important part in social and sexual signalling. As such it is an important target for cosmetic preparations, suntan lotions, anti-ageing compounds and more. Because unsightly skin can cause problems of social adjustment or even frank psychiatric illness, the distinction between a therapeutic agent and a cosmetic preparation can become blurred. In fact the market for 'cosmeceuticals' as they are called is huge: in 2012, over $8 billion was spent on these compounds (many of which have no proof of efficacy) in the USA alone (Nolan et al., 2012).

Here we look briefly at some common conditions affecting the skin and at some of the drugs used to treat them (see Table 27.1). In most cases, these drugs also have other uses and their mechanisms of action are described elsewhere in the book so the appropriate cross-references are given in the table. Inflammation is a common feature of skin diseases, and anti-inflammatory drugs, discussed in detail in Chapter 26, are often used. In some other instances, the drugs themselves, or their particular utility, are almost unique to skin pharmacology so they will be explained in a little more detail. Drugs used to treat skin infections and cancers are discussed in Chapters 51 and 56.

Topical application of drugs onto the skin can be used as a route for systemic administration (see Ch. 8), and is also used to treat the underlying tissues. For example, NSAIDs applied topically can reduce the inflammation of underlying joints and connective tissue with less unwanted effects than those seen after systemic administration (Klinge & Sawyer, 2013). However, we will not deal in depth with this topic here.

STRUCTURE OF SKIN

Skin comprises three main layers: the outermost layer, the *epidermis*, a middle layer, the *dermis*, and the innermost layer, the *subdermis*, sometimes called the *hypodermis* or *subcutis* (see Fig. 27.1).

The epidermis consists largely of keratinocytes. There are four layers of cells. The *stratum basale* is the innermost layer and lies adjacent to the *dermoepidermal junction*. It comprises mainly dividing keratinocytes interspersed with melanocytes. The latter cells produce granules of melanin in *melanosomes*, which are transferred to the dividing keratinocytes. As the keratinocytes divide and mature they progress towards the skin surface. In the next layer, they form the *stratum spinosum* ('spiny' layer), so called because *desmosomes* (intercellular protein links) begin to appear on the cells. Gradually, these cells begin to flatten adopting a *squamous* (scaly) morphology. They lose their nuclei and the cytoplasm acquires a granular appearance. Lying immediately above this is a thin translucent layer of tissue called the *stratum lucidum*. The

Table 27.1 Drug treatment of some common skin disorders

Disease	Class	Examples	Comments	Chapter
Acne	Antibacterials	Erythromycin, clindamycin	For mild-moderate acne. Sometimes systemic treatment is also used	50, 51
	Retinoids	Retinoin, isoretinoin, adapalene	For more severe disease. Sometimes systemic treatment is also used	–
Alopecia	Androgen antagonists	Finasteride, minoxidil	Generally in men only	35
Hirsutism	Hormone antagonists	Eflornithine, co-cypyrindiol	Usually in women only	35
Infections	Antibacterials	Mupirocin, neomycin sulfate, polymixins, retapamulin, sulfadiazine, fusidic acid, metronidazole	Usually given topically but some drugs may be given orally	50, 51
	Antivirals	Aciclovir, peniciclovir		52
	Antifungal	Amorolfine, clotrimazole, econazole, griseofulvin, ketconazole,miconazole, nystatin, terbinafine, tioconazole	–	53
	Antiparasite	Topical insecticides (e.g. permethrin).	–	54
Pruritus	Antihistamines, topical anaesthetics and related drugs	Crotamiton, diphenhydramine, doxepin	Antihistamines may be given topically or orally. Sometimes a 'sedating' antihistamine is useful	26, 33
Eczema	Glucocorticoids	Mild-potent (i.e. hydrocortisone, betamethasone esters)	May be combined with antibacterial or antifungal agent if infection is present	26, 33
	Retinoids	Alitretinoin	Given orally. Only used if glucocorticoid therapy has failed	–
Psoriasis	Vitamin D analogues	Calcipotriol, calcitriol, tacalcitol	DMARDS and anticytokine drugs used for severe cases	26, 36
	Retinoids	Tazarotene, acitretin	Oral retinoids sometimes used	–
	Glucocorticoids	Moderate–potent (i.e. hydrocortisone butyrate, clobestasol proprionate)	May be combined with antibacterial or antifungal agent if infection is present	26, 33
Rosacea	Antibacterials	Tetracycline, erythromycin, doxycycline, metronidazole	Glucocorticoids are contraindicated	50, 51
Urticaria	Antihistamines	Diphenhydramine, doxepin	Usually given orally. Sometimes a 'sedating' antihistamine is useful	26
Warts	Keratolytic agents and others	Salicylic acid, podophyllotoxin, imiquimod	–	–

DMARDs, disease-modifying antirheumatic drugs.

outermost layer of skin is the *stratum corneum*. By now, the keratinocytes are no longer viable. They have become fused together (cornified) and most tissues have 10–30 layers of these hardened sheets of tissue. The *corneocytes*, as they are now called, are surrounded with a hydrated proteinaceous envelope. Lipid bilayers occupy the extracellular space providing a hydrophilic waterproof layer. The water and lipid content of skin is critical to its function. If the moisture content of the hydrated layer falls, the skin loses its supple properties and cracks. The keratinocytes are normally replenished about every 45 days (Bergstresser & Taylor, 1977). Because of this, healthy skin constantly sheds the outer layer of cornified cells. If this does not occur, patches of dry skin begin to appear.

Below the epidermis lies the dermis. This layer varies in thickness. In some tissues it is very thick (e.g. the palms and the soles of the feet) and in others, very thin (e.g. the eyelids). Histologically, the dermis comprises a *papillary layer* and a deeper *reticular layer*. The main cell types are fibroblasts. These produce and secrete important structural elements of the skin such as glycoproteins, which contribute to the hydration of the tissue, and collagen and elastin that provide strength and elasticity. Other types of cells associated with the immune system are also present (see Ch. 6). The dermis is richly endowed with blood vessels and lymphatics and densely innervated.

Hair follicles, *sebaceous glands* and *sweat glands* are embedded in the dermis. Hair follicles are lined with specialised cells that produce keratin and associated melanocytes that produce pigment for the growing hair shaft. Associated with each hair follicle is an *erector pili* muscle that causes the hair shaft to become erect. Cold, fear and other strong emotional stimuli trigger this response giving the sensation of 'goose bumps'. Sebaceous glands associated with hair follicles coat the hair with waxy substance. The

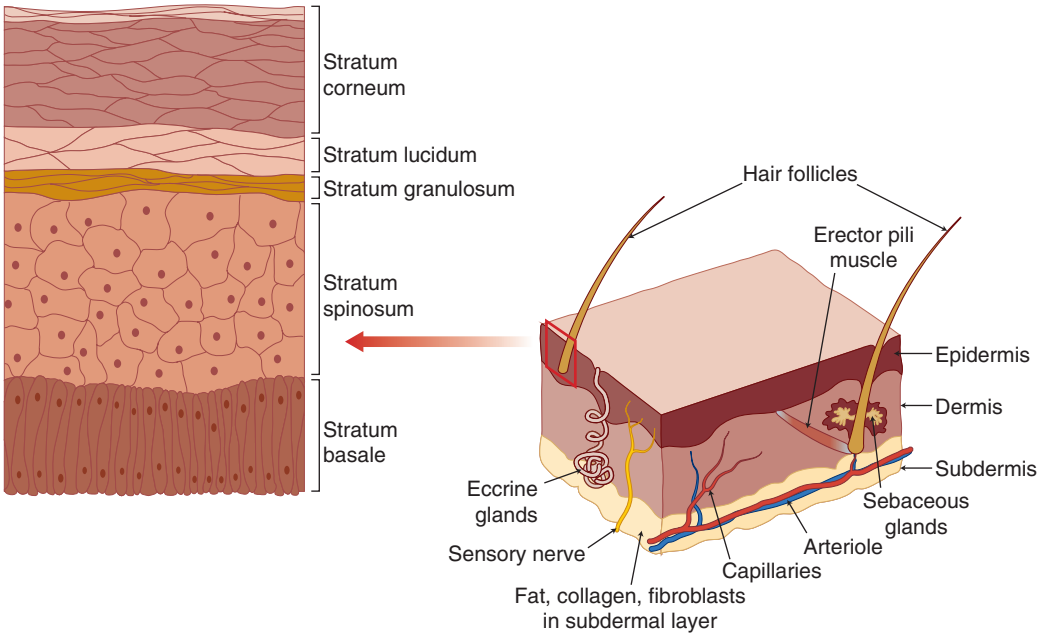

Fig. 27.1 A simplified diagram showing the structure of the skin. The skin comprises three main layers coloured differently in the right-hand drawing: epidermis (dark red/brown); dermis (pink); and subdermis (yellow). On the left is an enlarged diagram of the complex outer, epidermal, layer. Not shown are the apocrine glands within the hair follicles.

Skin

Skin is the largest and heaviest organ in the body. It is composed of three main components:

- *The epidermis*. This is the outermost layer and is comprised of four layers of keratinocytes with interspersed melanocytes. Keratinocytes divide in the basal layer and migrate upwards to the skin surface where they form cornified layers. Lipids in the extracellular spaces confer water-repellent properties.
- *The dermis*. The middle layer is of variable thickness. It consists of fibroblasts that produce structural components such as collagen and elastin as well as immunocompetent cells. Hair follicles and sweat glands are also embedded in this layer and it is densely innervated with nerves, blood vessels and lymphatics.
- *The subdermis* (*hypodermis* or *hypocutis*). This comprises connective tissue and varying amounts of adipose tissue.

Skin has four main functions:

- *A barrier*. Skin prevents the egress or ingress of water, other chemicals and microorganisms. It also acts as a mechanical and thermal barrier and a shock absorber.
- *Thermoregulation*. Vasodilatation of the rich capillary network of the skin, in combination with sweating, increases the loss of heat whilst vasoconstriction has the reverse effect.
- *Vitamin D synthesis*. In the presence of sunlight, vitamin D_3 is synthesised by cells in the epidermal layer.
- *A sensory organ*. Skin contains abundant sensory receptors for touch, heat, cold, pain and itch. Information arising from these dermal receptors is one of the chief ways in which we interact with the outside world.

growth of hair and the activity of these glands is controlled by androgens.

There are two types of sweat glands: *apocrine* glands are associated with hair, especially in the armpits and perineum. They empty their proteinaceous secretion into the hair follicle. *Eccrine* glands, on the other hand, are distributed over much of the skin surface.

The innermost layer of skin is the hypodermis or cutis. This comprises connective tissue and also adipose tissue, which may be particularly thick at some anatomical locations (e.g. the abdomen).

COMMON DISEASES OF THE SKIN

▼ Here we briefly review some common skin disorders, focusing on those for which specific drug treatment is available.

ACNE

▼ The most common form of the disease occurs during puberty, and mainly in boys. Changes in circulating androgens stimulate the sebaceous glands associated with hair follicles, which become enlarged and blocked with sebum and debris. The confined material

may become infected, causing an inflammatory reaction that compounds the problem. Normally acne disappears after puberty but some forms may persist or manifest in later life and require long-term treatment. If severe, acne can cause irreversible scarring and considerable psychological misery.

ROSACEA

▼ The diagnostic feature of rosacea is the presence of a chronic hyperaemia of the facial skin. There is often a characteristic pattern with the erythema spreading across the nose, the cheeks and forehead. The erythema is caused by vasodilatation and dilated blood vessels close to the surface of the skin are usually visible. The affected skin may become dry and flaky; there may be a stinging or burning sensation, and a tendency to flush in response to various stimuli, including exertion, emotional stress, heat, sunlight and spicy foods.

There is a genetic basis for the disorder. It is more prevalent in women than men and may be exacerbated during the menopause. The disease cannot be cured and the symptoms can be very long lasting and difficult to control, with both drug and other therapies playing a role. There is a debate about the cause of rosacea. However, a hypothesis that is gaining ground is that rosacea is a disorder of the innate immune system and that antimicrobial peptides in the skin are indirectly responsible for the symptoms (see Antal et al., 2011; Yamasaki & Gallo, 2011). Antibiotic treatment is usually the first choice where clinical management demands drugs.

BALDNESS AND HIRSUTISM

▼ There are two main types of baldness, *male pattern baldness (androgenic alopecia)* and *alopecia areata*. Androgenic alopecia is caused by rising androgen levels and so particularly affects men after puberty; it starts with bi-temporal recession and progresses. Androgens inhibit the growth of hair on the scalp but stimulate it elsewhere (e.g. the face, chest, back etc.). Alopecia areata is a condition where hair falls out in patches that come and go. Eventually, these patches may coalesce, leading to total baldness. The disease seems to be of autoimmune origin.

Hirsutism is common in men (who seldom complain) but less socially acceptable in women. Once again, rising androgen levels are the cause, stimulating the growth of hair on areas of the body where it does not normally occur in women (e.g. the face); this is commoner in some ethnic groups and seldom pathological but can be a symptom of androgenising endocrine tumours (such as *Sertoli–Leydig cell tumours*, which are rare functioning ovarian tumours).

ECZEMA

▼ This is a generic term and refers to a common (approximately 5–20% of children) condition where the skin becomes dry, itchy, flaky and inflamed. The distribution is distinctive, namely on flexor surfaces (e.g. wrists, elbows and behind the knees, in contrast to psoriasis). There are several potential causes. *Atopic eczema* is often seen in patients who also suffer from asthma or seasonal rhinitis (hay fever), although the long-held notion that eczema is primarily an immunological disorder has rather little to support it. It tends to run in families, indicating a genetic susceptibility. *Contact dermatitis* arises when the skin becomes 'sensitised' to a particular antigen. Nickel sensitivity is a classic example: contact with the metal either provokes the production of antibodies or modifies structural elements of the epidermis so that autoantibodies are produced. This is more often seen in women because it is a common component of (less-expensive) jewellery.[2] The pathophysiology is now believed to stem from disordered barrier function leading to epidermal water loss, and a vicious cycle of itching and scratching with release of inflammatory mediators. Penetration of allergens and interaction with IgE-bearing Langerhans cells can add a Th2-mediated immunological component. *Xerotic eczema* refers to eczema that is produced when the skin dries out. This is more common in the winter months, especially amongst older people.

PRURITUS

▼ Itch is a common symptom of skin diseases, but can also occur with systemic disorders, such as jaundice, or neurological disorders such as shingles (herpes zoster). Some drugs (e.g. opioids) also can cause itching. There is a complex relationship between the neural systems that detect and transduce pain and itch (see Greaves & Khalifa, 2004; Ikoma et al., 2006) and there may be a dedicated population of nociceptors that function as 'itch transducers'.

Skin diseases commonly causing itch include eczema, urticaria and psoriasis. These are largely caused by the release of inflammatory mediators in the skin from mast cells (e.g. histamine, leukotrienes, proteases and cytokines).

URTICARIA

▼ This term refers to a range of inflammatory changes in the skin characterised by the presence of raised wheals or bumps. They are normally surrounded by a red margin and are intensely itchy. There are many known causes, including exposure to the sun (*solar urticaria*[3]), heat or cold, insect bites or stings, foodstuffs or infection as well as some drugs. Many cases are allergic in nature while others have no known cause. A bizarre manifestation of urticaria seen in some people is *dermographia* – literally 'writing on the skin'. This is an exaggerated form of the 'triple response' caused by injecting histamine into the skin (see Ch. 17) and may be provoked by scratching or in some cases simply rubbing or stroking the skin.

Urticaria is associated with inflammatory changes in the dermis including mast cell degranulation and the accompanying release of mediators. It may co-exist with a related condition, *angioedema*, which primarily affects the blood vessels of the subdermal layer. Urticaria can resolve relatively rapidly or can persist for weeks (*chronic urticaria*). The disorder can be difficult to manage and glucocorticoids, which suppress most inflammatory responses, are usually ineffective.

PSORIASIS

▼ Psoriasis is an autoimmune condition affecting about 2–3% of Europeans. There is a genetic component and several susceptibility loci have been identified, most of which are connected with the operation of the immune system. Cytokines such as TNF, IL-17 and IL-23 are involved in the inflammatory mechanism and anticytokine biologics can be used to treat severe manifestations of the disease (see Ch. 6). Histologically, it manifests as inflammation accompanied by hyper-proliferation of keratinocytes. This leads to an accumulation of scaly dead skin at the sites of the disease. The most common form is *plaque psoriasis*. This presents as areas of scaly silvery-white skin surrounded by red margins. The distribution is usually quite characteristic, with plaques first appearing on the knees and elbows. The lesions are sometimes itchy (in fact the word psoriasis originates from Greek and literally means 'itchy skin', though in contrast to eczema, itch is by no means a predominant symptom) and may be painful.

Psoriasis can also affect the fingernails, giving a 'pitted' appearance, and/or the joints (typically but not exclusively the distal interphalangeal joints) or other connective tissue (*psoriatic arthritis*).

Psoriasis is generally a life-long condition but one that can appear and disappear for no apparent reason. Stress is said to be a precipitating factor as is dry skin. Several drugs (e.g. β-adrenoceptor antagonists, non-steroidal anti-inflammatory drugs [NSAIDs] and lithium) are purported precipitants (Basavaraj et al., 2010).

[2]However, the number of men suffering from the condition is rising because of the popularity of body piercing. If body art is your thing, insist on high-quality nickel-free jewellery.

[3]Not to be confused with miliaria (prickly heat), which is caused by blocked sweat glands.

WARTS

▼ Warts are caused by infection with one of the many types of human papilloma virus (HPV). They are characterised by small raised lesions with an irregular shape. As infection of the epidermis by the virus causes *hyperkeratinisation*, they also have a 'rough' feel.

The many varieties of HPV are usually specific for particular tissues, so different strains give rise to different types of warts at diverse anatomical locations. The most common type is usually found on hands and feet (e.g. as *verrucas*). Other types of HPV specifically infect the anogenital region, giving *anogenital warts*.

Most warts are benign in nature and disappear spontaneously after a period of time (usually weeks–months). However, some types of HPV are linked to cancers such as cervical cancer. It is hoped that, in time, immunisation against HPV will reduce the incidence of this disease.

OTHER INFECTIONS

▼ In addition to acne and rosacea, there are a number of other important bacterial skin infections that can be treated with appropriate antibiotics, either topical or systemic. These include superficial skin infections such as *erysipelas* and *impetigo*, and *cellulitis*, which is a more deep-seated infection mainly involving the dermis and subdermis.

Fungal infections of the skin are a common problem. *Tinea*, *candida* and other infections (see Ch. 53) affect skin at several sites (e.g. *tinea pedis* – 'athlete's foot'). These infections are easy to catch and can be difficult to eradicate completely.

The most common viral infections affecting the skin are *herpes simplex* (cold sores) and *herpes zoster* (shingles), which are treated with antiviral drugs (see Ch. 52). The most common parasite infections of the skin are head lice (*Pediculus humanis capitus*) crab lice (*Pthirus pubis*) and scabies (*Sarcoptes scabiei*).

DRUGS ACTING ON SKIN

FORMULATION

Targeting drugs to the skin is both easy and difficult. Unlike most therapeutic settings, drugs can be applied directly to the diseased tissue. There is a caveat, however: since skin is a highly effective barrier, it can prevent the entry of many medicinal agents and this can pose a problem. To reach its site of action (often the lower layer of the epidermis or the dermis) the drug has to pass through the epidermal layer with its highly enriched lipid and aqueous environment. The transdermal delivery of drugs is therefore a highly specialised topic (see Ch. 8). Generally speaking, absorption may be facilitated if the molecule is more hydrophobic in nature: thus, for example, glucocorticoids are often derivatised with fatty acid esters to render them more easily absorbed. The use of a waterproof *occlusion dressing* to cover the skin after applying the drug improves absorption by keeping the epidermis fully hydrated.

The vehicle in which the drug is dissolved is also important. Creams and ointments – essentially stable oil/water emulsions – can be tailored to individual drugs. For example a water-in-oil emulsion is preferable for a hydrophobic drug such as **ciclosporin** whilst an oil-in-water is better for a water-soluble drug such as an NSAID. The appearance and odour of the formulated drug are also important. Most patients would rather take a tablet than apply skin creams that may be greasy, smelly or unsightly (see Tan et al., 2012).

The actual physical condition of the skin is important in maintaining its barrier function and various agents can be used to protect the skin and promote repair. These include *emollients*, which re-hydrate the skin and *barrier creams* that help to prevent damage from irritants. Use of such agents is often indicated alongside treatment with drugs.

Many new ideas for formulating drugs for passage across the skin are under investigation, including the use of 'nanocarriers' and other sophisticated chemical measures (see Schroeter et al., 2010).

Drugs and the skin

Formulation. Because the skin comprises a unique combination of hydrophobic/hydrophilic structures, many drugs are not absorbed and special formulations may be necessary to promote penetration.

Many drugs used for skin conditions are also used to treat disorders in other organs. The main groups are:

- *Glucocorticoids*. Widely used to treat psoriasis, eczema and pruritus because of their anti-inflammatory properties. They are usually specially formulated to enhance topical penetration.
- *Antimicrobial agents*. Used topically or systemically to treat skin infections (e.g. acne, impetigo, cellulitis and rosacea).
- *Hormone antagonists*. Androgen antagonists are used topically or systemically to treat male pattern baldness or hirsutism in women.

Some drugs are used almost exclusively for skin disorders. These include:

- *Retinoids*. These are derivatives of vitamin A and include **tretinoin**, **isotretinoin**, **alitretinoin**, **tazarotene** and **adapalene**. They are used to treat acne, eczema and psoriasis. They are usually given topically, but can be given systemically.
- *Vitamin D derivatives*. Drugs such as **calcitriol**, **calcipotriol** and **tacalcitol** are used to treat psoriasis.

PRINCIPAL DRUGS USED IN SKIN DISORDERS

Many drugs in the dermatological arsenal are also used to treat other diseases and their mechanism of action is the same. The use of agents described below to treat specific skin disorders is shown in Table 27.1. We refer the reader to other chapters in the book where information about these agents may be found (see Table 27.1). Other drugs, such as analogues of vitamins A and D, are rather specific to skin pharmacology.

ANTIMICROBIAL AGENTS

Chapters 50–55 deal in depth with the mechanism of action of this group of drugs. Antibiotics can be applied topically in diseases such as impetigo and acne, or given systemically in the case of cellulitis or rosacea. Fungal infections of the skin are generally treated with topical fungicidal drugs but oral preparations of **ketoconazole** may be used under some circumstances. Herpes simplex infections may be treated with topical or systemic **aciclovir** or **penciclovir** (see Ch. 52).

GLUCOCORTICOIDS AND OTHER ANTI-INFLAMMATORY AGENTS

As one might predict, antihistamines are useful when controlling mild pruritus at least in some circumstances, e.g. eczema, insect bites and mild inflammation. Another topical drug which is useful in treating pruritus is **crotamiton**. This acts rapidly and has long lasting antipruritic effects. The mechanism of action is not known.

The main agents for treating inflammation of the skin are the glucocorticoids. These drugs are widely used to treat psoriasis, eczema and pruritus. Their general mechanism of action is described in Chapters 3 and 33. Preparations used in dermatological practice are often formulated as fatty acid esters of the active drugs. This promotes their absorption through the highly hydrophobic layers of the skin and also alters their efficacy: for example, the potency of **hydrocortisone** on the skin is greatly enhanced by formulating it as a butyrate ester.

▼ Whilst schemes around the world vary, the convention is to classify these drugs by potency. For example:

- *Mild*: e.g. hydrocortisone
- *Moderate*: e.g. **alclomethasone diproprionate**, **clobetasone butyrate**, **fludroxycortide** and **fluocortolone**
- *Potent*: e.g. **beclomethasone diproprionate**, **betamethasone** (various esters) **fluoccinolone acetonide**, **flucocinonide**, **fluticasone proprionate**, **mometasone fuorate** and **triamcinolone acetonide**
- *Very potent*: e.g. **clobetasol proprionate** and **diflucortolone valerate**.

The choice of glucocorticoid depends upon the severity of the disease and, because the thickness of skin varies from one location to the other, its anatomical site. They are sometimes used in combination with antibacterial or fungicidal drugs if they are to be used at the site of an infection.

The action of glucocorticoids on the skin is similar in mechanism to their effect elsewhere in the body. They are potent inhibitors of the release of inflammatory mediators from mast cells, of neutrophil activation and emigration, and immune cell activation (see Chs 26, 33). Their topical application produces vasoconstriction in the skin causing a characteristic 'blanching' reaction.[4] The mechanism is unknown.

Unwanted effects. Generally speaking, short-term treatment with low potency steroid preparations are safe; hydrocortisone formulations are available from pharmacies without prescription.

There are potentially serious side effects associated with prolonged usage or the more potent members of the class, however. These include:

- *Steroid 'rebound'*. If topical steroid therapy is suddenly discontinued, the underlying disease often returns in a more aggressive form. The biological basis of this is probably that the gluococorticoid receptor is downregulated during topical treatment and can no longer respond to normal circulating glucocorticoids. Gradually tapering the drug can avoid this problem.
- *Skin atrophy*. Catabolic effects of glucocorticoids (Ch. 33) can lead to atrophy of the skin that is only partially reversible upon stopping treatment.
- *Systemic effects*. Systemic absorption can cause depression of the hypothalamic–pituitary–adrenal axis, as described in Ch. 33. This is avoidable provided that the drug regime is well managed (Castela et al., 2012).
- *Spread of infection*. Because glucocorticoids suppress the immune system, there is a danger that they may encourage or reactivate infection. For this reason they are contraindicated in acne, where there is a co-existent infection.
- *'Steroid rosacea' (skin reddening and pimples)* is a recognised problem when treating facial skin with glucocorticoids.
- *Production of stretch marks (striae atrophica)* and *telangiectasia* (small superficial dilated blood vessels).

For more serious cases of eczema or psoriasis or where glucocorticoids are ineffective, topical or systemic application of immunosuppressants such as **ciclosporin, pimecrolimus** or **tacrolimus** may be used (Ch. 26). Biopharmaceuticals such as **adalimumab** and **infliximab** are also used in severe cases and the use of these 'cytokine modulators' in these diseases is set to increase (see Pastore et al., 2008; Williams, 2012).

DRUGS USED TO CONTROL HAIR GROWTH

Hair growth in both sexes is driven by androgens as is male-pattern baldness. Because of this, androgen antagonists, or compounds that modulate androgen metabolism, can be used to treat both hirsutism in women and androgenic alopecia in men.

Co-cyprindol is mixture of an antiandrogen **cyproterone acetate** and a female sex hormone **ethinylestrodiol**. Antagonising androgenic actions reduces sebum production by sebaceous glands and also hair growth (which is androgen-dependent) so it can be used for treating acne as well as hirsutism in women. Unwanted effects include venous thromboembolism and it is contraindicated in women with a family history of cardiovascular disease.

Finasteride inhibits the enzyme (5α-reductase) that converts testosterone to the more potent androgen, dihydrotestosterone (see Ch. 35). It is used for the treatment of androgenic alopecia as well as prostatic hypertrophy. It is applied topically but the treatment takes months to produce real changes. Unwanted effects resulting from its action on androgen metabolism include a reduction in libido, possibly impotence and tenderness of the breasts.

Eflornithine was originally developed as an antiprotozoal drug (see Ch. 54). It can be used topically to treat hirsutism because it irreversibly inhibits *ornithine decarboxylase* in hair follicles. This interrupts cell replication and the growth of new hair follicles. Unwanted effects include skin reactions and acne.

Minoxidil is a vasodilator drug that was originally developed for treating hypertension (see Ch. 22). Applied topically, it is converted in hair follicles to a more potent metabolite, minoxidil sulfate (some preparations contain this salt). Perhaps because of its ability to increase blood supply to hair follicles, it stimulates growth of new hair and the progression of the new follicle through successive phases of the cell cycle (Ch. 9). Existing follicles, usually stalled in their resting (telogen) phase, must first be 'shed' to make way for new, rapidly growing follicles, so there is initial hair loss – an unwelcome and slightly alarming

[4]This observation was used by Cornell and Stoughton in 1985 as the basis for the first quantitative assay of glucocorticoid potency in man.

action of the drug. Other unwanted effects are few but some local irritation may occur.

RETINOIDS

Disturbances in vitamin A metabolism are known to result in skin pathology. The vitamin is normally acquired in ester form from dietary sources. It is converted to *retinol* in the gut and this seems to be a storage form of the vitamin.

Vitamin A has many biological roles. As *retinal* it is an essential component of rhodopsin and hence crucial for normal vision. However, it can also undergo an irreversible oxidation to *retinoic acid*, which lacks any effects on the visual system, but has potent effects on skin homeostasis.

The retinoid drugs are derivatives of retinoic acid (see Fig. 27.2). The principal examples are **tretinoin**, **isotretinoin**, **alitretinoin**, **tazarotene** and **adapalene**. They are widely used for the treatment of acne, eczema and psoriasis. Topical application is the usual route of administration but oral therapy is sometimes used for severe cases.

Most workers believe that retinoids act by binding to RXR and RAR nuclear receptors (see Ch. 3 and Fig. 27.2) in their target cells, which include keratinocytes and the cells of sebaceous glands, although some have questioned this mechanism (Arechalde & Saurat, 2000). The main dermatological actions of retinoids include modulation of epidermal cell growth and reduction in sebaceous gland activity and sebum production. They also have pleiotropic actions on the adaptive and innate immune system that produce a net anti-inflammatory effect (Fisher & Voorhees, 1996; Orfanos et al., 1997).

Unwanted effects. Retinoids may cause dry or flaky skin, stinging or burning sensations and also joint pains (after oral administration). Most are teratogenic and can be used in women only in the presence of suitable contraception.

VITAMIN D ANALOGUES

Vitamin D is actually a mixture of several related substances. Although classed as a 'vitamin' and therefore by implication an essential dietary factor, vitamin D_3 (cholecalciferol) is synthesised by the skin in the presence of sufficient sunlight (in fact, *phototherapy* is an important therapeutic modality in some skin disorders for this and other reasons). Other forms of the vitamin (e.g. D_2) can be obtained from the diet. The vitamin plays a crucial role in calcium and phosphate metabolism and bone formation (see Ch. 36). It also has complex regulatory actions on the immune system, reducing the activity of the adaptive system but increasing the activity of the innate immune system.

The biologically active metabolite calcitriol (see Ch. 36) is synthesised in the body by a multi-step process that requires transformations in the liver and kidney. At the molecular level, vitamin D and its analogues act though the VDR group of nuclear receptors in keratinocytes, fibroblasts, Langerhans cells and sebaceous gland cells to modulate gene transcription. Amongst the effects seen after treatment, are antiproliferative and pro-differentiation actions on keratinocytes, increased apoptosis of plaque keratinocytes (Tiberio et al., 2009) and the inhibition of T cell activation (Tremezaygues & Reichrath, 2011).

The main analogues used are **calcitriol** itself, **calcipotriol**, and **tacalcitol**. Their principal clinical use is treating

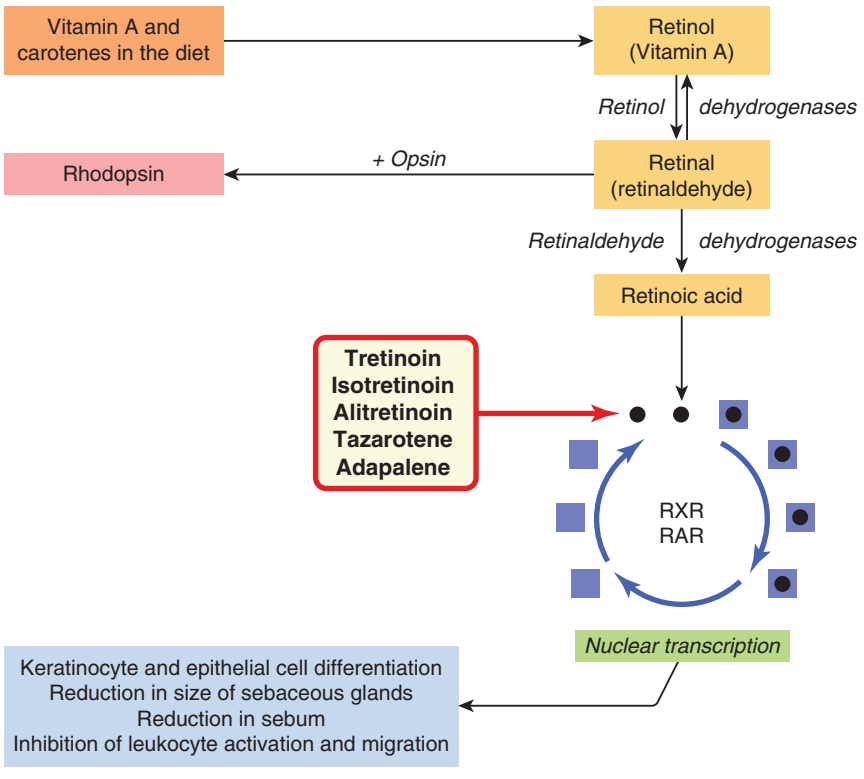

Fig. 27.2 The retinoid pathway. Vitamin A (retinol) is acquired largely through dietary sources and is reversibly converted to retinal (retinaldehyde). This may be combined with opsin to produce the visual pigment rhodopsin or irreversibly oxidised to retinoic acid. The later species can interact with nuclear receptors (RXR and RAR; see Ch. 3) to produce changes in genes that modulate keratinocyte differentiation, reduce the size and output of sebaceous glands and exert a general anti-inflammatory action. The synthetic congeners tretionoin, isotretinoin, alitretinoin, tazarotene and adapalene can act at the RXR and RAR also producing potent actions in skin disorders such as acne and psoriasis.

psoriasis. Oral administration is possible but they are generally administered topically, sometimes in combination with a glucocorticoid.

Unwanted effects. There is always a concern about the possible effects of the drugs on bone and they should be avoided in patients who have problems related to calcium or bone metabolism. Topical application can lead to skin irritation.

AGENTS ACTING BY OTHER MECHANISMS

Many ancillary agents are used in dermatology, including topical antiseptics, emollients, soothing lotions and other substances. Amongst this group are '**coal tars**', which are poorly defined mixtures containing thousands of aromatic hydrocarbons generated during the conversion of coal to coke or gas. They have been used in dermatological practice for decades. Though their mechanism of action is unknown, they can bring about a useful therapeutic benefit in eczema, psoriasis and some other skin conditions, and are often the first agents to be tried. Given their origin, one might expect coal tars to be carcinogenic, although in fact this does not appear to be the case (Roelofzen et al., 2010). Preparations containing coal tars are applied topically.

Amongst other drugs unique to skin pharmacology are **salicylic acid** and **podophyllotoxin**. Topical salicylic acid has a *keratolytic* effect in situations when excess skin is being produced (e.g. warts), causing epidermal layers to be shed. It is a common ingredient of numerous proprietary wart removers. Podophyllotoxin is a toxin extracted from plants of the podophyllum family. It is usually reserved for treating anogenital warts. It is applied topically and prevents the excess growth of skin probably because it inhibits tubulin polymerisation and hence arrests the normal cell cycle.

Another agent used for anogenital warts is **imiquimod**. This drug is an immune modifier and is also used for the topical treatment some types of skin cancer (e.g. basal cell carcinoma). Its mechanism of action is not known but it may increase immune surveillance mechanisms. Unwanted effects include local skin reactions.

CONCLUDING REMARKS

Despite the plethora of preparations available to treat skin disorders, there is clearly still an unfilled therapeutic need in several areas (e.g. rosacea) and, as always, reducing the unwanted effects of existing drugs (e.g. the glucocorticoids) is a further worthwhile objective that would greatly enhance their clinical utility.

It is perhaps surprising that 'itch' is still such a problem. Various new drug targets (e.g. NK_1-receptor antagonists, see Ch. 18) have been identified for treating the chronic disease (reviewed in Benecke et al., 2013).

The search for new drugs to treat psoriasis has largely focused upon the actions of biopharmaceuticals (see Gniadecki & Calverley, 2002; Pastore et al., 2008) with relatively little attention given to new small-molecule drugs.

In terms of improving the side effects of existing drugs some of the most interesting ideas arise from reconsidering the design of the glucocorticoids, vitamin D analogues and especially the retinoids. All these drugs act predominantly through nuclear receptors and recent thinking suggests that differentiating the mechanisms of transrepression and transactivation of genes by these drugs may be an achievable goal. Clearly, the prospect of separating the calcaemic from the anti-inflammatory effects of vitamin D analogues is very attractive (Tremezaygues & Reichrath, 2011). Likewise an improvement of the selectivity of retinoids would also be very welcome (Orfanos et al., 1997). Progress towards separating the therapeutic from the unwanted effects of the glucocorticoids is already apparently yielding fruit (see Ch. 28 for a discussion of this).

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28 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 51 and 56, 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_ACO_2) by an action on medullary chemoreceptors, and of oxygen (P_AO_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 non-myelinated afferent nerve fibres respond to chemical irritants and cold air, and also to inflammatory mediators. 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 other 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 submucosal mucus-secreting 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. However, β adrenoceptors are 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. 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*,

[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.

neurokinin A and *neurokinin B* (see Chs 19 and 42), 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. 42), as well as endogenous inflammatory mediators.

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.

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 51–55), malignancy (Ch. 56) 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 chronic obstructive pulmonary disease (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.[2] 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. 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.

Bronchial hyper-reactivity (or hyper-responsiveness) is 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. 28.1).

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. 18 and Table 6.2) in their bronchial mucosa. How these cells are activated is not fully understood, but allergens (Fig. 28.2) are one mechanism. The Th2 cytokines that are released do the following:

[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!

- 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 (see Ch. 17), 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 p. 351) 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.

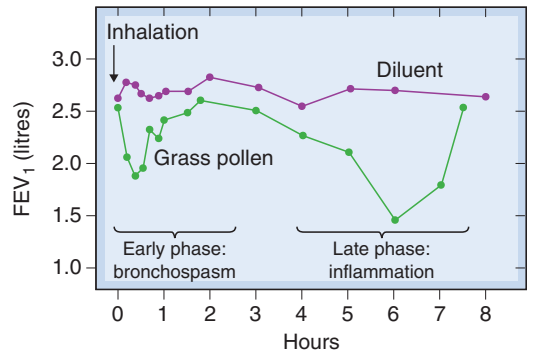

Fig. 28.1 Two phases of asthma demonstrated by the changes in forced expiratory volume in 1 second (FEV_1) after inhalation of grass pollen in an allergic subject. *(From Cockcroft DW 1983 Lancet ii, 253.)*

The immediate phase of an asthma 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. 18) attract leukocytes – particularly eosinophils and mononuclear cells – setting the stage for the late phase (Fig. 28.3).

The late phase

The late phase or delayed response (see Figs 28.1 and 28.3) may be nocturnal. It is, in essence, a progressing inflammatory reaction, initiation of which occurred during the first phase, the influx of Th2 lymphocytes

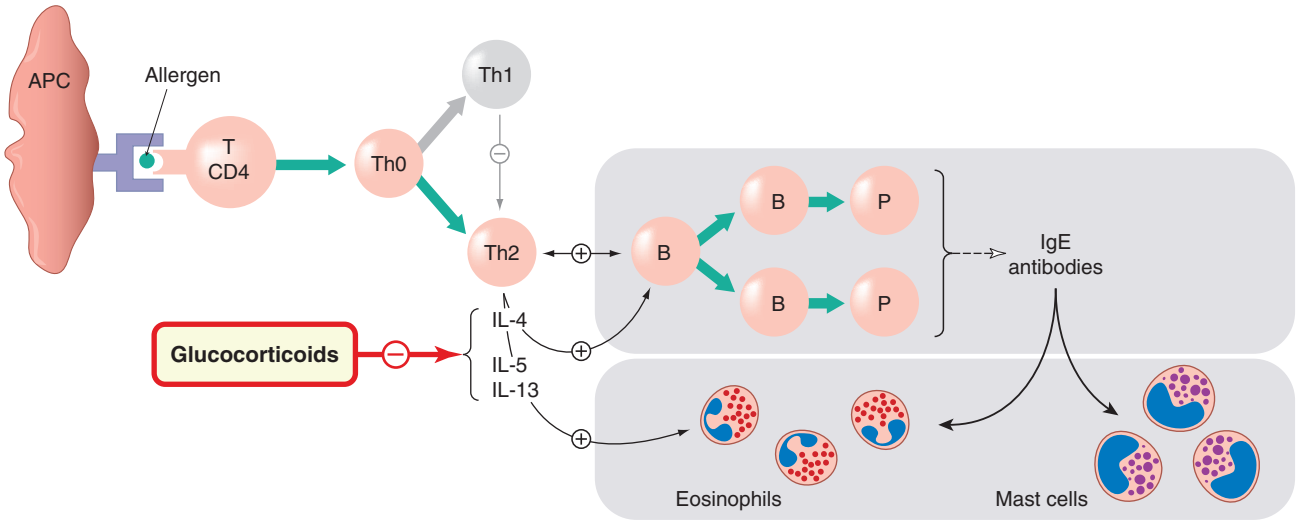

Fig. 28.2 The part played by T lymphocytes in allergic asthma. In genetically susceptible individuals, allergen (green circle) interacts with dendritic cells and $CD4^+$ T cells, leading to the development of Th0 lymphocytes, which give rise to a clone of Th2 lymphocytes. These then (1) generate a cytokine 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) generate 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.

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.

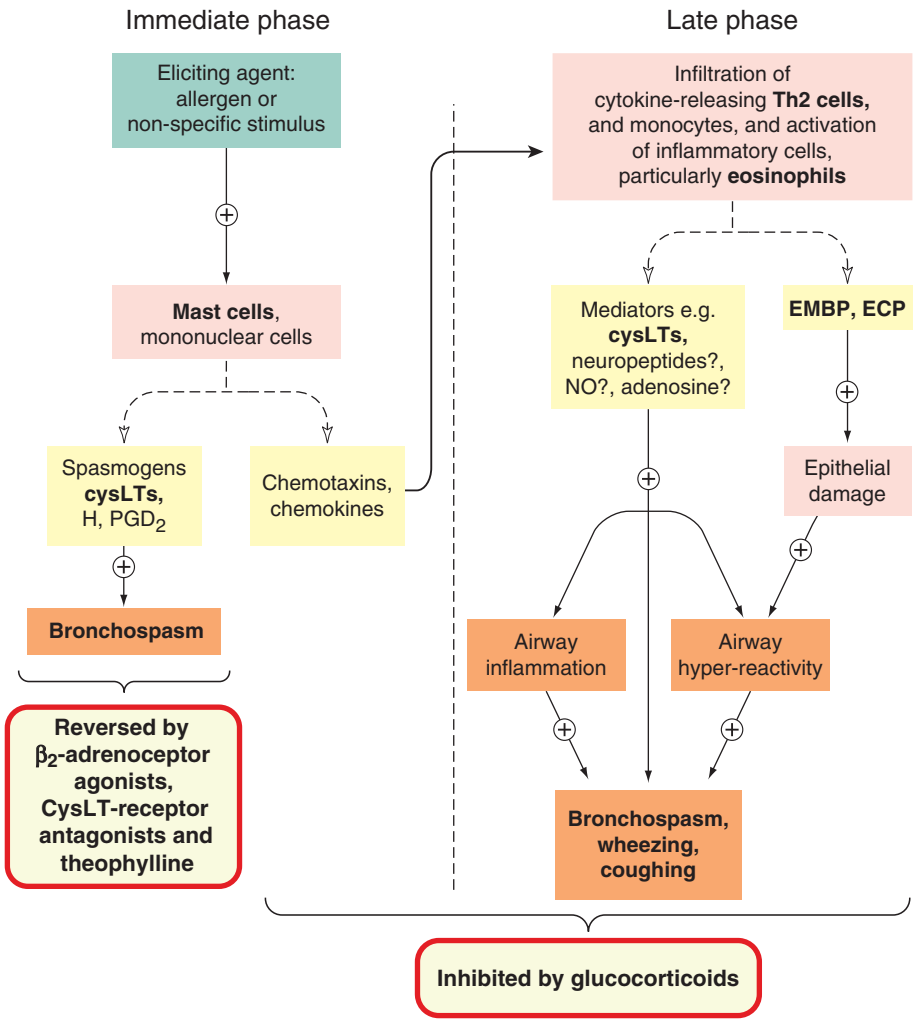

Fig. 28.3 Immediate and late phases of asthma, with the actions of the main drugs. CysLTs, cysteinyl leukotrienes (leukotrienes C_4 and D_4); ECP, eosinophil cationic protein; EMBP, eosinophil major basic protein; H, histamine; iNO, induced nitric oxide. (For more detail of the Th2-derived cytokines and chemokines, see Ch. 17 and Ch. 6, Fig. 6.4.)

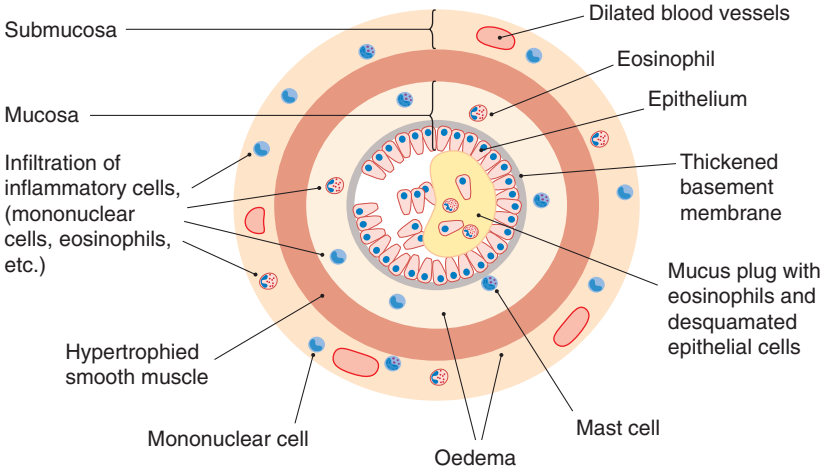

Fig. 28.4 Schematic diagram of a cross-section of a bronchiole, showing changes that occur with severe chronic asthma. The individual elements depicted are not, of course, drawn to scale.

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. 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. 18).

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 growth factors (Chs 5 and 18). Figure 28.4 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 (Ch. 26) 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. In addition, aspirin and similar drugs directly activate eosinophils and mast cells in these patients through IgE-independent mechanisms.

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. 28.3). 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 on the management of asthma (BTS/SIGN, 2012) specifies five therapeutic steps for adults and children with chronic asthma. Very mild disease may be controlled with short-acting bronchodilator (**salbutamol** or **terbutaline**) 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, step 3 is to add a long-acting bronchodilator (**salmeterol** or **formoterol**); this minimises the need for increased doses of inhaled corticosteroid. **Theophylline** and leukotriene antagonists, such as **montelukast**, also exert a corticosteroid-sparing effect, but this is less reliable. One or other is added (step 4) for patients who remain symptomatic and/or the dose of inhaled corticosteroid increased to the maximum recommended. Step 5 is addition of a regular oral corticosteroid (e.g. **prednisolone**). 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 p. 351) 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 spasmogen is involved. They also inhibit mediator release from mast cells and TNF-α release from monocytes, and increase mucus clearance by an action on cilia.

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 droplets), but some products 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.

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).

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*.

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.

Methylxanthines (see Chs 16 and 48)

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 Ch. 4, 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, 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. 48) and respiratory stimulation may be beneficial in patients with COPD and reduced respiration causing retention of CO_2. **Caffeine** has a special niche in treating hypoventilation of prematurity (see Ch. 48).

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

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

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.

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.

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**. It 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 atropine. 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, below, for clinical uses. **Tiotropium** is similar; it is a longer-acting drug used in maintenance treatment of COPD (see below).

Clinical use of inhaled muscarinic receptor antagonists (e.g. ipratropium)

- For asthma, as an adjunct to β_2-adrenoceptor agonists and steroids.
- For some patients with COPD, especially long-acting drugs (e.g. **tiotropium**).
- For bronchospasm precipitated by β_2-adrenoceptor antagonists.

Cysteinyl leukotriene receptor antagonists

Cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) act on $CysLT_1$ and $CysLT_2$ receptors (see Ch. 17), both of which 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 p. 348) 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. 28.3) 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. 33) 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 clinical box, p. 351).[4]

[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 33. An important action, of relevance for asthma, is that they restrain clonal proliferation of Th cells by reducing the transcription of the gene for IL-2 and 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 (Ch. 17, 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. 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.

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. Oral glucocorticoids (Ch. 33) are reserved for patients with the severest disease.

Unwanted effects

Serious unwanted effects are uncommon with inhaled steroids. Oropharyngeal candidiasis (thrush; Ch. 53) 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 of inhaled glucocorticoids can produce some adrenal suppression, particularly in children, and necessitate carrying a 'steroid card' (Ch. 33). 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 33 and Figure 33.7.

Cromoglicate and nedocromil

These two drugs, of similar chemical structure and properties, are now hardly used for the treatment of asthma.

[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!

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.

Although very safe, they have only weak anti-inflammatory effects and short duration of action. They are given by inhalation as aerosols or dry powders, and can 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.

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, 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. 18) – and by aspirin and related drugs in patients who are aspirin sensitive (see 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. 35) 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. 18), 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 (COPD) is a major global health problem – current projections suggest that it will be the third commonest cause of death by 2012. 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 resurgence of interest in new therapeutic approaches (see Barnes, 2008) has yet to bear fruit but there are a number of promising avenues.

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. 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 fibrosis of small airways, 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 (bronchitis), 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 de-acetylates histones, and suppresses production of proinflammatory cytokines. Corticosteroids recruit HDAC to activated genes, switching off inflammatory gene transcription

[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.

(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 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, 2013). 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 show promise and **roflumilast** is licensed as an adjunct to bronchodilators for patients with severe COPD and frequent exacerbations. 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 include 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**) are sometimes used briefly in acute respiratory failure (e.g. postoperatively) but have largely been replaced by mechanical 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).

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 with activity against *Haemophilus influenzae* (e.g. **cefuroxime**; Ch. 51), 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 act, not by binding to specific targets, but by lowering the surface tension of fluid lining the alveoli, allowing air to enter. They are effective in the prophylaxis and management of *respiratory distress syndrome* in newborn babies, especially premature babies in whom endogenous surfactant production is deficient. 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, often 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

Opioid analgesics are the most effective antitussive drugs in clinical use (Ch. 42).They act by an ill-defined effect in the brain stem, depressing an even more poorly defined 'cough centre' and 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 42.2) on sensory nerves in the bronchi are being assessed.

Codeine (methylmorphine) is a weak opioid (see Ch. 42) with considerably less addiction liability than a strong opioid, and is a mild cough suppressant. It decreases secretions in the bronchioles, which thickens sputum, and inhibits ciliary activity. Constipation is common. **Dextromethorphan** (a non-selective serotonin-uptake inhibitor and sigma-1-receptor agonist) and **pholcodine** have less adverse effects than codeine. Respiratory depression is a risk with all centrally acting cough suppressants. **Morphine** is used for palliative care in cases of lung cancer associated with distressing cough.

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29 The kidney and urinary system

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. Emphasis is on diuretics – drugs that increase the excretion of Na^+ ions and water, and reduce arterial blood pressure. We also consider briefly other drugs used to treat 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 the dosing regimens of many drugs must be adapted in patients with impaired renal function. Furthermore, the kidneys are a target for various kinds of drug toxicity (Ch. 57), due in part to the very high concentrations of drugs and drug metabolites in some renal tissues. 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 following renal transplantation) in Chapter 26 and antibacterial drugs (used to treat renal and urinary tract infections) in Chapter 51. Drugs, as well as surgical procedures, are also used to treat, lower urinary tract disorders which commonly cause urinary retention or incontinence. Patients with anaemia due to chronic renal failure benefit from **epoietin** (Ch. 25).

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 in composition 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 29.1).

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* (Fig. 29.1). 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. 29.1). 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. 29.2). 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). Various chemical 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

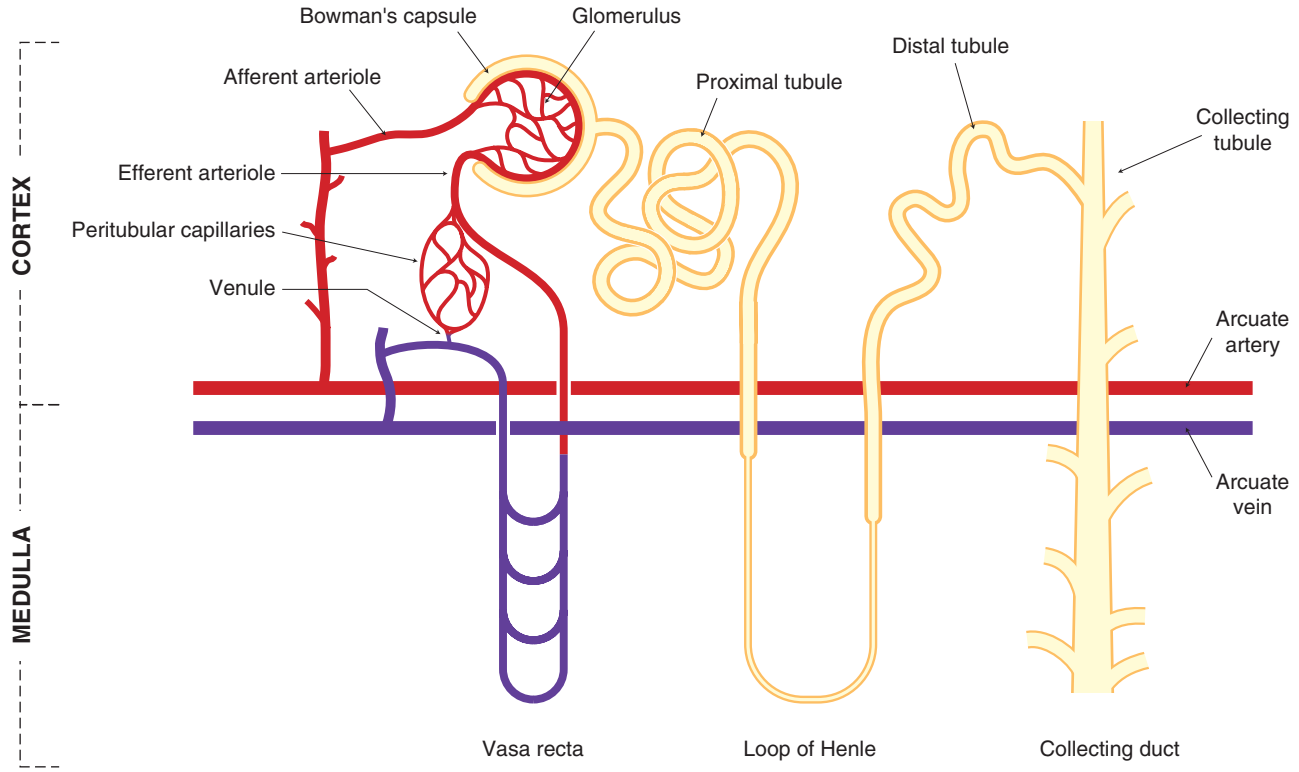

Fig. 29.1 Simplified diagram of a juxtamedullary nephron and its blood supply. The tubules and the blood vessels are shown separately for clarity. In the kidney, the peritubular capillary network surrounds the convoluted tubules, and the distal convoluted tubule passes close to the glomerulus, between the afferent and efferent arterioles. (This last is shown in more detail in Fig. 29.2.)

Table 29.1 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.

the oncotic pressure of the plasma proteins, to which the 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.

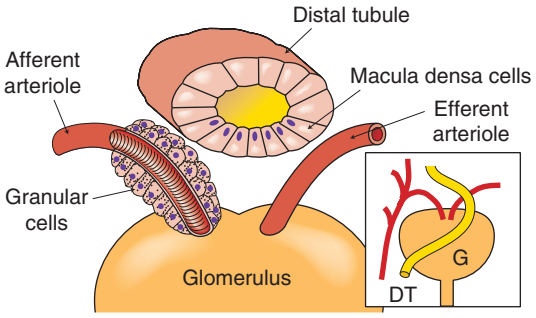

Fig. 29.2 The juxtaglomerular apparatus. The cutaway sections show the granular renin-containing cells round the afferent arteriole, and the macula densa cells in the distal convoluted tubule. The inset shows the general relationships between the structures. DT, distal tubule; G, glomerulus.

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, either in the same direction as Na^+ in which case they are called *symporters* or *co-transporters* or in the opposite direction in which case they are called *antiporters*. 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 glomerular filtrate.

Some of the transport processes in the proximal tubule are shown in Figures 29.3–29.5. The most important mechanism for Na^+ entry into proximal tubular cells from the filtrate occurs by Na^+/H^+ exchange (Fig. 29.5). Intracellular carbonic anhydrase is essential for production of H^+ for secretion into the lumen. Na^+ is reabsorbed from tubular fluid into the cytoplasm of proximal tubular cells in exchange for cytoplasmic H^+. It is then transported out of the cells into the interstitium 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. Reabsorbed Na^+ then diffuses into blood vessels.

▼ 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. 29.5A) – 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 the 3 Na^+:2 K^+ stoichiometry of the transporter. This leads to osmotic movement of water across the tight junction, in turn causing sodium reabsorption by convection (so-called solvent drag).

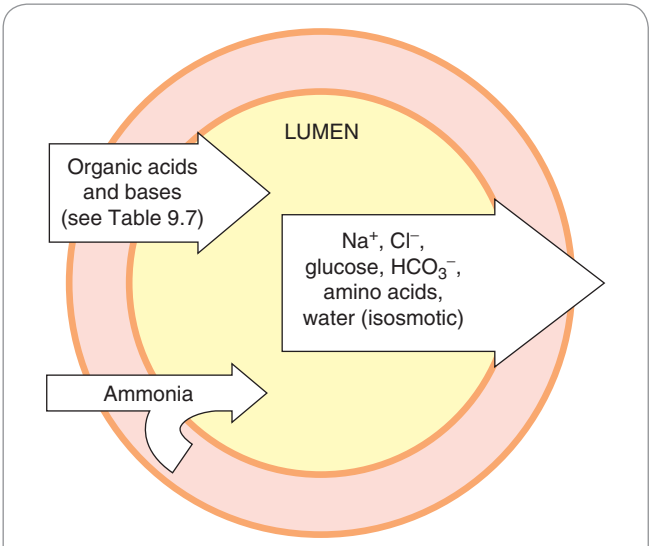

Fig. 29.3 Transport processes in the proximal convoluted tubule. The main driving force for the absorption of solutes and water from the lumen is the Na^+-K^+-ATPase in the basolateral membrane of the tubule cells. Many drugs are secreted into the proximal tubule (see Ch. 9). *(Redrawn from Burg 1985, pp 145-175 in The Kidney, third ed., Brenner BM, Rector FC (eds), WB Saunders, Philadelphia.)*

Many organic acids and bases are actively secreted into the tubule from the blood by specific transporters (see below, Fig. 29.3 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 29.1 and 29.4), 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.

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

[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. 29.5A).

[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.

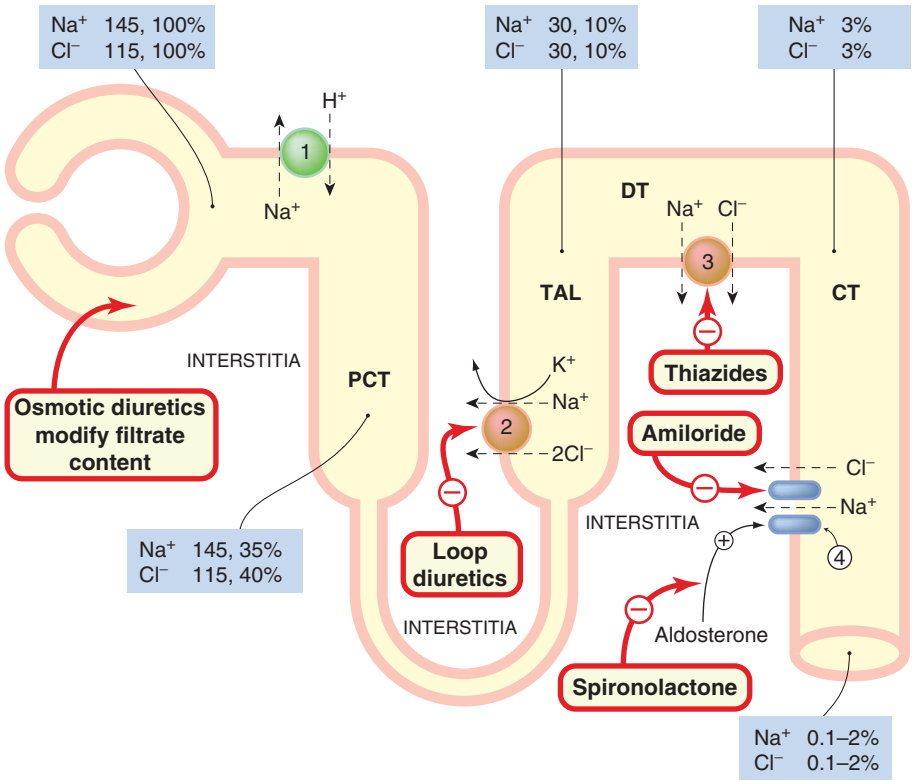

Fig. 29.4 Schematic showing the absorption of sodium and chloride in the nephron and the main sites of action of drugs. Cells are depicted as a pink border round the yellow tubular lumen. Mechanisms of ion absorption at the apical margin of the tubule cell: (1) Na^+/H^+ exchange; (2) $Na^+/K^+/2Cl^-$ 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.)*

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. 29.5B). 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. 29.4). 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 cytoplasmic 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. 29.5C).

The excretion of Ca^{2+} is regulated in this part of the nephron, *parathormone* and *calcitriol* both increasing Ca^{2+} reabsorption (see Ch. 36).

THE COLLECTING TUBULE AND COLLECTING DUCT

Distal convoluted tubules empty into collecting tubules, which coalesce to form collecting ducts (Fig. 29.1). Collecting tubules include principal cells, which reabsorb Na^+ and secrete K^+ (Fig. 29.5D), 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. 33).

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]

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

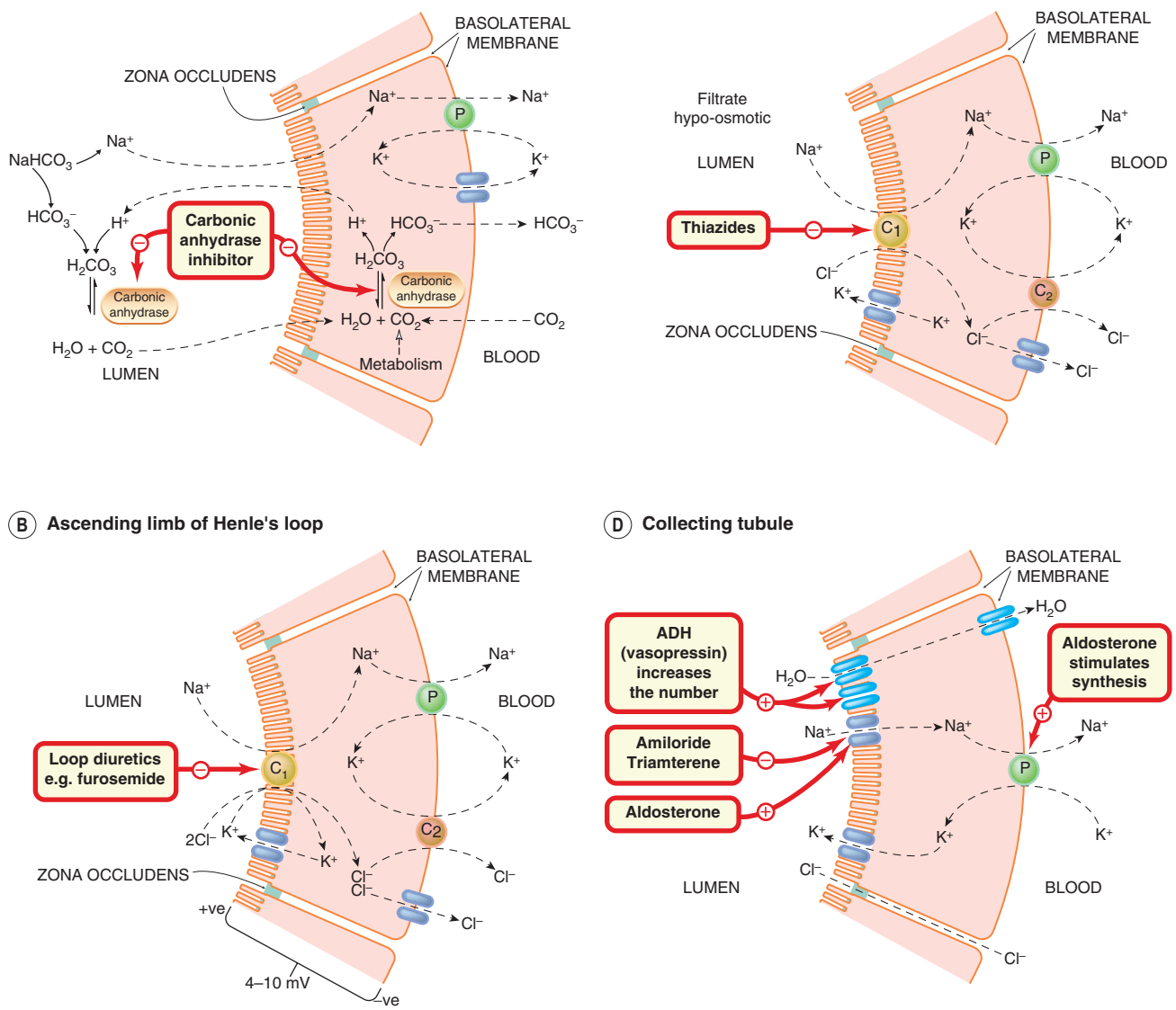

Fig. 29.5 Drug effects on renal tubular ion transport. [**A**] Bicarbonate ion reabsorption in the proximal convoluted tubule, showing the action of carbonic anhydrase inhibitors. [**B**] Ion transport in the thick ascending limb of Henle's loop, showing the site of action of loop diuretics. [**C**] Salt transport in the distal convoluted tubule, showing the site of action of thiazide diuretics. [**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. *(Adapted from Greger 2000.)*

- 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. 29.5D).

ADH and nephrogenic diabetes insipidus. ADH is secreted by the posterior pituitary (Ch. 33) and acts on V_2 receptors in the basolateral membranes of cells in the collecting tubules and ducts, increasing expression of *aquaporin* (water channels; see Ch. 8) in the apical membranes (Fig. 29.5D). 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. 33) or action on the kidney results in *diabetes insipidus*, an uncommon disorder in which patients excrete large volumes of dilute urine.

Ethanol (Ch. 49) 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. 46), **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. 56). Recently, more specific antagonists of ADH (e.g. **conivaptan**, **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_2 receptor or aquaporin.

Renal tubular function

- Protein-free glomerular filtrate enters via Bowman's capsule.
- Na^+-K^+-ATPase in the basolateral membrane is the main active transporter. It provides the Na^+-gradients (low cytoplamic Na^+ concentrations) for passive transporters in the apical membranes which facilitate Na^+ entry (reabsorption) from the tubular fluid down a concentration gradient.
- 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 in the proximal tubule and also for 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 epithelial Na^+ channels are activated by aldosterone and inhibited by **amiloride** and by **trimterene**. K^+ or H^+ is secreted into the tubule in exchange for Na^+ in this distal region.

ACID–BASE BALANCE

The kidneys (together with the lungs; Ch. 28) 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 acid and of 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. 21) – clinically important drug interactions.

Potassium ions are transported into collecting duct and collecting tubule cells from 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).

Conversely, 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 9.7) 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. 51). Similarly, several secreted organic cations are important drugs, for example **triamterene**, **amiloride**, **atropine** (Ch. 13), **morphine** (Ch. 42) and **quinine** (Ch. 54). 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 in the interstitial fluid are exchanged with cytoplasmic α-ketoglutarate by an antiport (i.e. an exchanger that couples uptake and release of α-ketoglutarate with, in the opposite direction, uptake and

release of a different organic anion) in the basolateral membrane, and diffuse passively into the tubular lumen (Fig. 29.3).

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 influence 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, local release of PGE_2 and PGI_2 compensates, preserving renal blood flow by their vasodilator action.

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 by inhibiting cyclo-oxygenase; 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]

[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.

DRUGS ACTING ON THE KIDNEY

DIURETICS

Diuretics increase the excretion of Na^+ and water. They decrease the reabsorption of Na^+ and an accompanying anion (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 29.1), even 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 29.4 and more detailed information on different classes of drugs in Figure 29.5.

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. 29.5B) are the most powerful diuretics (see Fig. 29.6 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 independent of 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'.

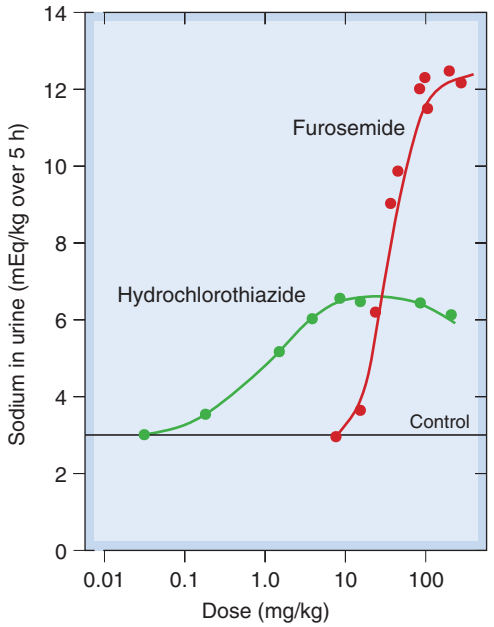

Fig. 29.6 Dose–response curves for furosemide and hydrochlorothiazide, showing differences in potency and maximum effect 'ceiling'. Note that these doses are not used clinically. *(Adapted from Timmerman RJ et al 1964 Curr Ther Res 6, 88.)*

Loop diuretics increase excretion of Ca^{2+} and Mg^{2+} and decrease excretion of uric acid.

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

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.

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. 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. Adverse reactions unrelated to the main pharmacological effect (e.g. rashes, bone marrow depression) can occur.

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. 29.5C).

[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.

Thiazides are less powerful than loop diuretics, at least in terms of peak increase in rate of urine formation, and 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 (ALLHAT, 2002), chlortalidone performed as well as newer antihypertensive drugs (an angiotensin-converting enzyme [ACE] inhibitor and a calcium antagonist). Thiazides bind 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 (Aung & Htay 2011).

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 thiazide-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.

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*.

Unwanted effects

Apart from an increase in *urinary frequency*, the commonest unwanted effect of thiazides not obviously related to their main renal action is *erectile dysfunction*. This emerged in an analysis of reasons given by patients for withdrawing 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. 31), 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.

Adverse reactions unrelated to the main pharmacology (e.g. rashes, blood dyscrasias) are not common 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. 29.5D) – 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. 33), thereby inhibiting distal Na^+ retention and K^+ secretion (see Fig. 29.5D).

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 other than in exceptional circumstances and then with close monitoring, and close

[7]The chemically related sulfonylurea group of drugs used to treat diabetes mellitus (Ch. 31) act in the opposite way, by closing K_{ATP} channels and enhancing insulin secretion.

monitoring of plasma creatinine and electrolytes is also 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 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.

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.

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. 29.5D).

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. 29.5A) – 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), in some types of infantile epilepsy (Ch. 45), and to accelerate acclimatisation to high altitude.

Urinary loss of bicarbonate depletes extracellular bicarbonate, and the diuretic effect of carbonic anhydrase inhibitors is consequently self-limiting. Acetazolamide is a sulfonamide and unwanted effects as occur with other sulfonamides such as rashes, blood dyscrasias and interstitial nephritis can occur.

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. 29.4).[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. In acute renal failure, 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 precipitating left ventricular failure) and hyponatraemia. Headache, nausea and vomiting can occur.

[8] In hyperglycaemia, glucose acts as an osmotic diuretic once plasma glucose exceeds the renal reabsorptive capacity (usually approximately 12 mmol/l), accounting for the cardinal symptom of polyuria in diabetes mellitus; see Chapter 31.

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.

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 inhibits urinary stone formation. Alkalinisation is important in preventing certain weak acid drugs with limited aqueous solubility, such as *sulfonamides* (see Ch. 51), 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 (see Ch. 26). 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.

DRUGS USED IN RENAL FAILURE

Many drugs used in renal failure (e.g. antihypertensives, vitamin D preparations and **epoietin**) are covered in other chapters. Electrolyte disorders are particularly important in renal failure, notably *hyperphosphataemia* and *hyperkalaemia*, which may require drug treatment.

HYPERPHOSPHATAEMIA

Phosphate metabolism is closely linked with that of calcium and is discussed in Chapter 36.

The antacid **aluminium hydroxide** (Ch. 30) binds phosphate in the gastrointestinal tract, reducing its absorption, but may increase plasma aluminium in dialysis patients.[9] Calcium-based phosphate-binding agents (e.g. calcium carbonate) are widely used. They are contraindicated in hypercalcaemia or hypercalciuria but until recently have

[9]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.

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 (Tonelli et al., 2010). Sevelamer is not absorbed from the gut 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. 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. 31). **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 ions into cells in exchange for intracellular protons that emerge to buffer the extracellular fluid.

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. However, 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. 33) combined with restricting fluid intake.

Symptoms from benign prostatic hyperplasia may be improved by α_1-adrenoceptor antagonists, for example **doxazosin** or **tamsulosin** (Ch. 14), or by an inhibitor of androgen synthesis such as **finasteride** (Ch. 35).

Muscarinic receptor antagonists (Ch. 13) such as **oxybutinin** are used for neurogenic detrusor muscle instability, but the dose is limited by their adverse effects. A selective β_3 agonist (**mirabegron**) has recently been licensed for overactive bladder (Ch. 14).

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30 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. It also 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 the site of many common pathologies, ranging from simple dyspepsia to complex autoimmune conditions such as Crohn's disease and medicines for treating 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 inflammatory disease.

THE INNERVATION AND HORMONES OF THE GASTROINTESTINAL TRACT

The blood vessels and the glands (exocrine, endocrine and paracrine) of 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*) lies between the outer, longitudinal and the middle, circular muscle layers, and the *submucous plexus* (*Meissner's plexus*) lies on the lumenal side of the circular muscle layer. These plexuses are interconnected and their ganglion cells receive preganglionic parasympathetic fibres from the vagus. These 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 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 (5-HT), purines, nitric oxide and a variety of pharmacologically active peptides (see Chs 12–20). 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 during their passage through 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 defecation
- 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 in 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 protective 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 SECERETION BY PARIETAL CELLS

Disturbances of acid secretion are important in the pathogenesis of peptic ulcer and constitute 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. To produce this, Cl^- is actively transported into *canaliculi* in the cells

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

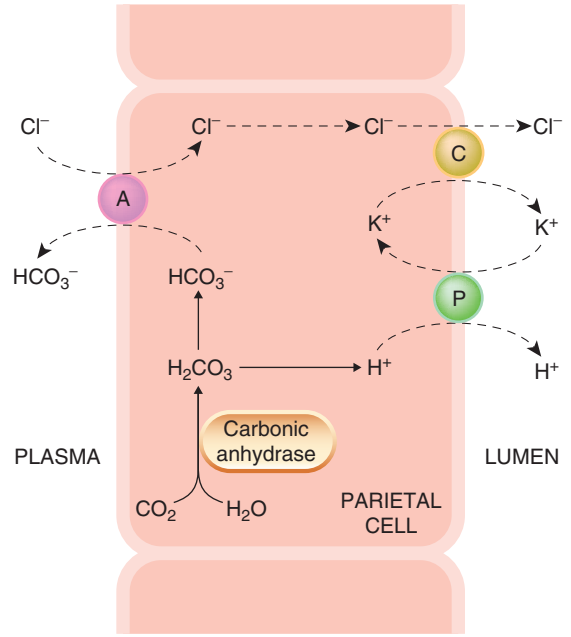

Fig. 30.1 A schematic illustration of the secretion of hydrochloric acid by the gastric parietal cell. Secretion involves a proton pump (P), which is an H^+-K^+-ATPase, a symport carrier (C) for K^+ and Cl^-, and an antiport (A), which exchanges Cl^- and HCO_3^-. An additional Na^+/H^+ antiport situated at the interface with the plasma may also have a role (not shown).

that communicate with the lumen of the gastric glands and thus with the stomach itself. This is accompanied by K^+ secretion, which is then exchanged for H^+ from within the cell by a K^+-H^+-ATPase (the 'proton pump', Fig. 30.1). Within the cell, 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* (enterochromaffin-like cells). These are 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 a polypeptide of 34 residues but also exists in shorter forms. It is synthesised by *G cells* in the gastric antrum and secreted into the portal blood (i.e. it acts in an endocrine fashion). Its main action is stimulation of acid secretion by ECL cells through its action at gastrin/cholecystokinin $(CCK)_2$ receptors,[2] 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. 30.2), 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 Chs 6 and 17), 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. The latter 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 peptide 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

[2]These two peptides share the same, biologically active, C-terminal pentapeptide sequence.

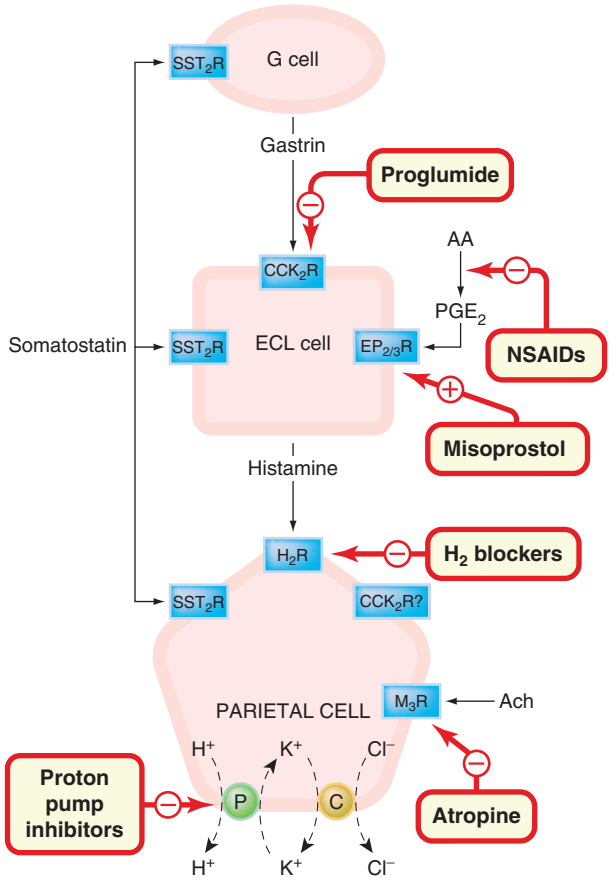

Fig. 30.2 Schematic diagram showing the regulation of the acid-secreting gastric parietal cell, illustrating the site of action of drugs influencing acid secretion. The initial step in controlling physiological secretion is the release of gastrin from G cells. This acts through its CCK_2 receptor on 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.

today is that the *gastrin–ECL–parietal cell axis* is the dominant mechanism for controlling acid secretion. According to this idea (see Fig. 30.2), 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.

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).

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).

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 secretion causes damage to the oesophagus) and the *Zollinger–Ellison syndrome* (a rare hypersecretory condition caused by a gastrin-producing tumour). If untreated, GORD can cause a dysplasia of the oesophgeal epithelium which may progress to a potentially dangerous pre-cancerous condition called *Barrett's oesophagus*.

The reasons why peptic ulcers develop are not fully understood, although infection of the stomach mucosa with *Helicobacter pylori*[3] – 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. 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).

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

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 Blaser, 1998, and Horn, 2000).

HISTAMINE H_2 RECEPTOR ANTAGONISTS

The discovery and development of histamine H_2-blocking drugs by Black and his colleagues in 1972 was a major breakthrough in the treatment of gastric ulcers – a condition that could hitherto only be treated by (sometimes rather heroic) surgery.[4] Indeed, the ability to distinguish between histamine receptor subtypes using pharmacological agents was, in itself, a major intellectual achievement. 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 main drugs used are **cimetidine**, **ranitidine** (sometimes in combination with **bismuth**), **nizatidine** and **famotidine**. There is little difference between them. The effect of cimetidine on gastric secretion in human subjects is shown in Figure 30.3. The clinical use of H_2 receptor antagonists is explained 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 from pharmacies for short-term use, without prescription.

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.

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 30.1 and 30.2). Both basal and stimulated gastric acid secretion (Fig. 30.4) is reduced. The drug comprises a racemic mixture of two enantiomers. As a weak base, it accumulates in the acid environment of the canaliculi of the stimulated parietal cell where it is converted into an

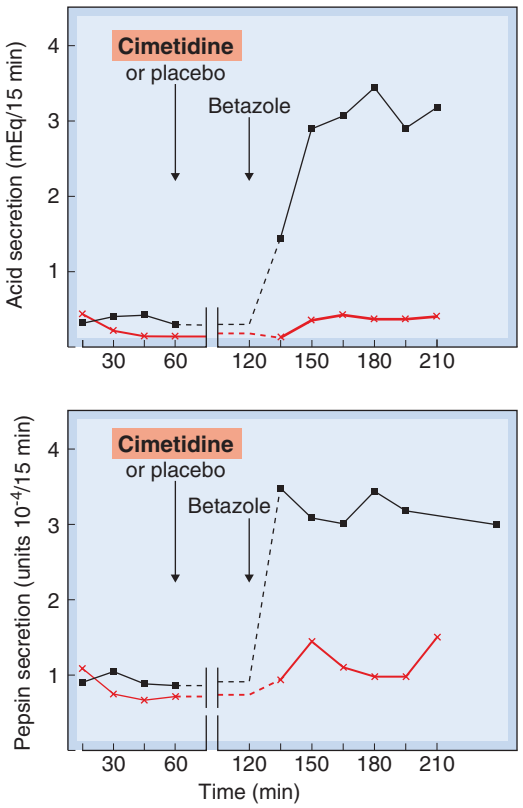

Fig. 30.3 The effect of cimetidine on betazole-stimulated gastric acid and pepsin secretion in humans. Either cimetidine or a placebo was given orally 60 min prior to a subcutaneous injection (1.5 mg/kg) of betazole, a relatively specific histamine H_2-receptor agonist that stimulates gastric acid secretion. *(Modified from Binder & Donaldson, 1978.)*

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**, **lansoprazole**):
  - *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.

[4]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.

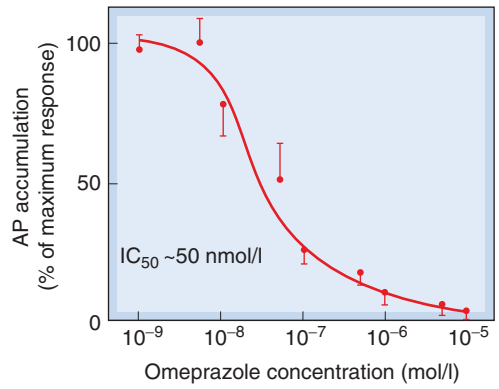

Fig. 30.4 The inhibitory action of omeprazole on acid secretion from isolated human gastric glands stimulated by 50 µmol/l histamine. Acid secretion was measured by the accumulation of a radiolabelled weak base, aminopyrine (AP), in the secretory channels. The data represent the mean and standard error of measurements from eight patients. *(Adapted from Lindberg P et al. 1987 Trends Pharmacol Sci 8, 399–402.)*

achiral form and is then able to react with, and inactivate, the ATPase. This preferential accumulation means that it has a specific effect on these cells. Other proton pump inhibitors (all of which have a similar mode of activation and pharmacology) include **esomeprazole** (the [S] isomer of omeprazole), **lansoprazole**, **pantoprazole** and **rabeprazole**. The clinical indication for these drugs is given in the clinical box (see above).

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. Following absorption in the small intestine, it passes from the blood into the parietal cells and then into the canaliculi where it exerts its effects. 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 secretion for 2–3 days, partly because of the accumulation in the canaliculi and partly because it inhibits the 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 and this 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. Preparations of these substances (e.g. **magnesium trisilicate** mixtures and some proprietary aluminium preparations) containing high concentrations of sodium 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. **Magnesium carbonate** is also used.

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.[5] 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. 29). Other preparations such as **hydrotalcite** contain mixtures of both aluminium and magnesium salts.

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, whereas simeticone is an anti-foaming agent, intended to relieve bloating and flatulence.

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 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. 51); other combinations are also used. Bismuth-containing preparations (see below) are sometimes added. While elimination of

[5]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.

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 and/or to provide a physical barrier over the surface of the ulcer.

Bismuth chelate

Bismuth chelate (tripotassium dicitratobismuthate) is sometimes 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^+ ions. 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 about 30% is still present in the stomach 3 h after administration. In the acid environment, the polymerised product forms a tenacious paste, which can sometimes produce an obstructive lump (known as a *bezoar*[6]) that gets stuck in the stomach. 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 apart from bezoar formation, include dry mouth, nausea, vomiting, headache and rashes.

Misoprostol

Prostaglandins of the E and I series have a generally homeostatic 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. 30.2), 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. 35). 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 but also opioids, general anaesthetics and digoxin. They also occur in motion sickness,[7] 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 a defensive response intended to rid the organism of toxic or irritating material. Poisonous compounds, bacterial toxins, many cytotoxic drugs (as well as mechanical distension) trigger the release, from enterochromaffin cells in the lining of the GI tract, of mediators such as 5-HT. These transmitters trigger signals in vagal afferent fibres. The physical act of vomiting is co-ordinated centrally by the *vomiting* (or *emetic*) *centre* in the medulla; see Figure 30.5. Actually, this is not a discrete anatomical location but a network of neural pathways that integrate signals arriving from other locations. One of these, in the *area postrema* is known as the *chemoreceptor trigger zone* (CTZ). The CTZ receives inputs from the labyrinth in the inner ear through the *vestibular nuclei* (which explains the mechanism of motion sickness) and vagal afferents arising from the GI tract. Toxic chemicals in the blood stream can also be detected directly by the CTZ because the blood–brain barrier is relatively permeable in this area. The CTZ is therefore a primary site of action of many emetic and antiemetic drugs (see Table 30.1).

The vomiting centre also receives signals directly from vagal afferents, as well as those relayed through the CTZ. In addition, it receives input from higher cortical centres, explaining why unpleasant or repulsive sights or smells, or strong emotional stimuli, can sometimes induce nausea and vomiting.

The main neurotransmitters involved in this neurocircuitry are acetylcholine, histamine, 5-HT, dopamine and substance P and receptors for these transmitters have been demonstrated in the relevant areas (see Chs 12–16 and 38). It has been hypothesised that enkephalins (see Ch. 42) are also implicated in the mediation of vomiting, acting possibly at δ (CTZ) or μ (vomiting centre) opioid receptors. Substance P (see Ch. 18) acting at neurokinin-1 receptors in the CTZ, and endocannabinoids (Ch. 19), may also be involved.

[6]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.

[7]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!

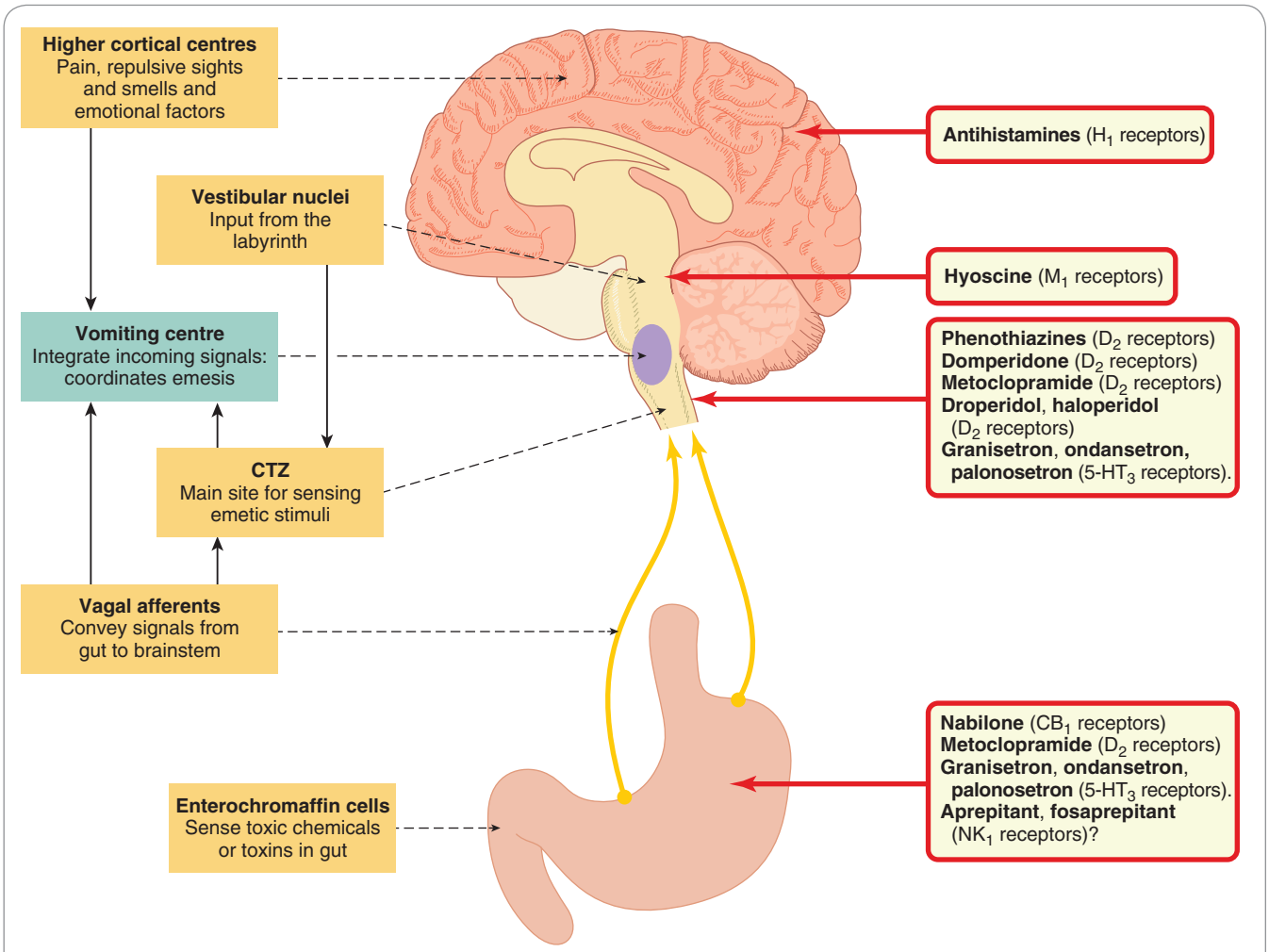

Fig. 30.5 Schematic diagram of the factors involved in the control of vomiting, with the probable sites of action of antiemetic drugs. There are three important centres located in the medulla. The chemoreceptor trigger zone (CTZ), the vomiting centre and the vestibular nuclei. The vomiting centre receives inputs from the CTZ, the GI tract (through vagal afferent connections) and higher cortical centres and coordinates the physical act of emesis. Vagal afferents arising from the GI tract also feed into the CTZ directly as does input from the vestibular nuclei, which in turn, receive inputs from the labyrinth. *(Based partly on a diagram from Rojas & Slusher, 2012)*

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.

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 drugs (see Ch. 56) can be almost unendurable.[8] 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. The clinical box below and Table 30.1 give an overview of their likely sites of action and their clinical utility.

RECEPTOR ANTAGONISTS

Many H_1 (see Ch. 26), muscarinic (see Ch. 13), 5-HT_3 (see Ch. 15), dopamine (see Ch. 46) and NK_1 (see Ch. 15) 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

[8]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'.

Table 30.1 Sites of action of common antiemetic drugs

Class	Drugs	Site of action	Comments
Antihistamines	Cinnarizine, cyclizine, promethazine	H_1 receptors in the CNS (causing sedation) and possibly anticholinergic actions in the vestibular apparatus	Widely effective regardless of cause of emesis
Antimuscarinics	Hyoscine	Anticholinergic actions in the vestibular apparatus and possibly elsewhere	Mainly MS
Cannabinoids	Nabilone	Probably CB_1 receptors in the GI tract	CINV
Dopamine antagonists	Phenothiazines: prochlorphenazine, perphenazine, trifluorphenazine, chlorpromazine	D_2 receptors in CTZ	CINV, PONV, NNV, RS
	Related drugs: droperidol, haloperidol	D_2 receptors in GI tract	CINV, PONV, RS
	Metoclopramide	D_2 receptors in the CTZ and GI tract	PONV, CINV
	Domperidone	D_2 receptors in CTZ	CINV
Glucocorticoids	Dexamethasone	Probably multiple sites of action, including the GI tract	CINV; often used in combination with other drugs
5-HT_3 antagonists	Granisteron, ondansetron, palonosetron	5-HT_3 receptors in CTZ and GI tract	PONV, CINV
Neurokinin-1 antagonists	Aprepitant, fosaprepitant	NK_1 receptors in CTZ, vomiting centre and possibly the GI tract	CINV; often given in combination with another drug

CINV, cytotoxic drug-induced vomiting; CNS, central nervous system; CTZ, chemoreceptor trigger zone; GI, gastrointestinal; PONV, postoperative nausea and vomiting; MS, motion sickness; RS, radiation sickness.

The reflex mechanism of vomiting

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**).

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. Menière'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. 19).

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.

Betahistine has complicated effects on histamine action, antagonising H_3 receptors but having a weak agonist activity on H_1 receptors. It is used to control the nausea and vertigo associated with *Menière's disease*.[9]

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

Granisetron, **ondansetron** and **palonosetron** (see Ch. 15) are of particular value in preventing and treating the vomiting and, to a lesser extent the nausea, commonly encountered postoperatively as well as 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 (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. 30.5) 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. 46).

Other antipsychotic drugs, such as **haloperidol**, the related compound **droperidol** and **levomepromazine** (Ch. 46), 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. 30.5), 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 and hepatic and biliary disorders. As metoclopramide also blocks dopamine receptors (see Ch. 44) 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 Chs 33 and 35), 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.

NK_1 receptor antagonists

Substance P causes vomiting when injected intravenously and is released by gastrointestinal vagal afferent nerves as well as in the vomiting centre itself. **Aprepitant** blocks substance P (NK_1) receptors (see Ch. 18) in the CTZ and vomiting centre. 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, which is administered intravenously.

OTHER ANTIEMETIC DRUGS

Anecdotal evidence originally suggested the possibility of using cannabinoids (see Ch. 19) 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. 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. 19).

High-dose glucocorticoids (particularly **dexamethasone**; see Chs 26 and 33) 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
- antispasmodic drugs, which decrease smooth muscle tone.

[9] A disabling condition named after the eponymous French physician who discovered that the nausea and vertigo that characterise this condition were associated with a disorder of the inner ear.

Clinical uses of drugs that affect the motility of the gastrointestinal tract are summarised in the clinical box below.

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 diarrhoea:
  - oral rehydration with isotonic solutions of NaCl plus glucose and starch-based cereal (important in infants)
  - antimotility agents, e.g. **loperamide** (unwanted effects: drowsiness and nausea).

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 defecation 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 defecation. 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 defecation 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) 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.

Prucalopride is a selective 5-HT_4 receptor agonist that has marked prokinetic properties on the gut. It is generally only used when other types of laxative treatment have failed.

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. The consequences range from mild discomfort and inconvenience to a medical emergency requiring hospitalisation, 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. This 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:

- maintenance of fluid and electrolyte balance
- use of anti-infective agents
- use of spasmolytic or other antidiarrhoeal agents.

The maintenance of fluid and electrolyte balance by means of oral rehydration is the first priority. Wider application of this cheap and simple remedy could save the lives of many infants in the developing world. Indeed, many patients require no other treatment.

In the ileum, as in 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. Those that are bacterial generally resolve fairly rapidly, so 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**. 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 51 and 54) may be necessary in these and other more serious infections.

TRAVELLERS' DIARRHOEA

Millions of people cross international borders each year. Many travel hopefully, but many return with GI symptoms such as diarrhoea, 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 travellers' diarrhoea are detailed by Gorbach (1987).[10]

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

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 opioids (Ch. 42) 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**. 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 opioids 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. Complete loss of intestinal motility (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 pharmacotherapy of travellers' 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.

'Endogenous opioids', enkephalins (Ch. 42), also play a role in regulation of intestinal secretion. **Racecadotril** is a prodrug of **thiorphan**, an inhibitor of enkephalinase. By preventing the breakdown of enkephalins, this drug reduces the excessive intestinal secretion seen during episodes of diarrhoea. It is used in combination with rehydration therapy.

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 gastrointestinal motility are also useful 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.

ADSORBENTS

Adsorbent agents are used in the symptomatic treatment of some types 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. Kaolin is sometimes given as a mixture with morphine (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 commonly used.

GLUCOCORTICOIDS

Glucocorticoids are potent anti-inflammatory agents and are dealt with in Chapters 26 and 33. The drugs of choice are generally **prednisolone** or **budesonide** (although others can be used). They are administered 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. Maintenance 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 include 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. 51).

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

Methotrexate and the immunosuppressants **ciclosporin**, **azathioprine** and **6-mercaptopurine** (see Ch. 26) are also sometimes used in patients with severe inflammatory bowel disease. The biologics **infliximab** and **adalimumab**, monoclonal antibodies directed against tumour necrosis factor (TNF)-α, (see Ch. 26) have also been used with success. These drugs are expensive, and in the UK their use is restricted to moderate and severe Crohn's disease that is unresponsive to glucocorticoids or immunomodulators.

The antiallergy drug sodium **cromoglicate** (see Ch. 28) 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* – 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

You might be forgiven for thinking that the widespread availability of several different types of safe antisecretory drug would have satisfied the current medical need for peptic ulcer treatment, but this is not so. Although the incidence of GI ulcers has dropped, thanks to the use of these drugs, other diseases associated with excess acid production (GORD, NSAID-induced damage) are on the increase, at least in the 'developed' countries. There are also many reasons why the existing drugs fail to perform adequately in some patients or become less active with longer duration treatments.

The quest for novel antisecretory drugs is therefore an ongoing task. Amongst the newer agents that are being actively considered are H_3 antagonists, gastrin receptor antagonists and potassium competitive acid-blocking drugs. The latter agents work because potassium ions are exchanged for protons by the proton pump (see Fig. 30.1) and so potassium antagonists would represent an alternative modality for inhibiting the secretion of acid. Unfortunately, the agents produced so far have been disappointing in clinical trial. An account of the unmet need in this area is given by Krznaric et al. (2011).

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Useful Web resources

<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*)