CHAPTER 36

Nonsteroidal Anti-Inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, Nonopioid Analgesics, & Drugs Used in Gout

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CASE STUDY

A 48-year-old man presents with complaints of bilateral morning stiffness in his wrists and knees and pain in these joints on exercise. On physical examination, the joints are slightly swollen. The rest of the examination is unremarkable. His laboratory findings are also negative except for slight anemia, elevated erythrocyte sedimentation rate, and positive rheumatoid factor. With the diagnosis of rheumatoid arthritis, he is started on a regimen of naproxen, 220 mg twice daily. After 1 week, the dosage is increased to 440 mg twice daily. His symptoms are reduced at this dosage, but he complains of significant heartburn that is not controlled by antacids. He is then switched to celecoxib, 200 mg twice daily, and on this regimen his joint symptoms and heartburn resolve. Two years later, he returns with increased joint symptoms. His hands, wrists, elbows, feet, and knees are all now involved and appear swollen, warm, and tender. What therapeutic options should be considered at this time? What are the possible complications?

THE IMMUNE RESPONSE

The immune response occurs when immunologically competent cells are activated in response to foreign organisms or antigenic substances liberated during the acute or chronic inflammatory response. The outcome of the immune response for the host may be deleterious if it leads to chronic inflammation without resolution of the underlying injurious process (see Chapter 55). Chronic inflammation involves the release of a number of mediators that are not prominent in the acute response. One of the most important conditions involving these mediators is rheumatoid arthritis, in which chronic inflammation results in pain and destruction of bone and cartilage that can lead to severe disability and in which systemic changes occur that can result in shortening of life.

The cell damage associated with inflammation acts on cell membranes to release leukocyte lysosomal enzymes; arachidonic

acid is then liberated from precursor compounds, and various eicosanoids are synthesized. As discussed in Chapter 18, the cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins, which have a variety of effects on blood vessels, on nerve endings, and on cells involved in inflammation. The lipoxygenase pathway of arachidonate metabolism yields leukotrienes, which have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.

The discovery of two cyclooxygenase isoforms (COX-1 and COX-2) led to the concept that the constitutive COX-1 isoform tends to be homeostatic, while COX-2 is induced during inflammation and facilitates the inflammatory response. On this basis, highly selective COX-2 inhibitors have been developed and marketed on the assumption that such selective inhibitors would be safer than nonselective COX-1 inhibitors but without loss of efficacy.

Kinins, neuropeptides, and histamine are also released at the site of tissue injury, as are complement components, cytokines, and other products of leukocytes and platelets. Stimulation of the neutrophil membranes produces oxygen-derived free radicals and other reactive molecules such as hydrogen peroxide and hydroxyl radicals. The interaction of these substances with arachidonic acid results in the generation of chemotactic substances, thus perpetuating the inflammatory process.

THERAPEUTIC STRATEGIES

The treatment of patients with inflammation involves two primary goals: first, the relief of symptoms and the maintenance of function, which are usually the major continuing complaints of the patient; and second, the slowing or arrest of the tissue-damaging process. In rheumatoid arthritis, response to therapy can be quantitated using several measures such as the Disease Activity Scale (DAS), the Clinical Disease Activity Index (CDAI), and the American College of Rheumatology Response index (ACR Response). The first two are continuous variables denoting both state and change, while the latter is solely a change measure. In the latter, the scoring values of ACR20, ACR50, and ACR70 denote the percentage of patients showing an improvement of 20%, 50%, or 70%, respectively, in a global assessment of signs and symptoms.

Reduction of inflammation with **nonsteroidal anti-inflammatory drugs (NSAIDs)** often results in relief of pain for significant periods. Furthermore, most of the nonopioid analgesics (aspirin, etc) have anti-inflammatory effects, so they are appropriate for the treatment of both acute and chronic inflammatory conditions.

The **glucocorticoids** also have powerful anti-inflammatory effects and when first introduced were considered to be the ultimate answer to the treatment of inflammatory arthritis. Although there are data that low-dose corticosteroids have disease-modifying properties, their toxicity makes them less favored than other medications, when it is possible to use the others. However, the glucocorticoids continue to have a significant role in the long-term treatment of arthritis.

Another important group of agents is characterized as **disease-modifying antirheumatic drugs (DMARDs)** and **biologics** (a subset of the DMARDs). They decrease inflammation, improve symptoms, and slow the bone damage associated with rheumatoid arthritis. They affect more basic inflammatory mechanisms than do glucocorticoids or the NSAIDs. They may also be more toxic than those alternative medications.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Salicylates and other similar agents used to treat rheumatic disease share the capacity to suppress the signs and symptoms of inflammation. These drugs also exert antipyretic and analgesic effects, but it is their anti-inflammatory properties that make them most useful in the management of disorders in which pain is related to the intensity of the inflammatory process.

Since aspirin, the original NSAID, has a number of adverse effects, many other NSAIDs have been developed in attempts to improve upon aspirin's efficacy and decrease its toxicity.

Chemistry & Pharmacokinetics

The NSAIDs are grouped in several chemical classes, as shown in Figure 36–1. This chemical diversity yields a broad range of pharmacokinetic characteristics (Table 36–1). Although there are many differences in the kinetics of NSAIDs, they have some general properties in common. All but one of the NSAIDs are weak organic acids as given; the exception, nabumetone, is a ketone prodrug that is metabolized to the acidic active drug.

Most of these drugs are well absorbed, and food does not substantially change their bioavailability. Most of the NSAIDs are highly metabolized, some by phase I followed by phase II mechanisms and others by direct glucuronidation (phase II) alone. NSAID metabolism proceeds, in large part, by way of the CYP3A or CYP2C families of P450 enzymes in the liver. While renal excretion is the most important route for final elimination, nearly all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation). In fact, the degree of lower gastrointestinal (GI) tract irritation correlates with the amount of enterohepatic circulation. Most of the NSAIDs are highly protein-bound (~ 98%), usually to albumin. Most of the NSAIDs (eg, ibuprofen, ketoprofen) are racemic mixtures, while one, naproxen, is provided as a single enantiomer and a few have no chiral center (eg, diclofenac).

All NSAIDs can be found in synovial fluid after repeated dosing. Drugs with short half-lives remain in the joints longer than would be predicted from their half-lives, while drugs with longer half-lives disappear from the synovial fluid at a rate proportionate to their half-lives.

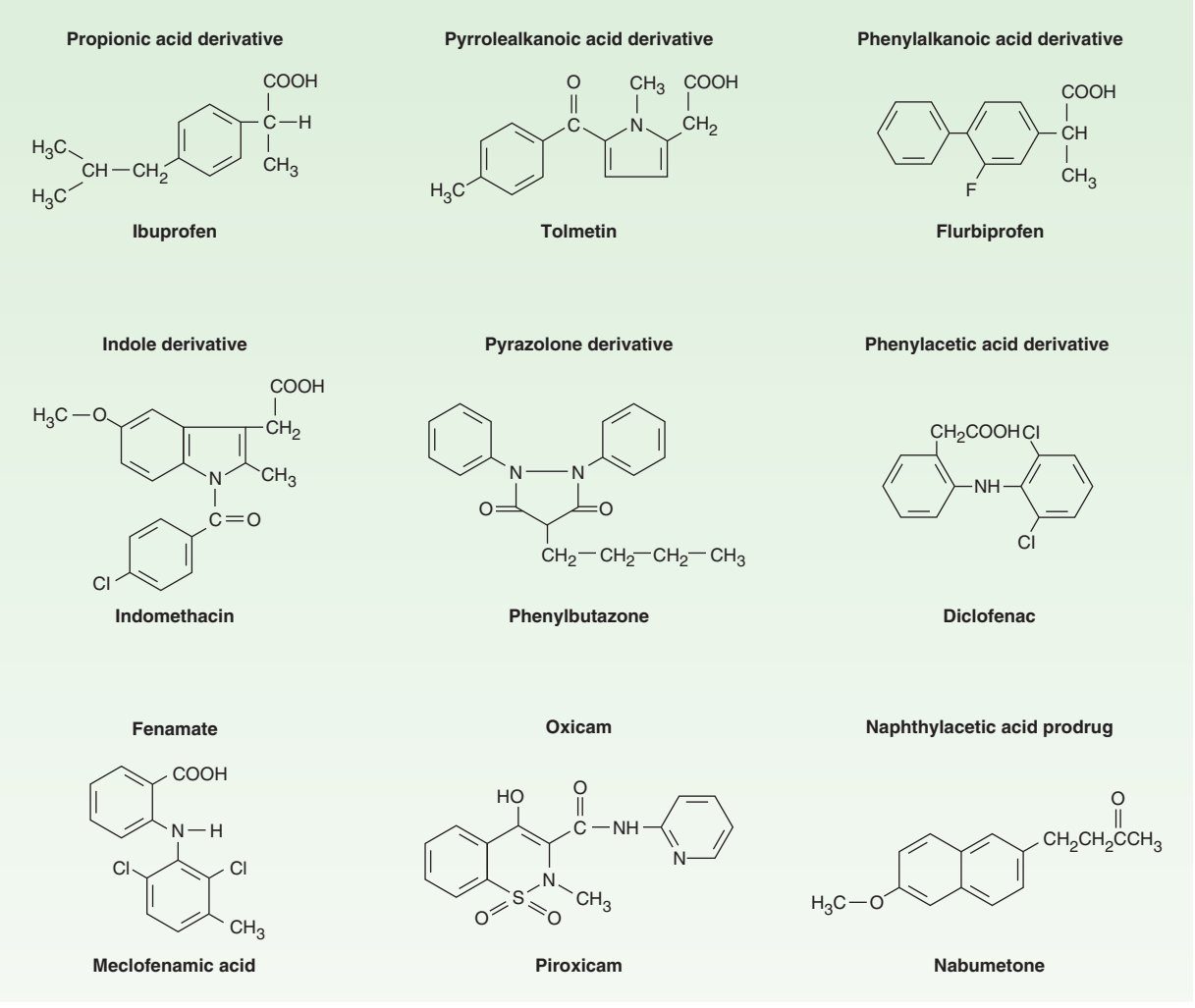


FIGURE 36–1 Chemical structures of some NSAIDs.

Pharmacodynamics

NSAID anti-inflammatory activity is mediated chiefly through inhibition of prostaglandin biosynthesis (Figure 36–2). Various NSAIDs have additional possible mechanisms of action, including inhibition of chemotaxis, down-regulation of interleukin-1 production, decreased production of free radicals and superoxide, and interference with calcium-mediated intracellular events. Aspirin irreversibly acetylates and blocks platelet cyclooxygenase, while the non-COX-selective NSAIDs are reversible inhibitors.

Selectivity for COX-1 versus COX-2 is variable and incomplete for the older NSAIDs, but selective COX-2 inhibitors have been synthesized. The selective COX-2 inhibitors do not affect platelet function at their usual doses. In testing using human whole blood, aspirin, ibuprofen, indomethacin, piroxicam, and sulindac are somewhat more effective in inhibiting COX-1. The efficacy of COX-2-selective drugs equals that of the older NSAIDs, while GI safety may be improved. On the other hand, selective COX-2 inhibitors may increase the incidence of edema and hypertension. As of August 2011, celecoxib and the less selective meloxicam were the only COX-2 inhibitors marketed in the USA. Rofecoxib and valdecoxib, two previously marketed, selective COX-2 inhibitors, were withdrawn from the market because of their association with increased cardiovascular thrombotic events. Celecoxib has a Food and Drug Administration initiated "black box" warning concerning cardiovascular risks. It has been recommended that all NSAID product labels be revised to mention cardiovascular risks.

The NSAIDs decrease the sensitivity of vessels to bradykinin and histamine, affect lymphokine production from T lymphocytes, and reverse the vasodilation of inflammation. To varying degrees, all newer NSAIDs are analgesic, anti-inflammatory, and antipyretic, and all (except the COX-2-selective agents and the nonacetylated salicylates) inhibit platelet aggregation. NSAIDs are all gastric irritants and can be associated with GI ulcers and bleeds as well, although as a group the newer agents tend to cause less GI irritation than aspirin. Nephrotoxicity has been observed for all of

TABLE 36–1 Properties of aspirin and some other nonsteroidal anti-inflammatory drugs.

Drug	Half-Life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-inflammatory Dosage
Aspirin	0.25	<2%	1200–1500 mg tid
Salicylate[1]	2–19	2–30%	See footnote 2
Celecoxib	11	27%[3]	100–200 mg bid
Diclofenac	1.1	<1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	<1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	<1%	300 mg tid
Ibuprofen	2	<1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	<1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid[4]
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone[5]	26	1%	1000–2000 mg qd[6]
Naproxen	14	<1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd[6]
Piroxicam	57	4–10%	20 mg qd[6]
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

[1]Major anti-inflammatory metabolite of aspirin.

[2]Salicylate is usually given in the form of aspirin.

[3]Total urinary excretion including metabolites.

[4]Recommended for treatment of acute (eg, surgical) pain only.

[5]Nabumetone is a prodrug; the half-life and urinary excretion are for its active metabolite.

[6]A single daily dose is sufficient because of the long half-life.

the drugs for which extensive experience has been reported. Nephrotoxicity is due, in part, to interference with the autoregulation of renal blood flow, which is modulated by prostaglandins. Hepatotoxicity can also occur with any NSAID.

Although these drugs effectively inhibit inflammation, there is no evidence that—in contrast to drugs such as methotrexate and other DMARDs—they alter the course of any arthritic disorder.

Several NSAIDs (including aspirin) reduce the incidence of colon cancer when taken chronically. Several large epidemiologic studies have shown a 50% reduction in relative risk when the drugs are taken for 5 years or longer. The mechanism for this protective effect is unclear.

The NSAIDs have a number of commonalities. Although not all NSAIDs are approved by the FDA for the whole range of rheumatic diseases, most are probably effective in rheumatoid arthritis, seronegative spondyloarthropathies (eg, psoriatic arthritis and arthritis associated with inflammatory bowel disease), osteoarthritis, localized musculoskeletal syndromes (eg, sprains and strains, low back pain), and gout (except tolmetin, which appears to be ineffective in gout).

Adverse effects are generally quite similar for all of the NSAIDs:

1. **Central nervous system:** Headaches, tinnitus, and dizziness.
2. **Cardiovascular:** Fluid retention, hypertension, edema, and rarely, myocardial infarction, and congestive heart failure.
3. **Gastrointestinal:** Abdominal pain, dysplasia, nausea, vomiting, and rarely, ulcers or bleeding.
4. **Hematologic:** Rare thrombocytopenia, neutropenia, or even aplastic anemia.
5. **Hepatic:** Abnormal liver function tests and rare liver failure.
6. **Pulmonary:** Asthma.
7. **Skin:** Rashes, all types, pruritus.
8. **Renal:** Renal insufficiency, renal failure, hyperkalemia, and proteinuria.

ASPIRIN

Aspirin's long use and availability without prescription diminishes its glamour compared with that of the newer NSAIDs. Aspirin is now rarely used as an anti-inflammatory medication and will be reviewed only in terms of its anti-platelet effects (ie, doses of 81–325 mg once daily).

Pharmacokinetics

Salicylic acid is a simple organic acid with a pK_a of 3.0. Aspirin (acetylsalicylic acid; ASA) has a pK_a of 3.5 (see Table 1–3). The salicylates are rapidly absorbed from the stomach and upper small intestine yielding a peak plasma salicylate level within 1–2 hours. Aspirin is absorbed as such and is rapidly hydrolyzed (serum half-life 15 minutes) to acetic acid and salicylate by esterases in tissue and blood (Figure 36–3). Salicylate is nonlinearly bound to albumin. Alkalinization of the urine increases the rate of excretion of free salicylate and its water-soluble conjugates.

Mechanisms of Action

Aspirin irreversibly inhibits platelet COX so that aspirin's anti-platelet effect lasts 8–10 days (the life of the platelet). In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a duration of action of 6–12 hours.

Clinical Uses

Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting (see Chapter 34).

Epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer, possibly related to its COX-inhibiting effects.

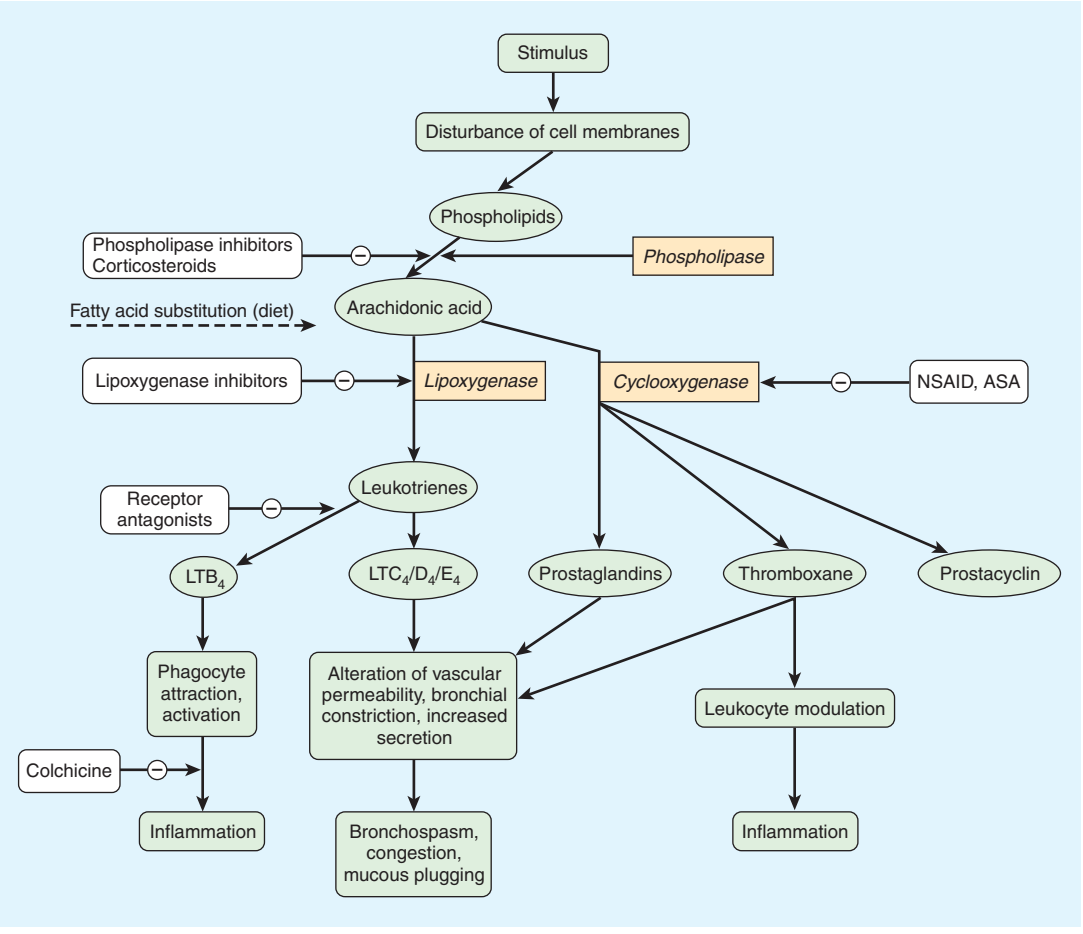


FIGURE 36–2 Prostanoid mediators derived from arachidonic acid and sites of drug action. ASA, acetylsalicylic acid (aspirin); LT, leukotriene; NSAID, nonsteroidal anti-inflammatory drug.

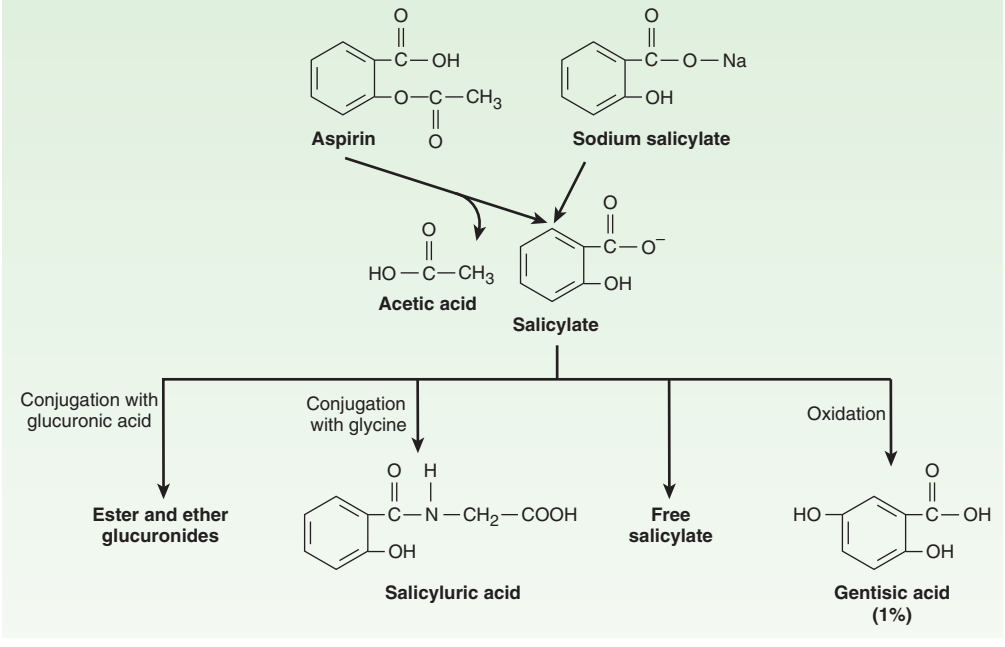


FIGURE 36–3 Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

Adverse Effects

In addition to the common side effects listed above, aspirin's main adverse effects at antithrombotic doses are gastric upset (intolerance) and gastric and duodenal ulcers. Hepatotoxicity, asthma, rashes, GI bleeding, and renal toxicity rarely if ever occur at antithrombotic doses.

The antiplatelet action of aspirin contraindicates its use by patients with hemophilia. Although previously not recommended during pregnancy, aspirin may be valuable in treating preeclampsia-eclampsia.

NONACETYLATED SALICYLATES

These drugs include magnesium choline salicylate, sodium salicylate, and salicyl salicylate. All nonacetylated salicylates are effective anti-inflammatory drugs, although they may be less effective analgesics than aspirin. Because they are much less effective than aspirin as COX inhibitors and they do not inhibit platelet aggregation, they may be preferable when COX inhibition is undesirable such as in patients with asthma, those with bleeding tendencies, and even (under close supervision) those with renal dysfunction.

The nonacetylated salicylates are administered in doses up to 3–4 g of salicylate a day and can be monitored using serum salicylate measurements.

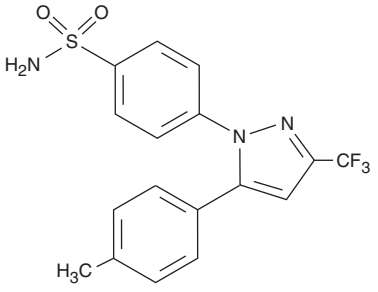
COX-2 SELECTIVE INHIBITORS

COX-2 selective inhibitors, or coxibs, were developed in an attempt to inhibit prostaglandin synthesis by the COX-2 isozyme induced at sites of inflammation without affecting the action of the constitutively active "housekeeping" COX-1 isozyme found in the GI tract, kidneys, and platelets. Coxibs selectively bind to and block the active site of the COX-2 enzyme much more effectively than that of COX-1. COX-2 inhibitors have analgesic, antipyretic, and anti-inflammatory effects similar to those of non-selective NSAIDs but with an approximate halving of GI adverse effects. Likewise, COX-2 inhibitors at usual doses have no impact on platelet aggregation, which is mediated by thromboxane produced by the COX-1 isozyme. In contrast, they do inhibit COX-2-mediated prostacyclin synthesis in the vascular endothelium. As a result, COX-2 inhibitors do not offer the cardioprotective effects of traditional nonselective NSAIDs, which has resulted in some patients taking low-dose aspirin in addition to a coxib regimen to maintain this effect. Unfortunately, because COX-2 is constitutively active within the kidney, recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with traditional NSAIDs. Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitors such as rofecoxib and valdecoxib, resulting in their withdrawal from the market.

Celecoxib

Celecoxib is a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1. Pharmacokinetic and dosage considerations are given in Table 36–1.

Celecoxib is associated with fewer endoscopic ulcers than most other NSAIDs. Probably because it is a sulfonamide, celecoxib may cause rashes. It does not affect platelet aggregation at usual doses. It interacts occasionally with warfarin—as would be expected of a drug metabolized via CYP2C9. Adverse effects are the common toxicities listed above.



Celecoxib

Meloxicam

Meloxicam is an enolcarboxamide related to piroxicam that preferentially inhibits COX-2 over COX-1, particularly at its lowest therapeutic dose of 7.5 mg/d. It is not as selective as celecoxib and may be considered "preferentially" selective rather than "highly" selective. It is associated with fewer clinical GI symptoms and complications than piroxicam, diclofenac, and naproxen. Similarly, while meloxicam is known to inhibit synthesis of thromboxane A_2, even at supratherapeutic doses, its blockade of thromboxane A_2 does not reach levels that result in decreased in vivo platelet function (see common adverse effects above).

NONSELECTIVE COX INHIBITORS

Diclofenac

Diclofenac is a phenylacetic acid derivative that is relatively nonselective as a COX inhibitor. Pharmacokinetic and dosage characteristics are set forth in Table 36–1.

Gastrointestinal ulceration may occur less frequently than with some other NSAIDs. A preparation combining diclofenac and misoprostol decreases upper gastrointestinal ulceration but may result in diarrhea. Another combination of diclofenac and omeprazole was also effective with respect to the prevention of recurrent bleeding, but renal adverse effects were common in high-risk patients. Diclofenac, 150 mg/d, appears to impair renal blood flow and glomerular filtration rate. Elevation of serum aminotransferases occurs more commonly with this drug than with other NSAIDs.

A 0.1% ophthalmic preparation is promoted for prevention of postoperative ophthalmic inflammation and can be used after intraocular lens implantation and strabismus surgery. A topical gel containing 3% diclofenac is effective for solar keratoses. Diclofenac in rectal suppository form can be considered for preemptive analgesia and postoperative nausea. In Europe, diclofenac is also available as an oral mouthwash and for intramuscular administration.

Diflunisal

Although diflunisal is derived from salicylic acid, it is not metabolized to salicylic acid or salicylate. It undergoes an enterohepatic cycle with reabsorption of its glucuronide metabolite followed by cleavage of the glucuronide to again release the active moiety. Diflunisal is subject to capacity-limited metabolism, with serum half-lives at various dosages approximating that of salicylates (Table 36–1). In rheumatoid arthritis the recommended dose is 500–1000 mg daily in two divided doses. It is claimed to be particularly effective for cancer pain with bone metastases and for pain control in dental (third molar) surgery. A 2% diflunisal oral ointment is a clinically useful analgesic for painful oral lesions.

Because its clearance depends on renal function as well as hepatic metabolism, diflunisal's dosage should be limited in patients with significant renal impairment.

Etodolac

Etodolac is a racemic acetic acid derivative with an intermediate half-life (Table 36–1). Etodolac does not undergo chiral inversion in the body. The dosage of etodolac is 200–400 mg three to four times daily.

Flurbiprofen

Flurbiprofen is a propionic acid derivative with a possibly more complex mechanism of action than other NSAIDs. Its (*S*)(–) enantiomer inhibits COX nonselectively, but it has been shown in rat tissue to also affect tumor necrosis factor-α (TNF-α) and nitric oxide synthesis. Hepatic metabolism is extensive; its (*R*)(+) and (*S*)(–) enantiomers are metabolized differently, and it does not undergo chiral conversion. It does demonstrate enterohepatic circulation.

Flurbiprofen is also available in a topical ophthalmic formulation for inhibition of intraoperative miosis. Flurbiprofen intravenously is effective for perioperative analgesia in minor ear, neck, and nose surgery and in lozenge form for sore throat.

Although its adverse effect profile is similar to that of other NSAIDs in most ways, flurbiprofen is also rarely associated with cogwheel rigidity, ataxia, tremor, and myoclonus.

Ibuprofen

Ibuprofen is a simple derivative of phenylpropionic acid (Figure 36–1). In doses of about 2400 mg daily, ibuprofen is equivalent to 4 g of aspirin in anti-inflammatory effect. Pharmacokinetic characteristics are given in Table 36–1.

Oral ibuprofen is often prescribed in lower doses (<2400 mg/d), at which it has analgesic but not anti-inflammatory efficacy. It is available over the counter in low-dose forms under several trade names.

Ibuprofen is effective in closing patent ductus arteriosus in preterm infants, with much the same efficacy and safety as indomethacin. The oral and intravenous routes are equally effective for this indication. A topical cream preparation appears to be absorbed into fascia and muscle; an (*S*)(–) formulation has been tested. Ibuprofen cream was more effective than placebo cream in the treatment of primary knee osteoarthritis. A liquid gel preparation of ibuprofen, 400 mg, provides prompt relief and good overall efficacy in postsurgical dental pain.

In comparison with indomethacin, ibuprofen decreases urine output less and also causes less fluid retention. The drug is relatively contraindicated in individuals with nasal polyps, angioedema, and bronchospastic reactivity to aspirin. Aseptic meningitis (particularly in patients with systemic lupus erythematosus), and fluid retention have been reported. Interaction with anticoagulants is uncommon. The concomitant administration of ibuprofen and aspirin antagonizes the irreversible platelet inhibition induced by aspirin. Thus, treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin. Furthermore, the use of ibuprofen concomitantly with aspirin may *decrease* the total anti-inflammatory effect. Common adverse effects are listed on page 638; rare hematologic effects include agranulocytosis and aplastic anemia.

Indomethacin

Indomethacin, introduced in 1963, is an indole derivative (Figure 36–1). It is a potent nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T-cell and B-cell proliferation.

It differs somewhat from other NSAIDs in its indications and toxicities.

It has been used to accelerate closure of patent ductus arteriosus. Indomethacin has been tried in numerous small or uncontrolled trials for many other conditions, including Sweet's syndrome, juvenile rheumatoid arthritis, pleurisy, nephrotic syndrome, diabetes insipidus, urticarial vasculitis, postepisiotomy pain, and prophylaxis of heterotopic ossification in arthroplasty.

An ophthalmic preparation is efficacious for conjunctival inflammation and to reduce pain after traumatic corneal abrasion. Gingival inflammation is reduced after administration of indomethacin oral rinse. Epidural injections produce a degree of pain relief similar to that achieved with methylprednisolone in postlaminectomy syndrome.

At usual doses, indomethacin has the common side effects listed above. The GI effects may include pancreatitis. Headache is experienced by 15–25% of patients and may be associated with dizziness, confusion, and depression. Rarely, psychosis with hallucinations has been reported. Renal papillary necrosis has also been observed. A number of interactions with other drugs have been reported (see Chapter 66). Probenecid prolongs indomethacin's half-life by inhibiting both renal and biliary clearance.

Ketoprofen

Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and lipoxygenase. Its pharmacokinetic characteristics are given in Table 36–1. Concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life.

The effectiveness of ketoprofen at dosages of 100–300 mg/d is equivalent to that of other NSAIDs. In spite of its dual effect on prostaglandins and leukotrienes, ketoprofen is not superior to other NSAIDs in clinical efficacy. Its major adverse effects are on the GI tract and the central nervous system (see common adverse effects above).

Ketorolac

Ketorolac is an NSAID promoted for systemic use mainly as an analgesic, not as an anti-inflammatory drug (although it has typical NSAID properties). Pharmacokinetics are presented in Table 36–1. The drug is an effective analgesic and has been used successfully to replace morphine in some situations involving mild to moderate postsurgical pain. It is most often given intramuscularly or intravenously, but an oral dose formulation is available. When used with an opioid, it may decrease the opioid requirement by 25–50%. An ophthalmic preparation is available for ocular inflammatory conditions. Toxicities are similar to those of other NSAIDs (see page 638), although renal toxicity may be more common with chronic use.

Nabumetone

Nabumetone is the only nonacid NSAID in current use; it is converted to the active acetic acid derivative in the body. It is given as a ketone prodrug that resembles naproxen in structure (Figure 36–1). Its half-life of more than 24 hours (Table 36–1) permits once-daily dosing, and the drug does not appear to undergo enterohepatic circulation. Renal impairment results in a doubling of its half-life and a 30% increase in the area under the curve.

Its properties are very similar to those of other NSAIDs, though it may be less damaging to the stomach than some other NSAIDs when given at a dosage of 1000 mg/d. Unfortunately, higher dosages (eg, 1500–2000 mg/d) are often needed, and this is a very expensive NSAID. Like naproxen, nabumetone has been associated with pseudoporphyria and photosensitivity in some patients. Other adverse effects mirror those of other NSAIDs.

Naproxen

Naproxen is a naphthylpropionic acid derivative. It is the only NSAID presently marketed as a single enantiomer. Naproxen's free fraction is significantly higher in women than in men, but half-life is similar in both sexes (Table 36–1). Naproxen is effective for the usual rheumatologic indications and is available in a slow-release formulation, as an oral suspension, and over the counter. A topical preparation and an ophthalmic solution are also available.

The incidence of upper GI bleeding in over-the-counter use is low but still double that of over-the-counter ibuprofen (perhaps due to a dose effect). Rare cases of allergic pneumonitis, leukocytoclastic vasculitis, and pseudoporphyria as well as the common NSAID-associated adverse effects have been noted.

Oxaprozin

Oxaprozin is another propionic acid derivative NSAID. As noted in Table 36–1, its major difference from the other members of this subgroup is a very long half-life (50–60 hours), although oxaprozin does not undergo enterohepatic circulation. It is mildly uricosuric, making it potentially more useful in gout than some other NSAIDs. Otherwise, the drug has the same benefits and risks that are associated with other NSAIDs.

Piroxicam

Piroxicam, an oxicam (Figure 36–1), is a nonselective COX inhibitor that at high concentrations also inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function. Its long half-life (Table 36–1) permits once-daily dosing.

Piroxicam can be used for the usual rheumatic indications. When piroxicam is used in dosages higher than 20 mg/d, an increased incidence of peptic ulcer and bleeding is encountered. Epidemiologic studies suggest that this risk is as much as 9.5 times higher with piroxicam than with other NSAIDs (see common adverse effects above).

Sulindac

Sulindac is a sulfoxide prodrug. It is reversibly metabolized to the active sulfide metabolite, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action to 12–16 hours.

In addition to its rheumatic disease indications, sulindac suppresses familial intestinal polyposis and it may inhibit the development of colon, breast, and prostate cancer in humans. It appears to inhibit the occurrence of GI cancer in rats. The latter effect may be caused by the sulfone rather than the sulfide.

Among the more severe adverse reactions, Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been observed. Like diclofenac, sulindac may have some propensity to cause elevation of serum aminotransferases; it is also sometimes associated with cholestatic liver damage, which disappears when the drug is stopped.

Tolmetin

Tolmetin is a nonselective COX inhibitor with a short half-life (1–2 hours) and is not often used. Its efficacy and toxicity profiles are similar to those of other NSAIDs with the following exceptions: it is ineffective (for unknown reasons) in the treatment of gout, and it may cause (rarely) thrombocytopenic purpura.

Other NSAIDs

Azapropazone, carprofen, meclofenamate, and **tenoxicam** are rarely used and are not reviewed here.

CHOICE OF NSAID

All NSAIDs, including aspirin, are about equally efficacious with a few exceptions—tolmetin seems not to be effective for gout, and aspirin is less effective than other NSAIDs (eg, indomethacin) for ankylosing spondylitis.

Thus, NSAIDs tend to be differentiated on the basis of toxicity and cost-effectiveness. For example, the GI and renal side effects of ketorolac limit its use. Some surveys suggest that indomethacin and tolmetin are the NSAIDs associated with the greatest toxicity, while salsalate, aspirin, and ibuprofen are least toxic. The selective COX-2 inhibitors were not included in these analyses.

For patients with renal insufficiency, nonacetylated salicylates may be best. Diclofenac and sulindac are associated with more liver function test abnormalities than other NSAIDs. The relatively expensive, selective COX-2 inhibitor celecoxib is probably safest for patients at high risk for GI bleeding but may have a higher risk of cardiovascular toxicity. Celecoxib or a nonselective NSAID plus omeprazole or misoprostol may be appropriate in patients at highest risk for GI bleeding; in this subpopulation of patients, they are cost-effective despite their high acquisition costs.

The choice of an NSAID thus requires a balance of efficacy, cost-effectiveness, safety, and numerous personal factors (eg, other drugs also being used, concurrent illness, compliance, medical insurance coverage), so that there is no best NSAID for all patients. There may, however, be one or two best NSAIDs for a specific person.

■ DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Rheumatoid arthritis is an immunologic disease that causes significant systemic effects, shortens life, and reduces mobility and quality of life. Interest has centered on finding treatments that might arrest—or at least slow—this progression by modifying the disease itself. The effects of disease-modifying therapies may take 6 weeks to 6 months to become clinically evident, although some biologics are effective within 2 weeks or less.

These therapies include nonbiologic disease-modifying antirheumatic drugs (usually designated "DMARDs") such as methotrexate, azathioprine, chloroquine and hydroxychloroquine, cyclophosphamide, cyclosporine, leflunomide, mycophenolate mofetil, and sulfasalazine. Gold salts, which were once extensively used, are no longer recommended because of their significant toxicities and questionable efficacy.

There are also several biologic DMARDs (designated "biologics") marketed for rheumatoid arthritis: a T-cell-modulating biologic (abatacept), a B-cell cytotoxic agent (rituximab), an anti-IL-6 receptor antibody (tocilizumab), and the TNF-α-blocking agents (five drugs).

These DMARDs and biologics are discussed alphabetically, independent of origin.

ABATACEPT

Mechanism of Action

Abatacept is a co-stimulation modulator biologic that inhibits the activation of T cells (see also Chapter 55). After a T cell has engaged an antigen-presenting cell (APC), a second signal is produced by CD28 on the T cell that interacts with CD80 or CD86 on the APC, leading to T-cell activation. Abatacept (which contains the endogenous ligand CTLA-4) binds to CD80 and 86, thereby inhibiting the binding to CD28 and preventing the activation of T cells.

Pharmacokinetics

Abatacept is given as three intravenous infusion "induction" doses (day 0, week 2, and week 4), followed by monthly infusions. The dose is based on body weight; patients weighing less than 60 kg receiving 500 mg, those 60–100 kg receiving 750 mg, and those more than 100 kg receiving 1000 mg. Dosing regimens in any adult group can be increased if needed. The terminal serum half-life is 13–16 days. Co-administration with methotrexate, NSAIDs, and corticosteroids does not influence abatacept clearance.

Indications

Abatacept can be used as monotherapy or in combination with other DMARDs in patients with moderate to severe rheumatoid arthritis who have had an inadequate response to other DMARDs. It reduces the clinical signs and symptoms of rheumatoid arthritis, including slowing of radiographic progression. It is also being tested in early rheumatoid arthritis.

Adverse Effects

There is a slightly increased risk of infection (as with other biologic DMARDs), predominantly of the upper respiratory tract. Concomitant use with TNF-α antagonists is not recommended due to the increased incidence of serious infection. Infusion-related reactions and hypersensitivity reactions, including anaphylaxis, have been reported but are rare. Anti-abatacept antibody formation is infrequent (<5%) and has no effect on clinical outcomes. There is a possible increase in lymphomas but not in other malignancies when using abatacept.

AZATHIOPRINE

Mechanism of Action

Azathioprine is a synthetic DMARD that acts through its major metabolite, 6-thioguanine. 6-Thioguanine suppresses inosinic acid synthesis, B-cell and T-cell function, immunoglobulin production, and interleukin-2 secretion (see Chapter 55).

Pharmacokinetics

The metabolism of azathioprine is bimodal in humans, with rapid metabolizers clearing the drug four times faster than slow metabolizers. Production of 6-thioguanine is dependent on thiopurine methyltransferase (TPMT), and patients with low or absent TPMT activity (0.3% of the population) are at particularly high risk of myelosuppression by excess concentrations of the parent drug, if dosage is not adjusted.

Indications

Azathioprine is approved for use in rheumatoid arthritis and is used at a dosage of 2 mg/kg/d. Controlled trials show efficacy in psoriatic arthritis, reactive arthritis, polymyositis, systemic lupus erythematosus, and Behçet's disease.

Adverse Effects

Azathioprine's toxicity includes bone marrow suppression, GI disturbances, and some increase in infection risk. As noted in Chapter 55, lymphomas may be increased with azathioprine use. Rarely, fever, rash, and hepatotoxicity signal acute allergic reactions.

CHLOROQUINE & HYDROXYCHLOROQUINE

Mechanism of Action

Chloroquine and hydroxychloroquine are nonbiologic drugs mainly used for malaria (see Chapter 52) and in the rheumatic diseases. The mechanism of the anti-inflammatory action of these drugs in rheumatic diseases is unclear. The following mechanisms have been proposed: suppression of T-lymphocyte responses to mitogens, decreased leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA and RNA synthesis, and the trapping of free radicals.

Pharmacokinetics

Antimalarials are rapidly absorbed and 50% protein-bound in the plasma. They are very extensively tissue-bound, particularly in melanin-containing tissues such as the eyes. The drugs are deaminated in the liver and have blood elimination half-lives of up to 45 days.

Indications

Antimalarials are approved for rheumatoid arthritis, but they are not considered very effective DMARDs. Dose-response and serum concentration-response relationships have been documented for hydroxychloroquine and dose-loading may increase rate of response. Although antimalarials improve symptoms, there is no evidence that these compounds alter bony damage in rheumatoid arthritis at their usual dosages (up to 6.4 mg/kg/d for hydroxychloroquine or 200 mg/d for chloroquine). It usually takes 3–6 months to obtain a response. Antimalarials are often used in the treatment of the skin manifestations, serositis, and joint pains of systemic lupus erythematosus, and they have been used in Sjögren's syndrome.

Adverse Effects

Although ocular toxicity (see Chapter 52) may occur at dosages greater than 250 mg/d for chloroquine and greater than 6.4 mg/kg/d for hydroxychloroquine, it rarely occurs at lower doses. Nevertheless, ophthalmologic monitoring every 12 months is advised. Other toxicities include dyspepsia, nausea, vomiting, abdominal pain, rashes, and nightmares. These drugs appear to be relatively safe in pregnancy.

CYCLOPHOSPHAMIDE

Mechanism of Action

Cyclophosphamide is a synthetic DMARD. Its major active metabolite is phosphoramide mustard, which cross-links DNA to prevent cell replication. It suppresses T-cell and B-cell function by 30–40%; T-cell suppression correlates with clinical response in the rheumatic diseases. Its pharmacokinetics and toxicities are discussed in Chapter 54.

Indications

Cyclophosphamide is active against rheumatoid arthritis when given orally at dosages of 2 mg/kg/d but not intravenously. It is used regularly to treat systemic lupus erythematosus, vasculitis, Wegener's granulomatosis, and other severe rheumatic diseases.

CYCLOSPORINE

Mechanism of Action

Cyclosporine is a peptide antibiotic but is considered a nonbiologic DMARD. Through regulation of gene transcription, it inhibits interleukin-1 and interleukin-2 receptor production and secondarily inhibits macrophage–T-cell interaction and T-cell responsiveness (see Chapter 55). T-cell-dependent B-cell function is also affected.

Pharmacokinetics

Cyclosporine absorption is incomplete and somewhat erratic, although a microemulsion formulation improves its consistency and provides 20–30% bioavailability. Grapefruit juice increases cyclosporine bioavailability by as much as 62%. Cyclosporine is metabolized by CYP3A and consequently is subject to a large number of drug interactions (see Chapters 55 and 66).

Indications

Cyclosporine is approved for use in rheumatoid arthritis and retards the appearance of new bony erosions. Its usual dosage is 3–5 mg/kg/d divided into two doses. Anecdotal reports suggest that it may be useful in systemic lupus erythematosus, polymyositis and dermatomyositis, Wegener's granulomatosis, and juvenile chronic arthritis.

Adverse Effects

Leukopenia, thrombocytopenia, and to a lesser extent, anemia, are predictable. High doses can be cardiotoxic and sterilty may occur after chronic dosing at anti-rheumatic doses, especially in women. Bladder cancer is very rare but must be looked for, even 5 years after cessation of use.

LEFLUNOMIDE

Mechanism of Action

Leflunomide, another nonbiologic DMARD, undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, A77-1726. This metabolite inhibits dihydroorotate dehydrogenase, leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G_1 phase of cell growth. Consequently, leflunomide inhibits T-cell proliferation and production of autoantibodies by B cells. Secondary effects include increases of interleukin-10 receptor mRNA, decreased interleukin-8 receptor type A mRNA, and decreased TNF-α-dependent nuclear factor kappa B (NF-κB) activation.

Pharmacokinetics

Leflunomide is completely absorbed and has a mean plasma half-life of 19 days. Its active metabolite, A77-1726, is thought to have approximately the same half-life and is subject to enterohepatic recirculation. Cholestyramine can enhance leflunomide excretion and increases total clearance by approximately 50%.

Indications

Leflunomide is as effective as methotrexate in rheumatoid arthritis, including inhibition of bony damage. In one study, combined treatment with methotrexate and leflunomide resulted in a 46.2% ACR20 response compared with 19.5% in patients receiving methotrexate alone.

Adverse Effects

Diarrhea occurs in approximately 25% of patients given leflunomide, although only about 3–5% discontinue the drug because of this side effect. Elevation in liver enzymes can occur. Both effects can be reduced by decreasing the dose of leflunomide. Other adverse effects associated with leflunomide are mild alopecia, weight gain, and increased blood pressure. Leukopenia and thrombocytopenia occur rarely. This drug is contraindicated in pregnancy.

METHOTREXATE

Methotrexate, a synthetic antimetabolite, is now considered the first-line DMARD for treatment of rheumatoid arthritis and is used in 50–70% of patients. It is active in this condition at much lower doses than those needed in cancer chemotherapy (see Chapter 54).

Mechanism of Action

Methotrexate's principal mechanism of action at the low doses used in the rheumatic diseases probably relates to inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase. AICAR, which accumulates intracellularly, competitively inhibits AMP deaminase, leading to an accumulation of AMP. The AMP is released and converted extracellularly to adenosine, which is a potent inhibitor of inflammation. As a result, the inflammatory functions of neutrophils, macrophages, dendritic cells, and lymphocytes are suppressed. Methotrexate has secondary effects on polymorphonuclear chemotaxis. There is some effect on dihydrofolate reductase and this affects lymphocyte and macrophage function, but this is not its principal mechanism of action. Methotrexate has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells. Additionally, it has also been shown to have inhibition of proinflammatory cytokines linked to rheumatoid synovitis.

Pharmacokinetics

The drug is approximately 70% absorbed after oral administration (see Chapter 54). It is metabolized to a less active hydroxylated metabolite. Both the parent compound and the metabolite are polyglutamated within cells where they stay for prolonged periods. Methotrexate's serum half-life is usually only 6–9 hours, although it may be as long as 24 hours in some individuals. Methotrexate's concentration is increased in the presence of hydroxychloroquine, which can reduce the clearance or increase the tubular reabsorption of methotrexate. This drug is excreted principally in the urine, but up to 30% may be excreted in bile.

Indications

Although the most common methotrexate dosing regimen for the treatment of rheumatoid arthritis is 15–25 mg weekly, there is an increased effect up to 30–35 mg weekly. The drug decreases the rate of appearance of new erosions. Evidence supports its use in juvenile chronic arthritis, and it has been used in psoriasis, psoriatic arthritis, ankylosing spondylitis, polymyositis, dermatomyositis, Wegener's granulomatosis, giant cell arteritis, systemic lupus erythematosus, and vasculitis.

Adverse Effects

Nausea and mucosal ulcers are the most common toxicities. Additionally, many other side effects such as leukopenia, anemia, stomatitis, GI ulcerations, and alopecia are probably the result of inhibiting cellular proliferation. Progressive dose-related hepatotoxicity in the form of enzyme elevation occurs frequently, but cirrhosis is rare (<1%). Liver toxicity is not related to serum methotrexate concentrations. Rare hypersensitivity-like lung reaction with acute shortness of breath has been documented, as have pseudo-lymphomatous reactions. The incidence of GI and liver function test abnormalities can be reduced by the use of leucovorin 24 hours after each weekly dose or by the use of daily folic acid, although this may decrease the efficacy of the methotrexate by about 10%. This drug is contraindicated in pregnancy.

MYCOPHENOLATE MOFETIL

Mechanism of Action

Mycophenolate mofetil (MMF), a semisynthetic DMARD, is converted to mycophenolic acid, the active form of the drug. The active product inhibits inosine monophosphate dehydrogenase,

leading to suppression of T- and B-lymphocyte proliferation. Downstream, it interferes with leukocyte adhesion to endothelial cells through inhibition of E-selectin, P-selectin, and intercellular adhesion molecule 1. MMF's pharmacokinetics and toxicities are discussed in Chapter 55.

Indications

MMF is effective for the treatment of renal disease due to systemic lupus erythematosus and may be useful in vasculitis and Wegener's granulomatosis. Although MMF is occasionally used at a dosage of 2 g/d to treat rheumatoid arthritis, there are no well-controlled data regarding its efficacy in this disease.

Adverse Effects

MMF is associated with nausea, dyspepsia and abdominal pain. Like azathioprine, it can cause hepatotoxicity although it is not associated with the acute febrile hepatotoxicity of that drug. MMF can cause leukopenia, thrombocytopenia, and anemia. MMF is associated with an increased incidence of infections. It is only rarely associated with malignancy.

RITUXIMAB

Mechanism of Action

Rituximab is a chimeric monoclonal antibody biologic agent that targets CD20 B lymphocytes (see Chapter 55). This depletion takes place through cell-mediated and complement-dependent cytotoxicity and stimulation of cell apoptosis. Depletion of B lymphocytes reduces inflammation by decreasing the presentation of antigens to T lymphocytes and inhibiting the secretion of proinflammatory cytokines. Rituximab rapidly depletes peripheral B cells, although this depletion correlates neither with efficacy nor with toxicity.

Pharmacokinetics

Rituximab is given as two intravenous infusions of 1000 mg, separated by 2 weeks. It may be repeated every 6–9 months, as needed. Repeated courses remain effective. Pretreatment with intravenous glucocorticoids given 30 minutes prior to infusion (usually 100 mg of methylprednisolone) decreases the incidence and severity of infusion reactions.

Indications

Rituximab is indicated for the treatment of moderately to severely active rheumatoid arthritis in combination with methotrexate in patients with an inadequate response to one or more TNF-α antagonists.

Adverse Effects

About 30% of patients develop rash with the first 1000 mg treatment; this incidence decreases to about 10% with the second infusion and progressively decreases with each course of therapy thereafter. These rashes do not usually require discontinuation of therapy but of course an urticarial or anaphylactoid reaction precludes further therapy. Immunoglobulins (particularly IgG and IgM) may decrease with repeated courses of therapy and infections can occur, although they do not seem directly associated with the decreases in immunoglobulins. Rituximab has not been associated with either activation of tuberculosis or the occurrence of lymphomas or other tumors (see Chapter 55). Other adverse effects, like cardiovascular events, are rare.

SULFASALAZINE

Mechanism of Action

Sulfasalazine, a synthetic DMARD, is metabolized to sulfapyridine and 5-aminosalicylic acid. The sulfapyridine is probably the active moiety when treating rheumatoid arthritis (unlike inflammatory bowel disease, see Chapter 62). Some authorities believe that the parent compound, sulfasalazine, also has an effect. In treated arthritis patients, IgA and IgM rheumatoid factor production are decreased. Suppression of T-cell responses to concanavalin and inhibition of in vitro B-cell proliferation have also been documented. In vitro, sulfasalazine or its metabolites inhibit the release of inflammatory cytokines, including those produced by monocytes or macrophages, eg, interleukins-1, -6, and -12, and TNF-α. These findings suggest a possible mechanism for the clinical efficacy of sulfasalazine in rheumatoid arthritis.

Pharmacokinetics

Only 10–20% of orally administered sulfasalazine is absorbed, although a fraction undergoes enterohepatic recirculation into the bowel where it is reduced by intestinal bacteria to liberate sulfapyridine and 5-aminosalicylic acid (see Figure 62–8). Sulfapyridine is well absorbed while 5-aminosalicylic acid remains unabsorbed. Some sulfasalazine is excreted unchanged in the urine whereas sulfapyridine is excreted after hepatic acetylation and hydroxylation. Sulfasalazine's half-life is 6–17 hours.

Indications

Sulfasalazine is effective in rheumatoid arthritis and reduces radiologic disease progression. It has also been used in juvenile chronic arthritis and in ankylosing spondylitis and its associated uveitis. The usual regimen is 2–3 g/d.

Adverse Effects

Approximately 30% of patients using sulfasalazine discontinue the drug because of toxicity. Common adverse effects include nausea, vomiting, headache, and rash. Hemolytic anemia and methemoglobinemia also occur, but rarely. Neutropenia occurs in 1–5% of patients, while thrombocytopenia is very rare. Pulmonary toxicity and positive double-stranded DNA (dsDNA) are occasionally seen, but drug-induced lupus is rare. Reversible infertility occurs in men, but sulfasalazine does not affect fertility in women. The drug does not appear to be teratogenic.

TOCILIZUMAB

Mechanism of Action

Tocilizumab, a newer biologic humanized antibody, binds to soluble and membrane-bound IL-6 receptors, and inhibit the IL-6-mediated signaling via these receptors. IL-6 is a proinflammatory cytokine produced by different cell types including T cells, B cells, monocytes, fibroblasts, and synovial and endothelial cells. IL-6 is involved in a variety of physiologic processes such as T-cell activation, hepatic acute-phase protein synthesis, and stimulation of the inflammatory processes involved in diseases such as rheumatoid arthritis.

Pharmacokinetics

The half-life of tocilizumab is dose-dependent, approximately 11 days for the 4 mg/kg dose and 13 days for the 8 mg/kg dose. IL-6 can suppress several CYP450 isoenzymes; thus, inhibiting IL-6 may restore CYP450 activities to higher levels. This may be clinically relevant for drugs that are CYP450 substrates and have a narrow therapeutic window (eg, cyclosporine or warfarin), and dosage adjustment of these medications may be needed.

Tocilizumab can be used in combination with nonbiologic DMARDs or as monotherapy. The recommended starting dose is 4 mg/kg intravenously every 4 weeks followed by an increase to 8 mg/kg dependent on clinical response. Additionally, dosage modifications are recommended on the basis of certain laboratory changes, elevated liver enzymes, neutropenia, and thrombocytopenia.

Indications

Tocilizumab is indicated for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonists.

Adverse Effects

Serious infections including tuberculosis, fungal, viral, and other opportunistic infections have occurred. Screening for tuberculosis should be done prior to beginning tocilizumab. The most common adverse reactions were upper respiratory tract infections, headache, hypertension, and elevated liver enzymes.

Neutropenia and reduction in platelet counts occur occasionally, and lipids (eg, cholesterol, triglycerides, LDL, and HDL) should be monitored. GI perforation has been reported when using tocilizumab in patients with diverticulitis or who are using corticosteroids.

TNF-α-BLOCKING AGENTS

Cytokines play a central role in the immune response (see Chapter 55) and in rheumatoid arthritis. Although a wide range of cytokines are expressed in the joints of rheumatoid arthritis patients, TNF-α appears to be particularly important in the inflammatory process.

TNF-α affects cellular function via activation of specific membrane-bound TNF receptors ($TNFR_1$, $TNFR_2$). Five biologic DMARDs interfering with TNF-α have been approved for the treatment of rheumatoid arthritis and other rheumatic diseases (Figure 36–4).

Adalimumab

A. Mechanism of Action

Adalimumab is a fully human IgG_1 anti-TNF monoclonal antibody. This compound complexes with soluble TNF-α and prevents its interaction with p55 and p75 cell surface receptors. This results in down-regulation of macrophage and T-cell function.

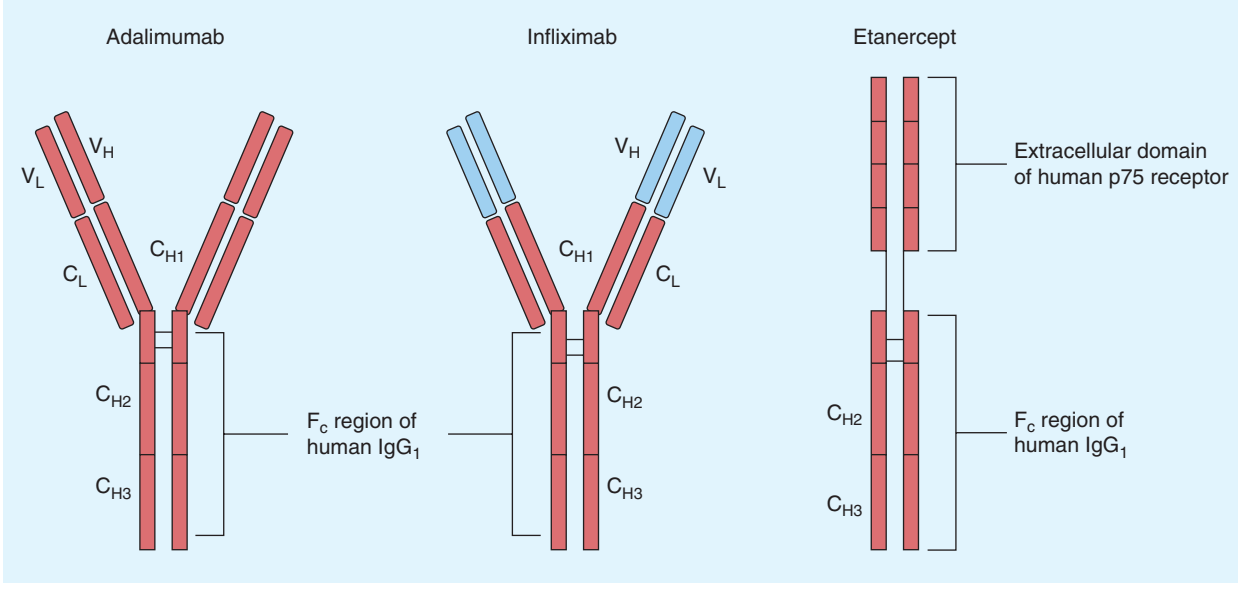


FIGURE 36–4 Structures of TNF-α antagonists used in rheumatoid arthritis. C_H, constant heavy chain; C_L, constant light chain; F_c, complex immunoglobulin region; V_H, variable heavy chain; V_L, variable light chain. Red regions, human derived; blue regions, mouse derived.

B. Pharmacokinetics

Adalimumab is given subcutaneously and has a half-life of 10–20 days. Its clearance is decreased by more than 40% in the presence of methotrexate, and the formation of human anti-monoclonal antibody is decreased when methotrexate is given at the same time. The usual dose in rheumatoid arthritis is 40 mg every other week; increased responses may be evident with the higher weekly dosing regimen. In psoriasis, 80 mg is given at week 0, 40 mg at week 1, and then 40 mg every other week thereafter.

C. Indications

The compound is approved for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis, and Crohn's disease. It decreases the rate of formation of new erosions. It is effective both as monotherapy and in combination with methotrexate and other DMARDs.

D. Adverse Effects

In common with the other TNF-α-blocking agents, the risk of bacterial infections and macrophage-dependent infection (including tuberculosis and other opportunistic infections) is increased, although it remains very low. Patients should be screened for latent or active tuberculosis before starting adalimumab or other TNF-α-blocking agents. There is no evidence of an increased incidence of solid malignancies. It is not clear if the incidence of lymphomas is increased by adalimumab. A low incidence of newly formed dsDNA antibodies and antinuclear antibodies (ANAs) has been documented when using adalimumab, but clinical lupus is extremely rare. Rare cases of leukopenia and vasculitis associated with adalimumab have been documented.

Certolizumab

A. Mechanism of Action

Certolizumab is a recombinant, humanized antibody Fab fragment conjugated to a polyethylene glycol (PEG) with specificity for human TNF-α. Certolizumab neutralizes membrane-bound and soluble TNF-α in a dose-dependent manner. Additionally, certolizumab does not contain an F_c region, found on a complete antibody, and does not fix complement or cause antibody-dependent cell-mediated cytotoxicity in vitro.

B. Pharmacokinetics

Certolizumab is given subcutaneously and has a half-life of 14 days. The clearance is decreased with decreasing body weight. Methotrexate does not alter the pharmacokinetics of certolizumab. However, methotrexate does decrease the appearance of anti-certolizumab antibodies. The usual dose for rheumatoid arthritis is 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week.

C. Indications

Certolizumab is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis. It can be used as monotherapy or in combination with nonbiologic DMARDs. Additionally, certolizumab is approved to reduce signs and symptoms and maintain clinical response in adult patients with Crohn's disease.

D. Adverse Effects

Consistent with other TNF-α blockers, the risk of serious infections, including tuberculosis, fungal, and other opportunistic pathogens, is increased and patients should be monitored closely. Prior to initiation of treatment, testing for latent tuberculosis should be performed. The association of lymphoma and other tumors with TNF-α blockers as a class, of which certolizumab is a member, is not fully understood.

Etanercept

A. Mechanism of Action

Etanercept is a recombinant fusion protein consisting of two soluble TNF p75 receptor moieties linked to the F_c portion of human IgG_1 (Figure 36–4); it binds TNF-α molecules and also inhibits lymphotoxin-α.

B. Pharmacokinetics

Etanercept is given subcutaneously in a dosage of 25 mg twice weekly or 50 mg weekly. In psoriasis, 50 mg is given twice weekly for 12 weeks followed by 50 mg weekly. The drug is slowly absorbed, with peak concentration 72 hours after drug administration. Etanercept has a mean serum elimination half-life of 4.5 days. Fifty milligrams given once weekly gives the same area under the curve and minimum serum concentrations as 25 mg twice weekly.

C. Indications

Etanercept is approved for the treatment of rheumatoid arthritis, juvenile chronic arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. It can be used as monotherapy, although over 70% of patients taking etanercept are also using methotrexate. Etanercept decreases the rate of formation of new erosions relative to methotrexate alone. It is also being used in other rheumatic syndromes such as scleroderma, Wegener's granulomatosis, giant cell arteritis, and sarcoidosis.

D. Adverse Effects

The incidence of bacterial infections is slightly increased, especially soft tissue infections and septic arthritis. Activation of latent tuberculosis is lower with etanercept than with other TNF-blocking agents. Nevertheless, patients should be screened for latent or active tuberculosis before starting this medication. Similarly, opportunistic infections can rarely occur when using etanercept. The incidence of solid malignancies is not increased, but as with other TNF-blocking agents, one must be aware of possible lymphomas (although their incidence may not be increased compared with other DMARDs or active rheumatoid arthritis itself). While positive ANAs and dsDNAs may be found in patients receiving this drug, these findings do not contraindicate continued use if clinical lupus symptoms do not occur. Injection site reactions occur in 20–40% of patients, although they rarely result in discontinuation of therapy. Anti-etanercept antibodies are present in up to 16% of treated patients, but they do not interfere with efficacy or predict toxicity.

Golimumab

A. Mechanism of Action

Golimumab is a human monoclonal antibody with a high affinity for soluble and membrane-bound TNF-α. Golimumab effectively neutralizes the inflammatory effects produced by TNF-α seen in diseases such as rheumatoid arthritis.

B. Pharmacokinetics

Golimumab is administered subcutaneously and has a half-life of approximately 14 days. Concomitant use with methotrexate showed increased serum levels of golimumab as well as a decrease in anti-golimumab antibodies. The recommended dose is 50 mg given every 4 weeks.

C. Indications

Golimumab, given with methotrexate, is indicated for the treatment of moderately to severely active rheumatoid arthritis in adult patients. It is also indicated for the treatment of psoriatic arthritis and ankylosing spondylitis.

D. Adverse Events

TNF-α blockers, including golimumab, increase the risk of serious infections, including tuberculosis, fungal, and other opportunistic pathogens. Prior to initiation of treatment, testing for latent tuberculosis should be performed. As with other TNF-α-blocking agents, there is a potential association with lymphoma; there is no association with other solid tumors (except possibly non-melanotic skin cancers).

Infliximab

A. Mechanism of Action

Infliximab (Figure 36–4) is a chimeric (25% mouse, 75% human) IgG_1 monoclonal antibody that binds with high affinity to soluble and possibly membrane-bound TNF-α. Its mechanism of action probably is the same as that of adalimumab.

B. Pharmacokinetics

Infliximab is given as an intravenous infusion with "induction" at 0, 2, and 6 weeks and maintenance every 8 weeks thereafter. Dosing is 3–10 mg/kg, although the usual dose is 3–5 mg/kg every 8 weeks. There is a relationship between serum concentration and effect, although individual clearances vary markedly. The terminal half-life is 9–12 days without accumulation after repeated dosing at the recommended interval of 8 weeks. After intermittent therapy, infliximab elicits human antichimeric antibodies in up to 62% of patients. Concurrent therapy with methotrexate markedly decreases the prevalence of human antichimeric antibodies.

C. Indications

Infliximab is approved for use in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. It is being used in other diseases, including psoriasis, ulcerative colitis, juvenile chronic arthritis, Wegener's granulomatosis, giant cell arteritis, and sarcoidosis. In rheumatoid arthritis, a regimen of infliximab plus methotrexate decreases the rate of formation of new erosions more than methotrexate alone over 12–24 months. Although it is recommended that methotrexate be used in conjunction with infliximab, a number of other DMARDs, including antimalarials, azathioprine, leflunomide, and cyclosporine, can be used as background therapy for this drug. Infliximab is also used as monotherapy, although this is neither approved by regulatory agencies nor advisable.

D. Adverse Effects

Like other TNF-α-blocking agents, infliximab is associated with an increased incidence of bacterial infections, including upper respiratory tract infections. As a potent macrophage inhibitor, infliximab can be associated with activation of latent tuberculosis, and patients should be screened for latent or active tuberculosis before starting therapy. Other infections have been documented, though rarely. There is no evidence of an increased incidence of solid malignancies and it is not clear whether the incidence of lymphoma is increased with infliximab. Because rare demyelinating syndromes have been reported, patients with multiple sclerosis or neuro-uveitis should not use infliximab. Rare cases of leukopenia, hepatitis, activation of hepatitis B, and vasculitis have been documented. The incidence of positive ANA and dsDNA antibodies is increased, although clinical lupus erythematosus remains an extremely rare occurrence and the presence of ANA and dsDNA does not contraindicate the use of infliximab. Infusion site reactions correlate with anti-infliximab antibodies. These reactions occur in approximately 3–11% of patients, and the combined use of antihistamines and H_2-blocking agents apparently prevents some of these reactions.

COMBINATION THERAPY WITH DMARDS

In a 1998 study, approximately half of North American rheumatologists treated moderately aggressive rheumatoid arthritis with combination therapy, and the use of drug combinations is probably much higher now. Combinations of DMARDs can be designed rationally on the basis of complementary mechanisms of action, non-overlapping pharmacokinetics, and non-overlapping toxicities.

When added to methotrexate background therapy, cyclosporine, chloroquine, hydroxychloroquine, leflunomide, infliximab, adalimumab, rituximab, and etanercept have all shown improved efficacy. In contrast, azathioprine, auranofin, or sulfasalazine plus methotrexate results in no additional therapeutic benefit. Other combinations have occasionally been used, including the combination of intramuscular gold with hydroxychloroquine.

While it might be anticipated that combination therapy could result in more toxicity, this is often not the case. Combination therapy for patients not responding adequately to monotherapy is becoming the rule in the treatment of rheumatoid arthritis.

GLUCOCORTICOID DRUGS

The general pharmacology of corticosteroids, including mechanism of action, pharmacokinetics, and other applications, is discussed in Chapter 39.

Indications

Corticosteroids have been used in 60–70% of rheumatoid arthritis patients. Their effects are prompt and dramatic, and they are capable of slowing the appearance of new bone erosions. Corticosteroids may be administered for certain serious extra-articular manifestations of rheumatoid arthritis such as pericarditis or eye involvement or during periods of exacerbation. When prednisone is required for long-term therapy, the dosage should not exceed 7.5 mg daily, and gradual reduction of the dose should be encouraged. Alternate-day corticosteroid therapy is usually unsuccessful in rheumatoid arthritis.

Other rheumatic diseases in which the corticosteroids' potent anti-inflammatory effects may be useful include vasculitis, systemic lupus erythematosus, Wegener's granulomatosis, psoriatic arthritis, giant cell arteritis, sarcoidosis, and gout.

Intra-articular corticosteroids are often helpful to alleviate painful symptoms and, when successful, are preferable to increasing the dosage of systemic medication.

Adverse Effects

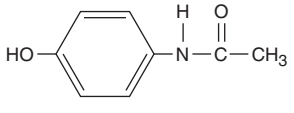
Prolonged use of these drugs leads to serious and disabling toxic effects as described in Chapter 39. There is controversy over whether many of these side effects occur at doses below 7.5 mg prednisone equivalent daily, although many experts believe that even 3–5 mg/d can cause these effects in susceptible individuals when this class of drugs is used over prolonged periods.

OTHER ANALGESICS

Acetaminophen is one of the most important drugs used in the treatment of mild to moderate pain when an anti-inflammatory effect is not necessary. Phenacetin, a prodrug that is metabolized to acetaminophen, is more toxic than its active metabolite and has no rational indications.

ACETAMINOPHEN

Acetaminophen is the active metabolite of phenacetin and is responsible for its analgesic effect. It is a weak COX-1 and COX-2 inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.



***N*-Acetyl-*p*-aminophenol (acetaminophen)**

Pharmacokinetics

Acetaminophen is administered orally. Absorption is related to the rate of gastric emptying, and peak blood concentrations are usually reached in 30–60 minutes. Acetaminophen is slightly bound to plasma proteins and is partially metabolized by hepatic microsomal enzymes and converted to acetaminophen sulfate and glucuronide, which are pharmacologically inactive (see Figure 4–5). Less than 5% is excreted unchanged. A minor but highly reactive metabolite (*N*-acetyl-*p*-benzoquinone) is important in large doses because it is toxic to both liver and kidney (see Chapter 4). The half-life of acetaminophen is 2–3 hours and is relatively unaffected by renal function. With toxic doses or liver disease, the half-life may be increased twofold or more.

Indications

Although said to be equivalent to aspirin as an analgesic and antipyretic agent, acetaminophen differs in that it lacks anti-inflammatory properties. It does not affect uric acid levels and lacks platelet-inhibiting effects. The drug is useful in mild to moderate pain such as headache, myalgia, postpartum pain, and other circumstances in which aspirin is an effective analgesic. Acetaminophen alone is inadequate therapy for inflammatory conditions such as rheumatoid arthritis, although it may be used as an analgesic adjunct to anti-inflammatory therapy. For mild analgesia, acetaminophen is the preferred drug in patients allergic to aspirin or when salicylates are poorly tolerated. It is preferable to aspirin in patients with hemophilia or a history of peptic ulcer and in those in whom bronchospasm is precipitated by aspirin. Unlike aspirin, acetaminophen does not antagonize the effects of uricosuric agents; it may be used concomitantly with probenecid in the treatment of gout. It is preferred to aspirin in children with viral infections.

Adverse Effects

In therapeutic doses, a mild increase in hepatic enzymes may occasionally occur in the absence of jaundice; this is reversible when the drug is withdrawn. With larger doses, dizziness, excitement, and disorientation may occur. Ingestion of 15 g of acetaminophen may be fatal, death being caused by severe hepatotoxicity with centrilobular necrosis, sometimes associated with acute renal tubular necrosis (see Chapters 4 and 58). Present data indicate that 4–6 g acetaminophen is associated with increased liver function test abnormalities. Doses greater than 4 g/d are not usually recommended and a history of alcoholism contraindicates even this dose. Early symptoms of hepatic damage include nausea, vomiting, diarrhea, and abdominal pain. Cases of renal damage without hepatic damage have occurred, even after usual doses of acetaminophen. Therapy is much less satisfactory than for aspirin overdose. In addition to supportive therapy, the measure that has proved most useful is the provision of sulfhydryl groups in the form of acetylcysteine to neutralize the toxic metabolites (see Chapter 58).

Hemolytic anemia and methemoglobinemia are very rare adverse events. Interstitial nephritis and papillary necrosis—serious complications of phenacetin—have not occurred nor has GI bleeding. Caution is necessary in patients with any type of liver disease.

Dosage

Acute pain and fever may be effectively treated with 325–500 mg four times daily and proportionately less for children. Dosing in adults is now recommended not to exceed 4 g/d, in most cases.

DRUGS USED IN GOUT

Gout is a metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage. Uric acid renal calculi, tophi, and interstitial nephritis may also occur. Gout is usually associated with a high serum uric acid level (hyperuricemia), a poorly soluble substance that is the major end product of purine metabolism. In most mammals, uricase converts uric acid to the more soluble allantoin; this enzyme is absent in humans. While clinical gouty episodes are associated with hyperuricemia, most individuals with hyperuricemia may never develop a clinical event from urate crystal deposition.

The treatment of gout aims to relieve acute gouty attacks and prevent recurrent gouty episodes and urate lithiasis. Therapies for acute gout are based on our current understanding of the pathophysiologic events that occur in this disease (Figure 36–5). Urate crystals are initially phagocytosed by synoviocytes, which then release prostaglandins, lysosomal enzymes, and interleukin-1. Attracted by these chemotactic mediators, polymorphonuclear leukocytes migrate into the joint space and amplify the ongoing inflammatory process. In the later phases of the attack, increased numbers of mononuclear phagocytes (macrophages) appear, ingest the urate crystals, and release more inflammatory mediators. This sequence of events suggests that the most effective agents for the management of acute urate crystal-induced inflammation are those that suppress different phases of leukocyte activation.

Before starting chronic urate-lowering therapy for gout, patients in whom hyperuricemia is associated with gout and urate lithiasis must be clearly distinguished from individuals with only hyperuricemia. The efficacy of long-term drug treatment in an asymptomatic hyperuricemic person is unproved. In some individuals, uric acid levels may be elevated up to 2 standard deviations above the mean for a lifetime without adverse consequences. Many different agents have been used for the treatment of acute and chronic gout. However, non-adherence to these drugs is exceedingly common; adherence has been documented to be as low as 26–18%, especially in younger patients. Providers should be aware of compliance as an important issue.

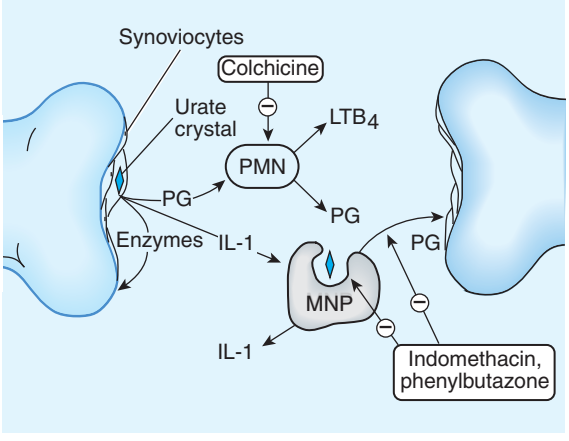


FIGURE 36–5 Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. PG, prostaglandin; IL-1, interleukin-1; LTB_4, leukotriene B_4.

COLCHICINE

Although NSAIDs are now the first-line drugs for acute gout, colchicine was the primary treatment for many years. Colchicine is an alkaloid isolated from the autumn crocus, *Colchicum autumnale*. Its structure is shown in Figure 36–6.

Pharmacokinetics

Colchicine is absorbed readily after oral administration, reaches peak plasma levels within 2 hours, and is eliminated with a serum half-life of 9 hours. Metabolites are excreted in the intestinal tract and urine.

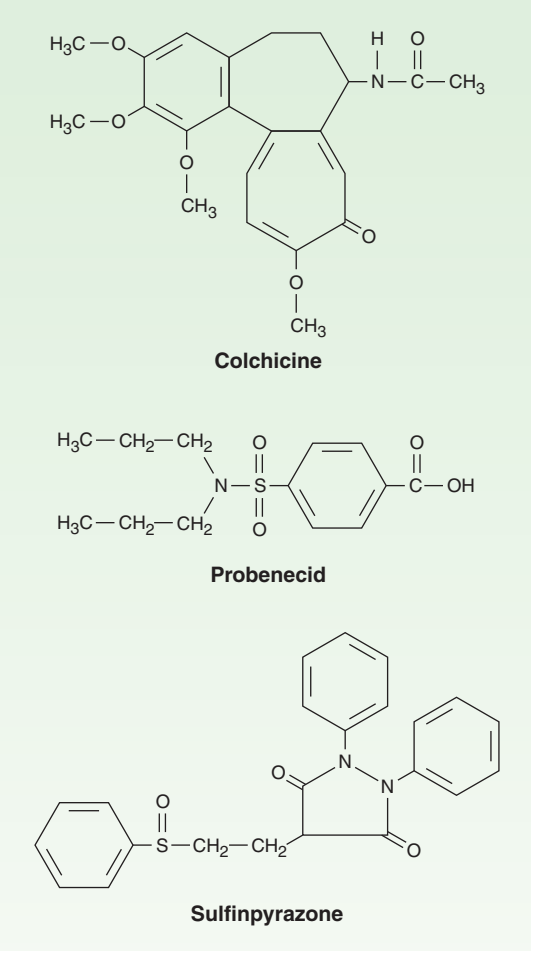


FIGURE 36–6 Colchicine and uricosuric drugs.

Pharmacodynamics

Colchicine relieves the pain and inflammation of gouty arthritis in 12–24 hours without altering the metabolism or excretion of urates and without other analgesic effects. Colchicine produces its anti-inflammatory effects by binding to the intracellular protein tubulin, thereby preventing its polymerization into microtubules and leading to the inhibition of leukocyte migration and phagocytosis. It also inhibits the formation of leukotriene B_4. Several of colchicine's adverse effects are produced by its inhibition of tubulin polymerization and cell mitosis.

Indications

Although colchicine is more specific in gout than the NSAIDs, NSAIDs (eg, indomethacin and other NSAIDs [except aspirin]) are sometimes used in its stead because of the troublesome diarrhea associated with colchicine therapy. Colchicine is now used between attacks (the "intercritical period") for prolonged prophylaxis (at low doses). It is effective in preventing attacks of acute Mediterranean fever and may have a mild beneficial effect in sarcoid arthritis and in hepatic cirrhosis. *(Although it has been given intravenously, this route is no longer approved by the FDA [2009].)*

Adverse Effects

Colchicine often causes diarrhea and may occasionally cause nausea, vomiting, and abdominal pain. Hepatic necrosis, acute renal failure, disseminated intravascular coagulation, and seizures have also been observed. Colchicine may rarely cause hair loss and bone marrow depression, as well as peripheral neuritis, myopathy, and, in some cases, death. The more severe adverse events have been associated with the intravenous administration of colchicine. Acute overdose is characterized by burning throat pain, bloody diarrhea, shock, hematuria, and oliguria. Fatal ascending central nervous system depression has been reported. Supportive care is the mainstay of treatment.

Dosage

In prophylaxis (the most common use), the dosage of colchicine is 0.6 mg one to three times daily. For terminating a gouty attack, traditional dosing has been an initial colchicine dose of 0.6 or 1.2 mg, followed by 0.6 mg every 2 hours until pain resolves, or nausea and diarrhea appear. However, a regimen of 1.2 mg followed by a single 0.6 mg oral dose was shown to be as effective as the higher dose therapy noted above. Adverse events were less with this lower dose regimen. In February 2008, the FDA requested that intravenous preparations containing colchicine be discontinued in the USA because of their potential life-threatening adverse effects. Therefore, intravenous use of colchicine is not recommended.

In July 2009, the FDA approved colchicine for the treatment of acute gout, allowing Colcrys (a branded colchicine) marketing exclusivity in the USA. Colchicine, per se, rather than Colcrys, is available throughout the rest of the world in a generic form.

NSAIDS IN GOUT

In addition to inhibiting prostaglandin synthase, indomethacin and other NSAIDs also inhibit urate crystal phagocytosis. Aspirin is not used because it causes renal retention of uric acid at low doses (≤ 2.6 g/d). It is uricosuric at doses greater than 3.6 g/d. Indomethacin is commonly used in the initial treatment of gout as a replacement for colchicine. For acute gout, 50 mg is given three times daily; when a response occurs, the dosage is reduced to 25 mg three times daily for 5–7 days.

All other NSAIDs except aspirin, salicylates, and tolmetin have been successfully used to treat acute gouty episodes. Oxaprozin, which lowers serum uric acid, is theoretically a good choice, although it should not be given to patients with uric acid stones because it increases uric acid excretion in the urine. These agents appear to be as effective and safe as the older drugs.

URICOSURIC AGENTS

Probenecid and sulfinpyrazone are uricosuric drugs employed to decrease the body pool of urate in patients with tophaceous gout or in those with increasingly frequent gouty attacks. In a patient who excretes large amounts of uric acid, the uricosuric agents should not be used.

Chemistry

Uricosuric drugs are organic acids (Figure 36–6) and, as such, act at the anionic transport sites of the renal tubule (see Chapter 15). Sulfinpyrazone is a metabolite of an analog of phenylbutazone.

Pharmacokinetics

Probenecid is completely reabsorbed by the renal tubules and is metabolized slowly with a terminal serum half-life of 5–8 hours. Sulfinpyrazone or its active hydroxylated derivative is rapidly excreted by the kidneys. Even so, the duration of its effect after oral administration is almost as long as that of probenecid, which is given once or twice daily.

Pharmacodynamics

Uric acid is freely filtered at the glomerulus. Like many other weak acids, it is also both reabsorbed and secreted in the middle segment (S2) of the proximal tubule. Uricosuric drugs—probenecid, sulfinpyrazone, and large doses of aspirin—affect these active transport sites so that net reabsorption of uric acid in the proximal tubule is decreased. Because aspirin in doses of less than 2.6 g daily causes net retention of uric acid by inhibiting the secretory transporter, it should not be used for analgesia in patients with gout. The secretion of other weak acids (eg, penicillin) is also reduced by uricosuric agents. Probenecid was originally developed to prolong penicillin blood levels.

As the urinary excretion of uric acid increases, the size of the urate pool decreases, although the plasma concentration may not be greatly reduced. In patients who respond favorably, tophaceous

deposits of urate are reabsorbed, with relief of arthritis and remineralization of bone. With the ensuing increase in uric acid excretion, a predisposition to the formation of renal stones is augmented rather than decreased; therefore, the urine volume should be maintained at a high level, and at least early in treatment, the urine pH should be kept above 6.0 by the administration of alkali.

Indications

Uricosuric therapy should be initiated in gouty patients with underexcretion of uric acid when allopurinol or febuxostat is contraindicated or when tophi are present. Therapy should not be started until 2–3 weeks after an acute attack.

Adverse Effects

Adverse effects do not provide a basis for preferring one or the other of the uricosuric agents. Both of these organic acids cause GI irritation, but sulfinpyrazone is more active in this regard. A rash may appear after the use of either compound. Nephrotic syndrome has occurred after the use of probenecid. Both sulfinpyrazone and probenecid may rarely cause aplastic anemia.

Contraindications & Cautions

It is essential to maintain a large urine volume to minimize the possibility of stone formation.

Dosage

Probenecid is usually started at a dosage of 0.5 g orally daily in divided doses, progressing to 1 g daily after 1 week. Sulfinpyrazone is started at a dosage of 200 mg orally daily, progressing to 400–800 mg daily. It should be given in divided doses with food to reduce adverse GI effects.

ALLOPURINOL

The preferred and standard-of-care therapy for gout during the period between acute episodes is allopurinol, which reduces total uric acid body burden by inhibiting xanthine oxidase.

Chemistry

The structure of allopurinol, an isomer of hypoxanthine, is shown in Figure 36–7.

Pharmacokinetics

Allopurinol is approximately 80% absorbed after oral administration and has a terminal serum half-life of 1–2 hours. Like uric acid, allopurinol is metabolized by xanthine oxidase, but the resulting compound, alloxanthine, retains the capacity to inhibit xanthine oxidase and has a long enough duration of action so that allopurinol is given only once a day.

Pharmacodynamics

Dietary purines are not an important source of uric acid. Quantitatively important amounts of purine are formed from amino acids, formate, and carbon dioxide in the body. Those purine ribonucleotides not incorporated into nucleic acids and derived from nucleic acid degradation are converted to xanthine or hypoxanthine and oxidized to uric acid (Figure 36–7). Allopurinol inhibits this last step, resulting in a fall in the plasma urate level and a decrease in the overall urate burden. The more soluble xanthine and hypoxanthine are increased.

Indications

Allopurinol is often the first-line agent for the treatment of chronic gout in the period between attacks and it aims to prolong

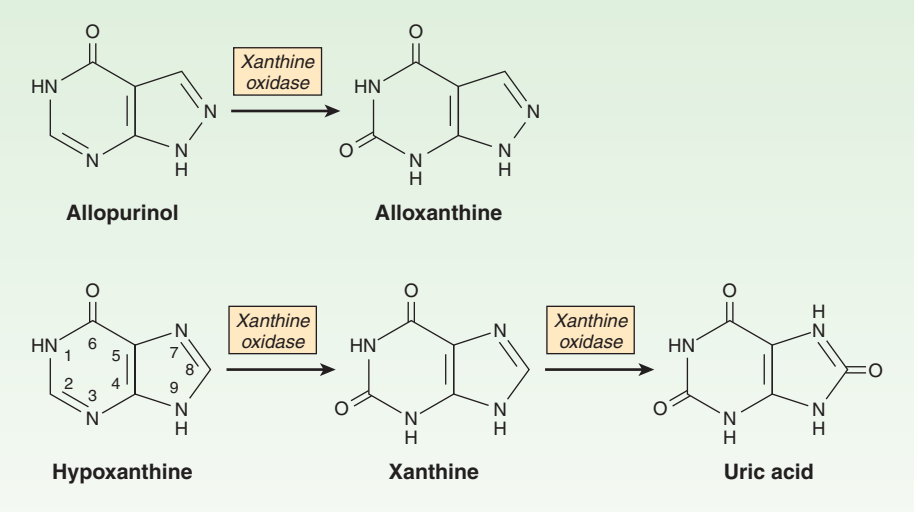


FIGURE 36–7 Inhibition of uric acid synthesis by allopurinol. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

the intercritical period. As with uricosuric agents, the therapy is begun with the expectation that it will be continued for years if not for life. When initiating allopurinol, colchicine or NSAID should be used until steady-state serum uric acid is normalized or decreased to less than 6 mg/dL and they should be continued for 3-6 months or even longer if required. Thereafter, colchicine or the NSAID can be cautiously stopped while continuing allopurinol therapy. In addition to gout, allopurinol is also used as an antiprotozoal agent (see Chapter 52) and is indicated to prevent the massive uricosuria following therapy of blood dyscrasias that could otherwise lead to renal calculi.

Adverse Effects

See above for prophylaxis against an acute attack during the initiation of allopurinol, which can occur as a result of acute changes in the serum uric acid level. Among the side effects, GI intolerance including nausea, vomiting, and diarrhea, peripheral neuritis and necrotizing vasculitis, bone marrow suppression, and rarely aplastic anemia may also occur. Hepatic toxicity and interstitial nephritis have been reported. An allergic skin reaction characterized by pruritic maculopapular lesions occurs in 3% of patients. Isolated cases of exfoliative dermatitis have been reported. In very rare cases, allopurinol has become bound to the lens, resulting in cataracts.

Interactions & Cautions

When chemotherapeutic purines (eg, azathioprine) are given concomitantly with allopurinol, their dosage must be reduced by about 75%. Allopurinol may also increase the effect of cyclophosphamide. Allopurinol inhibits the metabolism of probenecid and oral anticoagulants and may increase hepatic iron concentration. Safety in children and during pregnancy has not been established.

Dosage

The initial dosage of allopurinol is 100 mg/d. It should be titrated upward until serum uric acid is below 6 mg/dL; this level is commonly achieved at 300 mg/d but is not restricted to this dose; doses as high as 800 mg/d may be needed.

As noted above, colchicine or an NSAID should be given during the first several weeks of allopurinol therapy to prevent the gouty arthritis episodes that sometimes occur.

FEBUXOSTAT

Febuxostat is a non-purine xanthine oxidase inhibitor that was approved by the FDA in February 2009.

Pharmacokinetics

Febuxostat is more than 80% absorbed following oral administration. With maximum concentration achieved in approximately 1 hour and a half-life of 4–18 hours, once-daily dosing is effective. Febuxostat is extensively metabolized in the liver. All of the drug and its inactive metabolites appear in the urine, although less than 5% appears as unchanged drug.

Pharmacodynamics

Febuxostat is a potent and selective inhibitor of xanthine oxidase, thereby reducing the formation of xanthine and uric acid without affecting other enzymes in the purine or pyrimidine metabolic pathway. In clinical trials, febuxostat at daily dosing of 80 mg or 120 mg was more effective in lowering serum urate levels than allopurinol at a standard 300 mg daily dose. The urate-lowering effect was comparable regardless of the pathogenic cause of hyperuricemia—overproduction or underexcretion.

Indications

Febuxostat is approved at doses of 40, 80, or 120 mg the treatment of chronic hyperuricemia in gout patients. Although it appeared to be more effective then allopurinol as urate-lowering therapy, the allopurinol dosing was limited to 300 mg/d, thus not reflecting the actual dosing regimens used in clinical practice. At this time, the dose equivalence of allopurinol and febuxostat is unknown.

Adverse Effects

As with allopurinol, prophylactic treatment with colchicine or NSAIDs should be started at the beginning of therapy to avoid gout flares. The most frequent treatment-related adverse events are liver function abnormalities, diarrhea, headache, and nausea. Febuxostat appears to be well tolerated in patients with a history of allopurinol intolerance. There does not appear to be an increased risk of cardiovascular events.

Dosage

The recommended starting dose of febuxostat is 40 mg daily. Because of the concern for cardiovascular events in the original phase 3 trials, the FDA approved only 40 mg and 80 mg dosing. No dose adjustment is necessary for patients with renal impairment since it is highly metabolized into an inactive metabolite by the liver.

PEGLOTICASE

Pegloticase is the newest urate-lowering therapy; it was approved by the FDA in September 2010 for the treatment of refractory chronic gout.

Chemistry

Pegloticase is a recombinant mammalian uricase that is covalently attached to methoxy polyethylene glycol (mPEG) to prolong the circulating half-life and diminish immunogenic response.

Pharmacokinetics

Pegloticase is a rapidly acting intravenous drug, achieving a peak decline in uric acid level within 24–72 hours. The serum half-life ranges from 6.4 to 13.8 days. Several studies have shown earlier clearance of PEG-uricase (mean of 11 days) due to antibody response when compared to PEG-uricase antibody-negative subjects (mean of 16.1 days).

Pharmacodynamics

Urate oxidase enzyme, absent in humans and some higher primates, converts uric acid to allantoin. This product is highly soluble and can be easily eliminated by kidney. Pegloticase has been shown to maintain low urate levels for up to 21 days at doses of 4–12 mg, allowing for IV dosing every 2 weeks.

Adverse Effects

The most common adverse events include infusion reactions and gout flare (especially during the first 3 months of treatment). Nephrolithiasis, arthralgia, muscle spasm, headache, anemia, and nausea may occur. Other less frequent side effects noted include upper respiratory tract infection, peripheral edema, urinary tract infection, and diarrhea. There is some concern for hemolytic anemia in patients with glucose-6-phosphate dehydrogenase because of the formation of hydrogen peroxide by uricase; therefore, pegloticase should be avoided in these patients. Large numbers of patients show immune responses to pegloticase. The presence of antibody is associated with shortened circulating half-life, loss of response leading to a rise in plasma urate levels, and a higher rate of infusion reactions. Monitoring of plasma uric acid level, with rising level as an indicator of antibody production, allows for safer administration and monitoring of efficacy.

Dosage

The recommended dose for pegloticase is 8 mg IV every 2 weeks. As noted for other urate-lowering therapy, patients should be started on prophylaxis for acute gout flares (using colchicine) while initiating pegloticase.

GLUCOCORTICOIDS

Corticosteroids are sometimes used in the treatment of severe symptomatic gout, by intra-articular, systemic, or subcutaneous routes, depending on the degree of pain and inflammation.

The most commonly used oral corticosteroid is prednisone. The recommended dose is 30–50 mg/d for 1–2 days, tapered over 7–10 days. Intra-articular injection of 10 mg (small joints), 30 mg (wrist, ankle, elbow), and 40 mg (knee) of triamcinolone acetonide can be given if the patient is unable to take oral medications.

INTERLEUKIN-1 INHIBITORS

Drugs targeting the interleukin-1 pathway, such as anakinra, canakinumab, and rilonacept, are being investigated for the treatment of gout. Although the data are limited, these agents may provide a promising treatment option for acute gout in patients with contraindications to, or who are refractory to, traditional therapies like NSAIDs and/or colchicine. A recent study suggests that canakinumab, a fully human anti-IL-1β monoclonal antibody, can provide rapid and sustained pain relief at a dose of 150 mg subcutaneously. These medications are also being evaluated as therapies for prevention of gout flares while initiating urate-lowering therapy.

PREPARATIONS AVAILABLE

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Aspirin, acetylsalicylic acid (generic, Easprin, others)
Oral (regular, enteric-coated, buffered): 81, 165, 325, 500, 650, 800 mg tablets; 81, 650, 800 mg timed- or extended-release tablets
Rectal: 120, 200, 300, 600 mg suppositories

Bromfenac (Xibrom)
Ophthalmic: 0.09% solution

Celecoxib (Celebrex)
Oral: 50, 100, 200, 400 mg capsules

Choline salicylate (various)
Oral: 870 mg/5 mL liquid

Diclofenac (generic, Cataflam, Voltaren)
Oral: 50 mg tablets; 25, 50, 75 mg delayed-release tablets; 100 mg extended-release tablets
Ophthalmic: 0.1% solution

Diflunisal (generic, Dolobid)
Oral: 500 mg tablets

Etodolac (generic, Lodine)
Oral: 200, 300 mg capsules; 400, 500 mg tablets; 400, 500, 600 mg extended-release tablets

Fenoprofen (generic, Nalfon)
Oral: 200, 300 mg capsules; 600 mg tablets

Flurbiprofen (generic, Ansaid)
Oral: 50, 100 mg tablets
Ophthalmic (generic, Ocufen): 0.03% solution

Ibuprofen (generic, Motrin, Rufen, Advil [OTC], Nuprin [OTC], others)
Oral: 100, 200, 400, 600, 800 mg tablets; 50, 100 mg chewable tablets; 200 mg capsules; 100 mg/2.5 mL suspension, 100 mg/5 mL suspension; 40 mg/mL drops

Indomethacin (generic, Indocin)
Oral: 25, 50 mg capsules; 75 mg sustained-release capsules; 25 mg/5 mL suspension
Rectal: 50 mg suppositories

Ketoprofen (generic, Orudis)
Oral: 12.5 mg tablets; 25, 50, 75 mg capsules; 100, 150, 200 mg extended-release capsules

Ketorolac tromethamine (generic, Toradol)
Oral: 10 mg tablets
Parenteral: 15, 30 mg/mL for IM injection
Ophthalmic: 0.4, 0.5% solution

Magnesium salicylate (Doan's Pills, Magan, Mobidin)
Oral: 545, 600 mg tablets; 467, 500, 580 mg caplets

Meclofenamate sodium (generic)
Oral: 50, 100 mg capsules

Mefenamic acid (Ponstel)
Oral: 250 mg capsules

Meloxicam (Mobic)
Oral: 7.5, 15 mg tablets; 7.5 mg/5 mL suspension

Nabumetone (generic)
Oral: 500, 750 mg tablets

Naproxen (generic, Naprosyn, Anaprox, Aleve [OTC])
Oral: 200, 220, 250, 375, 500 mg tablets; 375, 550 mg controlled-release tablets; 375, 500 mg delayed-release tablets; 125 mg/5 mL suspension

Oxaprozin (generic, Daypro)
Oral: 600 mg tablets, capsules

Piroxicam (generic, Feldene)
Oral: 10, 20 mg capsules

Salsalate, salicylsalicylic acid (generic, Disalcid)
Oral: 500, 750 mg tablets; 500 mg capsules

Sodium salicylate (generic)
Oral: 325, 650 mg enteric-coated tablets

Sodium thiosalicylate (generic, Rexolate)
Parenteral: 50 mg/mL for IM injection

Sulindac (generic, Clinoril)
Oral: 150, 200 mg tablets

Suprofen (Profenal)
Topical: 1% ophthalmic solution

Tolmetin (generic, Tolectin)
Oral: 200, 600 mg tablets; 400 mg capsules

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Abatacept (Orencia)
Parenteral: 250 mg/vial lyophilized, for reconstitution for IV injection

Adalimumab (Humira)
Parenteral: 40 mg/0.8 mL for SC injection

Auranofin (Ridaura)
Oral: 3 mg capsules

Aurothioglucose (Solganal)
Parenteral: 50 mg/mL suspension for injection

Certolizumab (Cimzia)
Parenteral: 200 mg powder for solution for subcutaneous injection

Cyclophosphamide: see Chapter 54

Cyclosporine: see Chapter 55

Etanercept (Enbrel)
Parenteral: 50 mg/mL, 25 mg powder for SC injection

Gold sodium thiomalate (generic, Aurolate)
Parenteral: 50 mg/mL for injection

Golimumab (Simponi)
Parenteral: 50 mg per 0.5 mL solution for SC injection

Infliximab (Remicade)
Parenteral: 100 mg powder for IV infusion

Leflunomide (Arava)
Oral: 10, 20, 100 mg tablets

Methotrexate (generic, Rheumatrex)
Oral: 2.5 mg tablet dose packs; 5, 7.5, 10, 15 mg tablets

Mycophenolate mofetil: see Chapter 55

Penicillamine (Cuprimine, Depen)
Oral: 125, 250 mg capsules; 250 mg tablets

Rituximab (Rituxan)
Parenteral: 10 mg/mL for IV infusion

Sulfasalazine (generic, Azulfidine)
Oral: 500 mg tablets; 500 mg delayed-release tablets

Tocilizumab (Actemra)
Parenteral: 20 mg/mL concentrate for IV administration

ACETAMINOPHEN

Acetaminophen (generic, Tylenol, Tempra, Panadol, Acephen, others)
Oral: 160, 325, 500, 650 mg tablets; 80 mg chewable tablets; 160, 500, 650 mg caplets; 325, 500 mg capsules; 80, 120, 160 mg/5 mL elixir; 500 mg/15 mL elixir; 80 mg/1.66 mL, 100 mg/mL solution
Rectal: 80, 120, 125, 300, 325, 650 mg suppositories

DRUGS USED IN GOUT

Allopurinol (generic, Zyloprim)
Oral: 100, 300 mg tablets

Colchicine (generic, Colchrys)
Oral: 0.6 mg tablets

Febuxostat (Uloric)
Oral: 40, 80 mg tablets

Pegloticase (Krystexxa)
Parenteral: 8 mg/mL solution for IV infusion

Probenecid (generic)
Oral: 500 mg tablets

Sulfinpyrazone (generic, Anturane)
Oral: 100 mg tablets; 200 mg capsules

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CASE STUDY ANSWER

This patient had good control of his symptoms for 1 year but now has a prolonged flare, probably denoting worsening disease (not just a temporary flare). In addition to physical findings and measurement of acute-phase reactants such as sedimentation rate or C-reactive protein, it would be wise to get hand and feet radiographs to document whether he has developed joint damage. Assuming such damage is found, the appropriate approach would be either a combination of nonbiologic DMARDs (eg, adding sulfasalazine and hydroxychloroquine) or adding a biologic medication, usually a tumor necrosis factor inhibitor. Follow-up should be every 1–3 months to gauge response and toxicity. Adverse events requiring caution are an increased risk of infection, possible appearance of lymphoma and rare liver function test or hematologic abnormalities. Importantly, close follow-up should ensue, including changing medications every 3–6 months until full disease control is achieved.

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SECTION VII ENDOCRINE DRUGS

CHAPTER 37

Hypothalamic & Pituitary Hormones

Susan B. Masters, PhD, & Stephen M. Rosenthal, MD

CASE STUDY

A 3-year-old boy [height 85 cm, –3 standard deviations (SD); weight 13 kg, approximately 10th percentile) presents with short stature. Review of the past history and growth chart demonstrates normal birth weight and birth length, but a progressive fall off in height velocity relative to age-matched normal ranges starting at 6 months of age. Physical examination demonstrates short stature and mild generalized obesity. Genital examination reveals descended but small testes and a phallic length of –2 SD. Laboratory evaluation demonstrates growth hormone (GH) deficiency and a delayed bone age of 18 months. The patient is started on replacement with recombinant human GH at a dose of 40 mcg/kg/d subcutaneously. After 1 year of treatment, his height velocity has increased from 5 cm/yr to 11 cm/yr. How does GH stimulate growth in children? What other hormone deficiencies are suggested by the patient's physical examination? What other hormone supplementation is this patient likely to require?

The control of metabolism, growth, and reproduction is mediated by a combination of neural and endocrine systems located in the hypothalamus and pituitary gland. The pituitary weighs about 0.6 g and rests at the base of the brain in the bony sella turcica near the optic chiasm and the cavernous sinuses. The pituitary consists of an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis) (Figure 37–1). It is connected to the overlying hypothalamus by a stalk of neurosecretory fibers and blood vessels, including a portal venous system that drains the hypothalamus and perfuses the anterior pituitary. The portal venous system carries small regulatory hormones (Figure 37–1, Table 37–1) from the hypothalamus to the anterior pituitary.

The posterior lobe hormones are synthesized in the hypothalamus and transported via the neurosecretory fibers in the stalk of the pituitary to the posterior lobe, from which they are released into the circulation.

Drugs that mimic or block the effects of hypothalamic and pituitary hormones have pharmacologic applications in three primary areas: (1) as replacement therapy for hormone deficiency states; (2) as antagonists for diseases caused by excess production of pituitary hormones; and (3) as diagnostic tools for identifying several endocrine abnormalities.

■ ANTERIOR PITUITARY HORMONES & THEIR HYPOTHALAMIC REGULATORS

All the hormones produced by the anterior pituitary except prolactin (PRL) are key participants in hormonal systems in which they regulate the production of hormones and autocrine-paracrine factors by endocrine glands and other peripheral tissues. In these systems, the secretion of the pituitary hormone is under the control of one or more hypothalamic hormones. Each hypothalamic-pituitary-endocrine gland system or axis provides multiple opportunities for complex neuroendocrine regulation of growth and development, metabolism, and reproductive function.

ANTERIOR PITUITARY & HYPOTHALAMIC HORMONE RECEPTORS

The anterior pituitary hormones can be classified according to hormone structure and the types of receptors that they activate. **Growth hormone (GH)** and **prolactin**, single-chain protein hormones with significant homology, form one group. Both hormones activate receptors of the JAK/STAT superfamily (see Chapter 2). Three pituitary hormones—**thyroid-stimulating hormone (TSH, thyrotropin), follicle-stimulating hormone (FSH)**, and **luteinizing hormone (LH)**—are dimeric proteins that activate G protein-coupled receptors (see Chapter 2). TSH, FSH, and LH share a common α chain. Their β chains, though somewhat similar to each other, differ enough to confer receptor

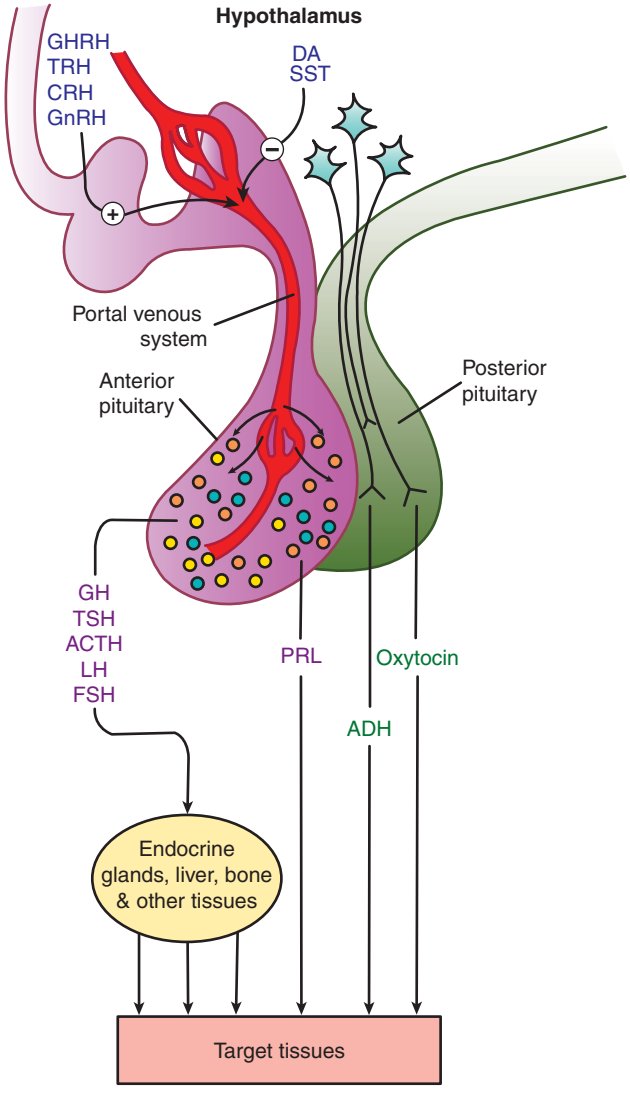

FIGURE 37–1 The hypothalamic-pituitary endocrine system. Except for prolactin, hormones released from the anterior pituitary stimulate the production of hormones by a peripheral endocrine gland, the liver, or other tissues. Prolactin and the hormones released from the posterior pituitary (vasopressin and oxytocin) act directly on target tissues. Hypothalamic factors regulate the release of anterior pituitary hormones. ACTH, adrenocorticotropin; ADH, antidiuretic hormone [vasopressin]; CRH, corticotropin-releasing hormone; DA, dopamine; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PRL, prolactin; SST, somatostatin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

ACRONYMS

ACTH	Adrenocorticotropic hormone (corticotropin)
CRH	Corticotropin-releasing hormone
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
hMG	Human menopausal gonadotropin
IGF	Insulin-like growth factor
LH	Luteinizing hormone
PRL	Prolactin
rhGH	Recombinant human growth hormone
SST	Somatostatin
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone (thyrotropin)

TABLE 37–1 Links between hypothalamic, anterior pituitary, and target organ hormone or mediator.[1]

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
Growth hormone (GH, somatotropin)	Growth hormone-releasing hormone (GHRH) (+) Somatostatin (–)	Liver, bone, muscle, kidney, and others	Insulin-like growth factor-I (IGF-I)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Cortisol
Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH) (+)[2]	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (–)	Breast	—

[1]All of these hormones act through G protein-coupled receptors except growth hormone and prolactin, which act through JAK/STAT receptors.

[2]Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

(+), stimulant; (–), inhibitor.

specificity. Finally, **adrenocorticotropic hormone (ACTH)**, a single peptide cleaved from a larger precursor that also contains the peptide β-endorphin (see Chapter 31), represents a third category. Like TSH, LH, and FSH, ACTH acts through a G protein-coupled receptor. A unique feature of the ACTH receptor (also known as the melanocortin 2 receptor) is that a transmembrane protein, melanocortin 2 receptor accessory protein, is essential for normal ACTH receptor trafficking and signaling.

TSH, FSH, LH, and ACTH share similarities in the regulation of their release from the pituitary. Each is under the control of a distinctive hypothalamic peptide that stimulates their production by acting on G protein-coupled receptors (Table 37–1). TSH release is regulated by **thyrotropin-releasing hormone (TRH)**, whereas the release of LH and FSH (known collectively as gonadotropins) is stimulated by pulses of **gonadotropin-releasing hormone (GnRH).** ACTH release is stimulated by **corticotropin-releasing hormone (CRH).** An important regulatory feature shared by these four structurally related hormones is that they and their hypothalamic releasing factors are subject to feedback inhibitory regulation by the hormones whose production they control. TSH and TRH production are inhibited by the two key thyroid hormones, thyroxine and triiodothyronine (see Chapter 38). Gonadotropin and GnRH production is inhibited in women by estrogen and progesterone, and in men by testosterone and other androgens. ACTH and CRH production are inhibited by cortisol. Feedback regulation is critical to the physiologic control of thyroid, adrenal cortical, and gonadal function and is also important in pharmacologic treatments that affect these systems.

The hypothalamic hormonal control of GH and prolactin differs from the regulatory systems for TSH, FSH, LH, and ACTH. The hypothalamus secretes two hormones that regulate GH; **growth hormone-releasing hormone (GHRH)** stimulates GH production, whereas the peptide **somatostatin (SST)** inhibits GH production. GH and its primary peripheral mediator, **insulin-like growth factor-I (IGF-I)**, also provide feedback to inhibit GH release. Prolactin production is inhibited by the catecholamine **dopamine** acting through the D_2 subtype of dopamine receptors. The hypothalamus does not produce a hormone that specifically stimulates prolactin secretion, although TRH can stimulate prolactin release, particularly when TRH concentrations are high in the setting of primary hypothyroidism.

Whereas all the pituitary and hypothalamic hormones described previously are available for use in humans, only a few are of major clinical importance. Because of the greater ease of administration of target endocrine gland hormones or their synthetic analogs, the related hypothalamic and pituitary hormones (TRH, TSH, CRH, ACTH, GHRH) are used infrequently as treatments. Some, such as ACTH, are used for specialized diagnostic testing. These agents are described in Tables 37–2 and 37–3 and are not discussed further in this chapter. In contrast, GH, SST, LH, FSH, GnRH, and dopamine or analogs of these hormones are commonly used and are described in the following text.

TABLE 37–2 Clinical uses of hypothalamic hormones and their analogs.

Hypothalamic Hormone	Clinical Uses
Growth hormone-releasing hormone (GHRH)	Used rarely as a diagnostic test for GH and GHRH sufficiency
Thyrotropin-releasing hormone (TRH, protirelin)	May be used to diagnose TRH or TSH deficiencies
Corticotropin-releasing hormone (CRH)	Used rarely to distinguish Cushing's disease from ectopic ACTH secretion
Gonadotropin-releasing hormone (GnRH)	May be used in pulses to treat infertility caused by GnRH deficiency Analogs used in long-acting formulations to inhibit gonadal function in children with precocious puberty, in some transgender/gender variant early pubertal adolescents (to block endogenous puberty), in men with prostate cancer and women undergoing assisted reproductive technology (ART) or women who require ovarian suppression for a gynecologic disorder
Dopamine	Dopamine agonists (eg, bromocriptine, cabergoline) used for treatment of hyperprolactinemia

TABLE 37–3 Diagnostic uses of thyroid-stimulating hormone and adrenocorticotropin.

Hormone	Diagnostic Use
Thyroid-stimulating hormone (TSH; thyrotropin)	In patients who have been treated surgically for thyroid carcinoma, to test for recurrence by assessing TSH-stimulated whole-body ^{131}I scans and serum thyroglobulin determinations
Adrenocorticotropin (ACTH)	In patients suspected of adrenal insufficiency, either central (CRH/ACTH deficiency) or peripheral (cortisol deficiency), in particular in suspected cases of congenital adrenal hyperplasia. (See Figure 39–1 and Chapter 39.)

GROWTH HORMONE (SOMATOTROPIN)

Growth hormone, an anterior pituitary hormone, is required during childhood and adolescence for attainment of normal adult size and has important effects throughout postnatal life on lipid and carbohydrate metabolism, and on lean body mass and bone density. Its growth-promoting effects are primarily mediated via **IGF-I** (also known as **somatomedin C).** Individuals with congenital or acquired deficiency of GH during childhood or adolescence fail to reach their predicted adult height and have disproportionately increased body fat and decreased muscle mass. Adults with GH deficiency also have disproportionately low lean body mass.

Chemistry & Pharmacokinetics

A. Structure

Growth hormone is a 191-amino-acid peptide with two sulfhydryl bridges. Its structure closely resembles that of prolactin. In the past, medicinal GH was isolated from the pituitaries of human cadavers. However, this form of GH was found to be contaminated with prions that could cause Creutzfeldt-Jakob disease. For this reason, it is no longer used. **Somatropin**, the recombinant form of GH, has a 191-amino-acid sequence that is identical with the predominant native form of human GH.

B. Absorption, Metabolism, and Excretion

Circulating endogenous GH has a half-life of 20–25 minutes and is predominantly cleared by the liver. Recombinant human GH (rhGH) is administered subcutaneously 6–7 times per week. Peak levels occur in 2–4 hours and active blood levels persist for approximately 36 hours.

Pharmacodynamics

Growth hormone mediates its effects via cell surface receptors of the JAK/STAT cytokine receptor superfamily. Growth hormone has two distinct GH receptor binding sites. Dimerization of two GH receptors is stimulated by a single GH molecule and activates signaling cascades mediated by receptor-associated JAK tyrosine kinases and STATs (see Chapter 2). GH has complex effects on growth, body composition, and carbohydrate, protein, and lipid metabolism. The growth-promoting effects are mediated principally through an increase in the production of IGF-I. Much of the circulating IGF-I is produced in the liver. GH also stimulates production of IGF-I in bone, cartilage, muscle, kidney, and other tissues, where it plays autocrine or paracrine roles. GH stimulates longitudinal bone growth until the epiphyses close—near the end of puberty. In both children and adults, GH has anabolic effects in muscle and catabolic effects in lipid cells that shift the balance of body mass to an increase in muscle mass and a reduction in adiposity. The direct and indirect effects of GH on carbohydrate metabolism are mixed, in part because GH and IGF-I have opposite effects on insulin sensitivity. GH reduces insulin sensitivity, which results in mild hyperinsulinemia, whereas IGF-I has insulin-like effects on glucose transport. In patients who are unable to respond to GH because of severe GH resistance (caused by GH receptor mutations, post-GH receptor signaling mutations, or GH antibodies), the administration of recombinant human IGF-I may cause hypoglycemia because of its insulin-like effects.

Clinical Pharmacology

A. Growth Hormone Deficiency

GH deficiency can have a genetic basis, may be associated with midline developmental defect syndromes (eg, septo-optic dysplasia), or can be acquired as a result of damage to the pituitary or hypothalamus by a trauma (including breech or traumatic delivery), intracranial tumors, infection, infiltrative or hemorrhagic processes, or irradiation. Neonates with isolated GH deficiency are typically of normal size at birth because prenatal growth is not GH-dependent. In contrast, IGF-I is essential for normal prenatal and postnatal growth. Through poorly understood mechanisms, IGF-I expression and postnatal growth become GH-dependent during the first year of life. In childhood, GH deficiency typically presents as short stature, often with mild adiposity. Another early sign of GH deficiency is hypoglycemia due to unopposed action of insulin, to which young children are especially sensitive. Criteria for diagnosis of GH deficiency usually include (1) a subnormal height velocity for age and (2) a subnormal serum GH response following stimulation with at least two GH secretagogues. The prevalence of GH deficiency is approximately 1:5000. Therapy with rhGH permits many children with short stature due to GH deficiency to achieve normal adult height.

In the past, it was believed that adults with GH deficiency do not exhibit a significant syndrome. However, more detailed studies suggest that adults with GH deficiency often have generalized obesity, reduced muscle mass, asthenia, and reduced cardiac output. GH-deficient adults who have been treated with GH have been shown to experience a reversal of many of these manifestations.

B. Growth Hormone Treatment of Pediatric Patients with Short Stature

Although the greatest improvement in growth occurs in patients with GH deficiency, exogenous GH has some effect on height in

TABLE 37–4 Clinical uses of recombinant human growth hormone.

Primary Therapeutic Objective	Clinical Condition
Growth	Growth failure in pediatric patients associated with:
	Growth hormone deficiency
	Chronic renal insufficiency pre-transplant
	Noonan syndrome
	Prader-Willi syndrome
	Short stature homeobox-containing gene (SHOX) deficiency
	Turner syndrome
	Small for gestational age with failure to catch up by age 2 years
	Idiopathic short stature
Improved metabolic state, increased lean body mass, sense of well-being	Growth hormone deficiency in adults
Increased lean body mass, weight, and physical endurance	Wasting in patients with HIV infection
Improved gastrointestinal function	Short bowel syndrome in patients who are also receiving specialized nutritional support

children with short stature caused by factors other than GH deficiency. GH has been approved for several conditions (Table 37–4) and has been used experimentally or off-label in many others. **Prader-Willi syndrome** is an autosomal dominant genetic disease associated with growth failure, obesity, and carbohydrate intolerance. In children with Prader-Willi syndrome and growth failure, GH treatment decreases body fat and increases lean body mass, linear growth, and energy expenditure.

GH treatment has also been shown to have a strong beneficial effect on final height of girls with **Turner syndrome** (45 X karyotype and variants). In clinical trials, GH treatment has been shown to increase final height in girls with Turner syndrome by 10–15 cm (4–6 inches). Because girls with Turner syndrome also have either absent or rudimentary ovaries, GH must be judiciously combined with gonadal steroids to achieve maximal height. Other conditions of pediatric growth failure for which GH treatment is FDA-approved include chronic renal insufficiency pre-transplant and small-for-gestational-age at birth in which the child's height remains more than 2 standard deviations below the norm at 2 years of age.

A controversial but approved use of GH is for children with **idiopathic short stature** (ISS). This is a heterogeneous population that has in common no identifiable cause of the short stature. Some have arbitrarily defined ISS clinically as having a height at least 2.25 standard deviations below the norm for children of the same age and an unlikelihood of achieving an adult height that will be less than 2.25 standard deviations below the norm. In this group of children, many years of GH therapy result in an average increase in adult height of 4–7 cm (1.57–2.76 inches) at a cost of $5000–$40,000 per year. The complex issues involved in the cost-risk-benefit relationship of this use of GH are important because an estimated 400,000 children in the United States fit the diagnostic criteria for ISS.

Treatment of children with short stature should be carried out by specialists experienced in GH administration. GH dose requirements vary with the condition being treated, with GH-deficient children typically being most responsive. Children must be observed closely for slowing of growth velocity, which could indicate a need to increase the dosage or the possibility of epiphyseal fusion or intercurrent problems such as hypothyroidism or malnutrition.

Other Uses of Growth Hormone

Growth hormone affects many organ systems and also has a net anabolic effect. It has been tested in a number of conditions that are associated with a severe catabolic state and is approved for the treatment of wasting in patients with AIDS. In 2004, GH was approved for treatment of patients with short bowel syndrome who are dependent on total parenteral nutrition (TPN). After intestinal resection or bypass, the remaining functional intestine in many patients undergoes extensive adaptation that allows it to adequately absorb nutrients. However, other patients fail to adequately adapt and develop a malabsorption syndrome. GH has been shown to increase intestinal growth and improve its function in experimental animals. Benefits of GH treatment for patients with short bowel syndrome and dependence on total parenteral nutrition have mostly been short-lived in the clinical studies that have been published to date. Growth hormone is administered with glutamine, which also has trophic effects on the intestinal mucosa.

GH is a popular component of "anti-aging" programs. Serum levels of GH normally decline with aging; anti-aging programs claim that injection of GH or administration of drugs purported to increase GH release are effective anti-aging remedies. These claims are largely unsubstantiated. In contrast studies in mice and the nematode *C elegans* have clearly demonstrated that analogs of human GH and IGF-I consistently *shorten* life span and that loss-of-function mutations in the signaling pathways for the GH and IGF-I analogs lengthen life span. Another use of GH is by athletes for a purported increase in muscle mass and athletic performance. GH is one of the drugs banned by the Olympic Committee.

Although GH has important effects on lipid and carbohydrate metabolism and on lean body mass, it does not seem likely to be a fruitful direct target for efforts to develop new drugs to treat obesity. However, some of the hormonal and neuroendocrine systems that regulate GH secretion are being investigated as possible targets for antiobesity drugs (see Box: Treatment of Obesity).

In 1993, the FDA approved the use of recombinant bovine growth hormone (rbGH) in dairy cattle to increase milk production. Although milk and meat from rbGH-treated cows appear to be safe, these cows have a higher incidence of mastitis, which could increase antibiotic use and result in greater antibiotic residues in milk and meat.

TREATMENT OF OBESITY[1]

It is said that the developed world is experiencing an "epidemic of obesity." This statement is based on statistics showing that in the USA, for example, 30–40% of the population is above optimal weight and that the excess weight (especially abdominal fat) is often associated with the **metabolic syndrome** and increased risks of cardiovascular disease and diabetes. Since eating behavior is an expression of endocrine, neurophysiologic, and psychological processes, prevention and treatment of obesity are complex. It is not surprising that there is considerable scientific and financial interest in developing pharmacologic therapy for the condition.

Although obesity can be defined as excess adipose tissue, it is currently quantitated by means of the body mass index (BMI), calculated from BMI = weight (in kilograms)/height^2 (in meters). Using this measure, a normal BMI is defined as 18.5–24.9; overweight, 25–29.9; obese, 30–39.9; and morbidly obese (ie, at very high risk), ≥ 40. Some extremely muscular individuals may have a BMI higher than 25 and no excess fat; however, the BMI scale generally correlates with the degree of obesity and with risk.

Although the cause of obesity can be simply stated as energy intake (dietary calories) exceeding energy output (resting metabolism plus exercise), the actual physiology of weight control is extremely complex, and the pathophysiology of obesity is still poorly understood. Many hormones and neuronal mechanisms regulate intake (appetite, satiety), processing (absorption, conversion to fat, glycogen, etc), and output (thermogenesis, muscle work). The fact that a large number of hormones reduce appetite (Table 37–4.1, see online version of this book) might appear to offer many targets for weight-reducing drug therapy, but despite intensive research, no available pharmacologic therapy has succeeded in maintaining a weight loss of over 10% for 1 year. Furthermore, the social and psychological aspects of eating are powerful influences that are independent of or only partially dependent on the physiologic control mechanisms. In contrast, bariatric (weight-reducing) surgery readily achieves a sustained weight loss of 10–40%. Furthermore, surgery that bypasses the stomach and upper small intestine (but not simple restrictive banding) rapidly reverses some aspects of the metabolic syndrome even before significant weight is lost. However, even a 5–10% loss of weight is associated with a reduction in blood pressure and improved glycemic control.

Until approximately 15 years ago, the most popular and successful appetite suppressants were the nonselective 5-HT$_2$ agonists: fenfluramine and dexfenfluramine. Combined with phentermine as Fen-Phen and Dex-Phen, they were moderately effective. However, these drugs were found to cause pulmonary hypertension and cardiac valve defects and were withdrawn.

Older drugs still available in the United States and some other countries include phenylpropanolamine, benzphetamine, amphetamine, methamphetamine, phentermine, diethylpropion, mazindol, and phendimetrazine. These drugs are all amphetamine mimics and are central nervous system appetite suppressants; they are generally helpful only during the first few weeks of therapy. Their toxicity is significant and includes hypertension (with a risk of cerebral hemorrhage) and addiction liability.

Orlistat is the only non-amphetamine drug currently approved in the United States for the treatment of obesity. Two other drugs that have been intensely studied are listed in Table 37–5. Clinical trials and phase 4 reports suggest that orlistat is modestly effective for the duration of therapy (up to 1 year) and is probably safer than the amphetamine mimics. However, it does not produce more than a 5–10% loss of weight. Sibutramine was marketed for several years but was withdrawn because of increasing evidence of cardiovascular toxicity. Lorcaserin received intense study through 2010 and was submitted for approval to the FDA, but this was denied on the basis of considerations of inadequate safety and effectiveness.

Because of the low efficacy of the drugs listed in Table 37–5, intensive research continues. (Some drugs approved for other indications that reduce appetite and possible future weight loss drugs are set forth in Table 37–5.1, see online version of this book). Because of the redundancy of the physiologic mechanisms for control of body weight, it seems likely that polypharmacy targeting multiple pathways will be needed to achieve success.

[1]Contributed by B.G. Katzung.

Toxicity & Contraindications

Children generally tolerate GH treatment well. Adverse events are relatively rare and include pseudotumor cerebri; slipped capital femoral epiphysis; progression of scoliosis; edema; hyperglycemia; and increased risk of asphyxiation in severely obese patients with Prader-Willi syndrome and upper airway obstruction or sleep apnea. Patients with Turner syndrome have an increased risk of otitis media while taking GH. In children with GH deficiency, periodic evaluation of the other anterior pituitary hormones may reveal concurrent deficiencies, which also require treatment (eg, with hydrocortisone, levothyroxine, or gonadal hormones). Pancreatitis, gynecomastia, and nevus growth have occurred in patients receiving GH. Adults tend to have more adverse effects from GH therapy. Peripheral edema, myalgias, and arthralgias (especially in the hands and wrists) occur commonly but remit with dosage reduction. Carpal tunnel syndrome can occur. GH treatment increases the activity of cytochrome P450 isoforms, which may reduce the serum levels of drugs

TABLE 37–5 Newer anti-obesity drugs and their effects.

	Orlistat	Sibutramine	Lorcaserin
Target organ	Gut	CNS	CNS (peripheral ?)
Target molecule	GI lipase inhibitor	SERT and NET inhibitor	Selective 5-HT_{2C} receptor agonist
Mechanism of action	Reduces absorption of fats since triglycerides not split	Reduces appetite	Reduces appetite
Toxicity	GI: Flatulence, steatorrhea, fecal incontinence	Tachycardia, hypertension, infarction	Headache; tumorigenesis in rats
Dosage	130 mg tid	10–15 mg qd	10–20 mg qd
Availability	Over the counter	Prescription; withdrawn in 2010	NDA approval denied by FDA

CNS, central nervous system; GI, gastrointestinal; SERT, serotonin reuptake transporter; NET, norepinephrine reuptake transporter; tid, three times daily; qd, daily.

metabolized by that enzyme system (see Chapter 4). There has been no increased incidence of malignancy among patients receiving GH therapy, but GH treatment is contraindicated in a patient with a known active malignancy. Proliferative retinopathy may rarely occur. GH treatment of critically ill patients appears to *increase* mortality.

MECASERMIN

A small number of children with growth failure have severe IGF-I deficiency that is not responsive to exogenous GH. Causes include mutations in the GH receptor and in the GH receptor signaling pathway, neutralizing antibodies to GH, and IGF-I gene defects. In 2005, the FDA approved two forms of recombinant human IGF-I (rhIGF-I) for treatment of severe IGF-I deficiency that is not responsive to GH: mecasermin and mecasermin rinfabate. Mecasermin is rhIGF-I alone, while mecasermin rinfabate is a complex of recombinant human IGF-I (rhIGF-I) and recombinant human insulin-like growth factor-binding protein-3 (rhIGFBP-3). This binding protein significantly increases the circulating half-life of rhIGF-I. Normally, the great majority of the circulating IGF-I is bound to IGFBP-3, which is produced principally by the liver under the control of GH. Mecasermin rinfabate is not currently available in the United States. Mecasermin is administered subcutaneously twice daily at a recommended starting dosage of 0.04–0.08 mg/kg and increased weekly up to a maximum twice-daily dosage of 0.12 mg/kg.

The most important adverse effect observed with mecasermin is hypoglycemia. To avoid hypoglycemia, the prescribing instructions require consumption of a carbohydrate-containing meal or snack 20 minutes before or after mecasermin administration. Several patients have experienced intracranial hypertension and asymptomatic elevation of liver enzymes.

GROWTH HORMONE ANTAGONISTS

The need for antagonists of GH stems from the tendency of GH-producing cells (somatotrophs) in the anterior pituitary to form GH-secreting tumors. Pituitary adenomas occur most commonly in adults. In adults, GH-secreting adenomas cause **acromegaly**, which is characterized by abnormal growth of cartilage and bone tissue, and many organs including skin, muscle, heart, liver, and the gastrointestinal tract. Acromegaly adversely affects the skeletal, muscular, cardiovascular, respiratory, and metabolic systems. When a GH-secreting adenoma occurs before the long bone epiphyses close, it leads to the rare condition, **gigantism**. Small GH-secreting adenomas can be treated with GH antagonists. These include somatostatin analogs and dopamine receptor agonists, which reduce the production of GH, and the novel GH receptor antagonist **pegvisomant**, which prevents GH from activating GH signaling pathways. Larger pituitary adenomas produce greater amounts of GH and also can impair visual and central nervous system function by encroaching on nearby brain structures. These are treated with transsphenoidal surgery or radiation.

Somatostatin Analogs

Somatostatin, a 14-amino-acid peptide (Figure 37–2), is found in the hypothalamus, other parts of the central nervous system, the pancreas, and other sites in the gastrointestinal tract. It inhibits the release of GH, TSH, glucagon, insulin, and gastrin.

Exogenous somatostatin is rapidly cleared from the circulation, with an initial half-life of 1–3 minutes. The kidney appears to play an important role in its metabolism and excretion.

Somatostatin has limited therapeutic usefulness because of its short duration of action and multiple effects in many secretory

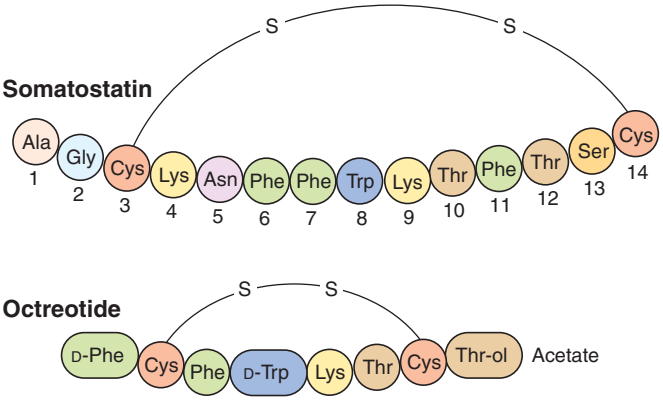

FIGURE 37–2 **Above:** Amino acid sequence of somatostatin. **Below:** Sequence of the synthetic analog, octreotide.

systems. A series of longer-acting somatostatin analogs that retain biologic activity have been developed. **Octreotide**, the most widely used somatostatin analog (Figure 37–2), is 45 times more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion. Because of this relatively reduced effect on pancreatic beta cells, hyperglycemia rarely occurs during treatment. The plasma elimination half-life of octreotide is about 80 minutes, 30 times longer than that of somatostatin.

Octreotide, 50–200 mcg given subcutaneously every 8 hours, reduces symptoms caused by a variety of hormone-secreting tumors: acromegaly; the carcinoid syndrome; gastrinoma; glucagonoma; nesidioblastosis; the watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome; and diabetic diarrhea. Somatostatin receptor scintigraphy, using radiolabeled octreotide, is useful in localizing neuroendocrine tumors having somatostatin receptors and helps predict the response to octreotide therapy. Octreotide is also useful for the acute control of bleeding from esophageal varices.

Octreotide acetate injectable long-acting suspension is a slow-release microsphere formulation. It is instituted only after a brief course of shorter-acting octreotide has been demonstrated to be effective and tolerated. Injections into alternate gluteal muscles are repeated at 4-week intervals in doses of 20–40 mg.

Adverse effects of octreotide therapy include nausea, vomiting, abdominal cramps, flatulence, and steatorrhea with bulky bowel movements. Biliary sludge and gallstones may occur after 6 months of use in 20–30% of patients. However, the yearly incidence of symptomatic gallstones is about 1%. Cardiac effects include sinus bradycardia (25%) and conduction disturbances (10%). Pain at the site of injection is common, especially with the long-acting octreotide suspension. Vitamin B_{12} deficiency may occur with long-term use of octreotide.

A long-acting formulation of **lanreotide**, another octapeptide somatostatin analog, was approved by the FDA in 2007 for treatment of acromegaly. Lanreotide appears to have effects comparable to those of octreotide on reducing GH levels and normalizing IGF-I concentrations.

Pegvisomant

Pegvisomant is a GH receptor antagonist used to treat acromegaly. It is the polyethylene glycol (PEG) derivative of a mutant GH, B2036. Like native GH, pegvisomant has two GH receptor binding sites. However, one of the pegvisomant GH receptor binding sites has increased affinity for the GH receptor, whereas its second GH receptor binding site has reduced affinity. This differential receptor affinity allows the initial step (GH receptor dimerization) but blocks the conformational changes required for signal transduction. Pegvisomant is a less potent GH receptor antagonist than is B2036, but pegylation reduces its clearance and improves its overall clinical effectiveness. When pegvisomant was administered subcutaneously to 160 patients with acromegaly daily for 12 months or more, serum levels of IGF-I fell into the normal range in 97%; two patients experienced growth of their GH-secreting pituitary tumors and two patients developed increases in liver enzymes.

THE GONADOTROPINS (FOLLICLE-STIMULATING HORMONE & LUTEINIZING HORMONE) & HUMAN CHORIONIC GONADOTROPIN

The gonadotropins are produced by a single type of pituitary cell, the gonadotroph. These hormones serve complementary functions in the reproductive process. In women, the principal function of FSH is to direct ovarian follicle development. Both FSH and LH are needed for ovarian steroidogenesis. In the ovary, LH stimulates androgen production by theca cells in the follicular stage of the menstrual cycle, whereas FSH stimulates the conversion by granulosa cells of androgens to estrogens. In the luteal phase of the menstrual cycle, estrogen and progesterone production is primarily under the control first of LH and then, if pregnancy occurs, under the control of human chorionic gonadotropin (hCG). Human chorionic gonadotropin is a placental protein nearly identical with LH; its actions are mediated through LH receptors.

In men, FSH is the primary regulator of spermatogenesis, whereas LH is the main stimulus for testosterone synthesis in Leydig cells. FSH helps maintain high local androgen concentrations in the vicinity of developing sperm by stimulating the production of androgen-binding protein in Sertoli cells. FSH also stimulates the conversion by Sertoli cells of testosterone to estrogen.

FSH, LH, and hCG are available in several pharmaceutical forms. They are used in states of infertility to stimulate spermatogenesis in men and to induce ovulation in women. Their most common clinical use is for the controlled ovulation hyperstimulation that is the cornerstone of assisted reproductive technologies such as in vitro fertilization (IVF, see below).

Chemistry & Pharmacokinetics

All three hormones—FSH, LH, and hCG—are heterodimers that share an identical α chain in addition to a distinct β chain that confers receptor specificity. The β chains of hCG and LH are nearly identical, and these two hormones are used interchangeably. All the gonadotropin preparations are administered by subcutaneous or intramuscular injection, usually on a daily basis. Half-lives vary by preparation and route of injection from 10 to 40 hours.

A. Menotropins

The first commercial gonadotropin product was extracted from the urine of postmenopausal women, which contains a substance with FSH-like properties (but with 4% of the potency of FSH) and an LH-like substance. This purified extract of FSH and LH is known as **menotropins**, or human menopausal gonadotropins **(hMG)**.

B. Follicle-Stimulating Hormone

Three forms of purified FSH are available. **Urofollitropin**, also known as uFSH, is a purified preparation of human FSH extracted from the urine of postmenopausal women. Virtually all

the LH activity has been removed through a form of immunoaffinity chromatography that uses anti-hCG antibodies. Two recombinant forms of FSH **(rFSH)** are also available: **follitropin alfa** and **follitropin beta.** The amino acid sequences of these two products are identical to that of human FSH. They differ from each other and urofollitropin in the composition of carbohydrate side chains. The rFSH preparations have a shorter half-life than preparations derived from human urine but stimulate estrogen secretion at least as efficiently and, in some studies, more efficiently. The rFSH preparations are considerably more expensive.

C. Luteinizing Hormone

Lutropin alfa, the recombinant form of human LH, was introduced in the United States in 2004. When given by subcutaneous injection, it has a half-life of about 10 hours. Lutropin has only been approved for use in combination with follitropin alfa for stimulation of follicular development in infertile women with profound LH deficiency. It has not been approved for use with the other preparations of FSH nor for simulating the endogenous LH surge that is needed to complete follicular development and precipitate ovulation.

D. Human Chorionic Gonadotropin

hCG is produced by the human placenta and excreted into the urine, whence it can be extracted and purified. It is a glycoprotein consisting of a 92-amino-acid α chain virtually identical to that of FSH, LH, and TSH, and a β chain of 145 amino acids that resembles that of LH except for the presence of a carboxyl terminal sequence of 30 amino acids not present in LH. **Choriogonadotropin alfa** (rhCG) is a recombinant form of hCG. Because of its greater consistency in biologic activity, rhCG is packaged and dosed on the basis of weight rather than units of activity. All of the other gonadotropins, including rFSH, are packaged and dosed on the basis of units of activity. The preparation of hCG that is purified from human urine is administered by intramuscular injection, whereas rhCG is administered by subcutaneous injection.

Pharmacodynamics

The gonadotropins and hCG exert their effects through G protein-coupled receptors. LH and FSH have complex effects on reproductive tissues in both sexes. In women, these effects change over the time course of a menstrual cycle as a result of a complex interplay between concentration-dependent effects of the gonadotropins, cross-talk between LH, FSH, and gonadal steroids, and the influence of other ovarian hormones. A coordinated pattern of FSH and LH secretion during the menstrual cycle (see Figure 40–1) is required for normal follicle development, ovulation, and pregnancy.

During the first 8 weeks of pregnancy, the progesterone and estrogen required to maintain pregnancy are produced by the ovarian corpus luteum. For the first few days after ovulation, the corpus luteum is maintained by maternal LH. However, as maternal LH concentrations fall owing to increasing concentrations of progesterone and estrogen, the corpus luteum will continue to function only if the role of maternal LH is taken over by hCG produced by the embryo and its new placenta.

Clinical Pharmacology

A. Ovulation Induction

The gonadotropins are used to induce ovulation in women with anovulation that is secondary to hypogonadotropic hypogonadism, polycystic ovary syndrome, obesity, and other causes. Because of the high cost of gonadotropins and the need for close monitoring during their administration, they are generally reserved for anovulatory women who fail to respond to other less complicated forms of treatment (eg, clomiphene; see Chapter 40). Gonadotropins are also used for **controlled ovarian hyperstimulation** in assisted reproductive technology procedures. A number of protocols make use of gonadotropins in ovulation induction and controlled ovulation hyperstimulation, and new protocols are continually being developed to improve the rates of success and to decrease the two primary risks of ovulation induction: multiple pregnancies and the **ovarian hyperstimulation syndrome** (OHSS; see below).

Although the details differ, all of these protocols are based on the complex physiology that underlies a normal menstrual cycle. Like a menstrual cycle, ovulation induction is discussed in relation to a cycle that begins on the first day of a menstrual bleed (Figure 37–3). Shortly after the first day (usually on day 3), daily injections with one of the FSH preparations (hMG, urofollitropin) are begun and are continued for approximately 7–12 days. In women with hypogonadotropic hypogonadism, follicle development requires treatment with a combination of FSH and LH because these women do not produce the basal level of LH that is required for adequate ovarian estrogen production and normal follicle development. The dose and duration of FSH treatment are based on the response as measured by the serum estradiol concentration and by ultrasound evaluation of ovarian follicle development and endometrial thickness. When exogenous gonadotropins are used to stimulate follicle development, there is risk of a premature endogenous surge in LH owing to the rapidly changing hormonal milieu. To prevent this, gonadotropins are almost always administered in conjunction with a drug that blocks the effects of endogenous GnRH—either continuous administration of a GnRH agonist, which down-regulates GnRH receptors or a GnRH receptor antagonist (see below and Figure 37–3).

When appropriate follicular maturation has occurred, the FSH and the GnRH agonist or GnRH antagonist injections are discontinued; the following day, hCG (5000–10,000 IU) is administered intramuscularly to induce final follicular maturation and, in ovulation induction protocols, ovulation. The hCG administration is followed by insemination in ovulation induction and by oocyte retrieval in assisted reproductive technology procedures. Because use of GnRH agonists or antagonists during the follicular phase of ovulation induction suppresses endogenous LH production, it is important to provide exogenous hormonal support of the luteal phase. In clinical trials, exogenous progesterone, hCG, or a combination of the two have been effective at providing adequate luteal support. However, progesterone is preferred for luteal

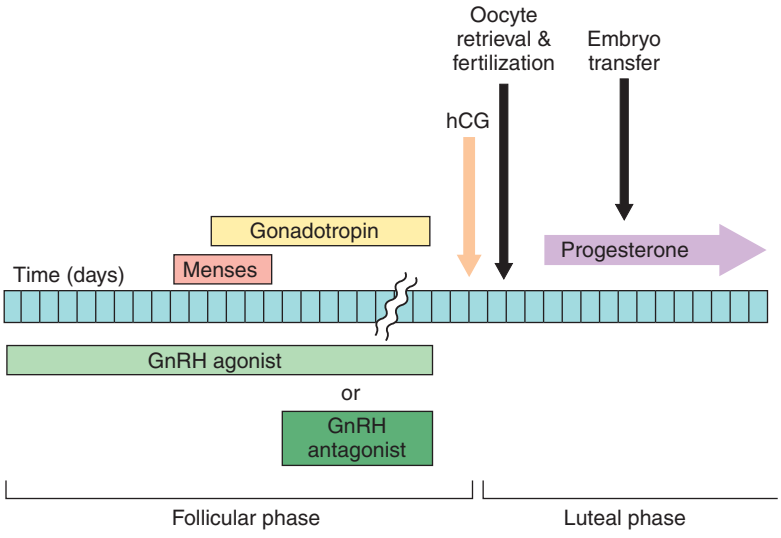

FIGURE 37–3 Controlled ovarian hyperstimulation in preparation for an assisted reproductive technology such as in vitro fertilization. Follicular phase: Follicle development is stimulated with gonadotropin injections that begin about 3 days after menses begin. When the follicles are ready, as assessed by measurement of serum estrogen concentration and ultrasound measurement of follicle size, final oocyte maturation is induced by an injection of hCG. Luteal phase: Shortly thereafter oocytes are retrieved and fertilized in vitro. The recipient's luteal phase is supported with injections of progesterone. To prevent a premature luteinizing-hormone surge, endogenous gonadotropin secretion is inhibited during the follicular phase with either a GnRH agonist or a GnRH antagonist. In most protocols, the GnRH agonist is started midway through the preceding luteal cycle.

support because hCG carries a higher risk of the ovarian hyperstimulation syndrome (see below).

B. Male Infertility

Most of the signs and symptoms of hypogonadism in males (eg, delayed puberty, retention of prepubertal secondary sex characteristics after puberty) can be adequately treated with exogenous androgen; however, treatment of infertility in hypogonadal men requires the activity of both LH and FSH. For many years, conventional therapy has consisted of initial treatment for 8–12 weeks with injections of 1000–2500 IU hCG several times per week. After the initial phase, hMG is injected at a dose of 75–150 units three times per week. In men with hypogonadal hypogonadism, it takes an average of 4–6 months of such treatment for sperm to appear in the ejaculate. With the more recent availability of urofollitropin, rFSH, and rLH, a number of alternative protocols have been developed. An advance that has indirectly benefited gonadotropin treatment of male infertility is intracytoplasmic sperm injection (ICSI), in which a single sperm is injected directly into a mature oocyte that has been retrieved after controlled ovarian hyperstimulation of a female partner. With the advent of ICSI, the minimum threshold of spermatogenesis required for pregnancy is greatly lowered.

C. Outdated Uses

Chorionic gonadotropin is approved for the treatment of prepubertal cryptorchidism. Prepubertal boys generally between 4 and 9 years of age were treated with IM injections of hCG for 2–6 weeks. However, this clinical use is no longer supported because the long-term efficacy of hormonal treatment of cryptorchidism (~ 20%) is much lower than the long-term efficacy of surgical treatment (> 95%), and because of concerns that early childhood treatment with hCG treatment has a negative impact on germ cells in addition to increasing the risk of precocious puberty.

In the United States, chorionic gonadotropin has a black-box warning against its use for weight loss. The use of hCG plus severe calorie restriction for weight loss was popularized by a publication in the 1950s claiming that the hCG selectively mobilizes body fat stores. This practice continues today, despite a preponderance of subsequent scientific evidence from placebo-controlled trials that hCG does not provide any weight loss benefit beyond the weight loss associated with severe calorie restriction alone.

Toxicity & Contraindications

In women treated with gonadotropins and hCG, the two most serious complications are the **ovarian hyperstimulation syndrome** and **multiple pregnancies.** Overstimulation of the ovary during ovulation induction often leads to uncomplicated ovarian enlargement that usually resolves spontaneously. The ovarian hyperstimulation syndrome is a more serious complication that occurs in 0.5–4% of patients. It is characterized by ovarian enlargement, ascites, hydrothorax, and hypovolemia, sometimes resulting in shock. Hemoperitoneum (from a ruptured ovarian cyst), fever, and arterial thromboembolism can occur.

The probability of multiple pregnancies is greatly increased when ovulation induction and assisted reproductive technologies

are used. In ovulation induction, the risk of a multiple pregnancy is estimated to be 15–20%, whereas the percentage of multiple pregnancies in the general population is closer to 1%. Multiple pregnancies carry an increased risk of complications, such as gestational diabetes, preeclampsia, and preterm labor. For in vitro fertilization procedures, the risk of a multiple pregnancy is primarily determined by the number of embryos transferred to the recipient. A strong trend in recent years has been to transfer fewer embryos.

Other reported adverse effects of gonadotropin treatment are headache, depression, edema, precocious puberty, and (rarely) production of antibodies to hCG. In men treated with gonadotropins, the risk of gynecomastia is directly correlated with the level of testosterone produced in response to treatment. An association between ovarian cancer, infertility, and fertility drugs has been reported. However, it is not known which, if any, fertility drugs are causally related to cancer.

GONADOTROPIN-RELEASING HORMONE & ITS ANALOGS

Gonadotropin-releasing hormone is secreted by neurons in the hypothalamus. It travels through the hypothalamic-pituitary venous portal plexus to the anterior pituitary, where it binds to G protein-coupled receptors on the plasma membranes of gonadotroph cells. *Pulsatile* GnRH secretion is required to stimulate the gonadotroph cell to produce and release LH and FSH.

Sustained *nonpulsatile* administration of GnRH or GnRH analogs *inhibits* the release of FSH and LH by the pituitary in both women and men, resulting in hypogonadism. GnRH agonists are used to produce gonadal suppression in men with prostate cancer. They are also used in women who are undergoing assisted reproductive technology procedures or who have a gynecologic problem that is benefited by ovarian suppression.

Chemistry & Pharmacokinetics

A. Structure

GnRH is a decapeptide found in all mammals. **Gonadorelin** is an acetate salt of synthetic human GnRH. Synthetic analogs of GnRH include **goserelin, histrelin, leuprolide, nafarelin,** and **triptorelin.** These analogs all have D-amino acids at position 6, and all but nafarelin have ethylamide substituted for glycine at position 10. Both modifications make them more potent and longer-lasting than native GnRH and gonadorelin.

B. Pharmacokinetics

Gonadorelin can be administered intravenously or subcutaneously. GnRH analogs can be administered subcutaneously, intramuscularly, via nasal spray (nafarelin), or as a subcutaneous implant. The half-life of intravenous gonadorelin is 4 minutes, and the half-lives of subcutaneous and intranasal GnRH analogs are approximately 3 hours. The duration of clinical uses of GnRH agonists varies from a few days for ovulation induction to a number of years for treatment of metastatic prostate cancer. Therefore, preparations have been developed with a range of durations of action from several hours (for daily administration) to 1, 4, 6, or 12 months (depot forms).

Pharmacodynamics

The physiologic actions of GnRH exhibit complex dose-response relationships that change dramatically from the fetal period through the end of puberty. This is not surprising in view of the complex role that GnRH plays in normal reproduction, particularly in female reproduction. Pulsatile GnRH release occurs and is responsible for stimulating LH and FSH production during the fetal and neonatal period. Subsequently, from the age of 2 years until the onset of puberty, GnRH secretion falls off and the pituitary simultaneously exhibits very low sensitivity to GnRH. Just before puberty, an increase in the frequency and amplitude of GnRH release occurs and then, in early puberty, pituitary sensitivity to GnRH increases, which is due in part to the effect of increasing concentrations of gonadal steroids. In females, it usually takes several months to a year after the onset of puberty for the hypothalamic-pituitary system to produce an LH surge and ovulation. By the end of puberty, the system is well established so that menstrual cycles proceed at relatively constant intervals. The amplitude and frequency of GnRH pulses vary in a regular pattern through the menstrual cycle with the highest amplitudes occurring during the luteal phase and the highest frequency occurring late in the follicular phase. Lower pulse frequencies favor FSH secretion, whereas higher pulse frequencies favor LH secretion. Gonadal steroids as well as the peptide hormones activin and inhibin have complex modulatory effects on the gonadotropin response to GnRH.

In the pharmacologic use of GnRH and its analogs, pulsatile intravenous administration of gonadorelin every 1–4 hours stimulates FSH and LH secretion. Continuous administration of gonadorelin or its longer-acting analogs produces a biphasic response. During the first 7–10 days, an agonist effect results in increased concentrations of gonadal hormones in males and females; this initial phase is referred to as a *flare*. After this period, the continued presence of GnRH results in an inhibitory action that manifests as a drop in the concentration of gonadotropins and gonadal steroids. The inhibitory action is due to a combination of receptor down-regulation and changes in the signaling pathways activated by GnRH.

Clinical Pharmacology

The GnRH agonists are occasionally used for stimulation of gonadotropin production. They are used far more commonly for suppression of gonadotropin release.

A. Stimulation

1. Female infertility—In the current era of widespread availability of gonadotropins and assisted reproductive technology, the use of pulsatile GnRH administration to treat infertility is uncommon. Although pulsatile GnRH is less likely than gonadotropins

to cause multiple pregnancies and the ovarian hyperstimulation syndrome, the inconvenience and cost associated with continuous use of an intravenous pump and difficulties obtaining native GnRH (gonadorelin) are barriers to pulsatile GnRH. When this approach is used, a portable battery-powered programmable pump and intravenous tubing deliver pulses of gonadorelin every 90 minutes.

Gonadorelin or a GnRH agonist analog can be used to initiate an LH surge and ovulation in women with infertility who are undergoing ovulation induction with gonadotropins. Traditionally, hCG has been used to initiate ovulation in this situation. However, there is some evidence that gonadorelin or a GnRH agonist is less likely than hCG to cause multiple ova to be released and less likely to cause the ovarian hyperstimulation syndrome.

2. Male infertility—It is possible to use pulsatile gonadorelin for infertility in men with hypothalamic hypogonadotropic hypogonadism. A portable pump infuses gonadorelin intravenously every 90 minutes. Serum testosterone levels and semen analyses must be done regularly. At least 3–6 months of pulsatile infusions are required before significant numbers of sperm are seen. As described above, treatment of hypogonadotropic hypogonadism is more commonly done with hCG and hMG or their recombinant equivalents.

3. Diagnosis of LH responsiveness—GnRH can be useful in determining whether delayed puberty in a hypogonadotropic adolescent is due to constitutional delay or to hypogonadotropic hypogonadism. The LH response (but not the FSH response) to a single dose of GnRH can distinguish between these two conditions. Serum LH levels are measured before and at various times after an intravenous or subcutaneous bolus of GnRH. An increase in serum LH with a peak that exceeds 15.6 mIU/mL is normal and suggests impending puberty. An impaired LH response suggests hypogonadotropic hypogonadism due to either pituitary or hypothalamic disease, but does not rule out constitutional delay of adolescence.

B. Suppression of Gonadotropin Production

1. Controlled ovarian hyperstimulation—In the controlled ovarian hyperstimulation that provides multiple mature oocytes for assisted reproductive technologies such as in vitro fertilization, it is critical to suppress an endogenous LH surge that could prematurely trigger ovulation. This suppression is most commonly achieved by daily subcutaneous injections of leuprolide or daily nasal applications of nafarelin. For leuprolide, treatment is commonly initiated with 1.0 mg daily for about 10 days or until menstrual bleeding occurs. At that point, the dose is reduced to 0.5 mg daily until hCG is administered (Figure 37–3). For nafarelin, the beginning dosage is generally 400 mcg twice a day, which is decreased to 200 mcg when menstrual bleeding occurs. In women who respond poorly to the standard protocol, alternative protocols that use shorter courses and lower doses of GnRH agonists may improve the follicular response to gonadotropins.

2. Endometriosis—Endometriosis is a syndrome of cyclical abdominal pain in premenopausal women that is due to the presence of estrogen-sensitive endometrium-like tissue outside the uterus. The pain of endometriosis is often reduced by abolishing exposure to the cyclical changes in the concentrations of estrogen and progesterone that are a normal part of the menstrual cycle. The ovarian suppression induced by continuous treatment with a GnRH agonist greatly reduces estrogen and progesterone concentrations and prevents cyclical changes. The preferred duration of treatment with a GnRH agonist is limited to 6 months because ovarian suppression beyond this period can result in decreased bone density. Leuprolide, goserelin, and nafarelin are approved for this indication. Leuprolide and goserelin are administered as depot preparations that provide 1 or 3 months of continuous GnRH agonist activity. Nafarelin is administered twice daily as a nasal spray at a dose of 0.2 mg per spray.

3. Uterine leiomyomata (uterine fibroids)—Uterine leiomyomata are benign, estrogen-sensitive, fibrous growths in the uterus that can cause menorrhagia, with associated anemia and pelvic pain. Treatment for 3–6 months with a GnRH agonist reduces fibroid size and, when combined with supplemental iron, improves anemia. Leuprolide, goserelin, and nafarelin are approved for this indication. The doses and routes of administration are similar to those described for treatment of endometriosis.

4. Prostate cancer—Antiandrogen therapy is the primary medical therapy for prostate cancer. Combined antiandrogen therapy with continuous GnRH agonist and an androgen receptor antagonist such as flutamide (see Chapter 40) is as effective as surgical castration in reducing serum testosterone concentrations and effects. Leuprolide, goserelin, histrelin, and triptorelin are approved for this indication. The preferred formulation is one of the long-acting depot forms that provide 1, 3, 4, 6, or 12 months of active drug therapy. During the first 7–10 days of GnRH analog therapy, serum testosterone levels increase because of the agonist action of the drug; this can precipitate pain in patients with bone metastases, and tumor growth and neurologic symptoms in patients with vertebral metastases. It can also temporarily worsen symptoms of urinary obstruction. Such tumor flares can usually be avoided with the concomitant administration of bicalutamide or one of the other androgen receptor antagonists (see Chapter 40). Within about 2 weeks, serum testosterone levels fall to the hypogonadal range.

5. Central precocious puberty—Continuous administration of a GnRH agonist is indicated for treatment of central precocious puberty (onset of secondary sex characteristics before 7–8 years in girls or 9 years in boys). Before embarking on treatment with a GnRH agonist, one must confirm central precocious puberty by demonstrating a pubertal gonadotropin response to GnRH or a "test dose" of a GnRH analog. Treatment is typically indicated in a child whose final height would be otherwise significantly compromised (as evidenced by a significantly advanced bone age) or in whom the development of pubertal secondary sexual characteristics

or menses causes significant emotional distress. While central precocious puberty is most often idiopathic, it is important to rule out central nervous system pathology with MRI imaging of the hypothalamic-pituitary area.

Treatment is most commonly carried out with either a monthly intramuscular depot injection of leuprolide acetate or with a once-yearly implant of histrelin acetate. Daily subcutaneous regimens and multiple daily nasal spray regimens of GnRH agonists are also available. Treatment with a GnRH agonist is generally continued to age 11 in females and age 12 in males.

6. Other—Other clinical uses for the gonadal suppression provided by continuous GnRH agonist treatment include advanced breast and ovarian cancer; thinning of the endometrial lining in preparation for an endometrial ablation procedure in women with dysfunctional uterine bleeding; and treatment of amenorrhea and infertility in women with polycystic ovary disease. Recently published clinical practice guidelines recommend the use of continuous GnRH agonist administration in early pubertal transgender adolescents to block endogenous puberty prior to subsequent treatment with cross-gender gonadal hormones.

Toxicity

Gonadorelin can cause headache, light-headedness, nausea, and flushing. Local swelling often occurs at subcutaneous injection sites. Generalized hypersensitivity dermatitis has occurred after long-term subcutaneous administration. Rare acute hypersensitivity reactions include bronchospasm and anaphylaxis. Sudden pituitary apoplexy and blindness have been reported following administration of GnRH to a patient with a gonadotropin-secreting pituitary tumor.

Continuous treatment of women with a GnRH analog (leuprolide, nafarelin, goserelin) causes the typical symptoms of menopause, which include hot flushes, sweats, and headaches. Depression, diminished libido, generalized pain, vaginal dryness, and breast atrophy may also occur. Ovarian cysts may develop within the first 2 months of therapy and generally resolve after an additional 6 weeks; however, the cysts may persist and require discontinuation of therapy. Reduced bone density and osteoporosis may occur with prolonged use, so patients should be monitored with bone densitometry before repeated treatment courses. Depending on the condition being treated with the GnRH agonist, it may be possible to ameliorate the signs and symptoms of the hypoestrogenic state without losing clinical efficacy by adding back a small dose of a progestin alone or in combination with a low dose of an estrogen. Contraindications to the use of GnRH agonists in women include pregnancy and breast-feeding.

In men treated with continuous GnRH agonist administration, adverse effects include hot flushes and sweats, edema, gynecomastia, decreased libido, decreased hematocrit, reduced bone density, asthenia, and injection site reactions. GnRH analog treatment of children is generally well tolerated. However, temporary exacerbation of precocious puberty may occur during the first few weeks of therapy. Nafarelin nasal spray may cause or aggravate sinusitis.

GNRH RECEPTOR ANTAGONISTS

Three synthetic decapeptides that function as competitive antagonists of GnRH receptors are available for clinical use. **Ganirelix, cetrorelix,** and **degarelix** inhibit the secretion of FSH and LH in a dose-dependent manner. Ganirelix and cetrorelix are approved for use in controlled ovarian hyperstimulation procedures, whereas degarelix is approved for men with advanced prostate cancer.

Pharmacokinetics

Ganirelix and cetrorelix are absorbed rapidly after subcutaneous injection. Administration of 0.25 mg daily maintains GnRH antagonism. Alternatively, a single 3.0-mg dose of cetrorelix suppresses LH secretion for 96 hours. Degarelix therapy is initiated with 240 mg administered as two subcutaneous injections. Maintenance dosing is with an 80-mg subcutaneous injection every 28 days.

Clinical Pharmacology

A. Suppression of Gonadotropin Production

GnRH antagonists are approved for preventing the LH surge during controlled ovarian hyperstimulation. They offer several advantages over continuous treatment with a GnRH agonist. Because GnRH antagonists produce an immediate antagonist effect, their use can be delayed until day 6–8 of the in vitro fertilization cycle (Figure 37–3), and thus the duration of administration is shorter. They also appear to have a less negative impact on the ovarian response to gonadotropin stimulation, which permits a decrease in the total duration and dose of gonadotropin. Finally, GnRH antagonists are associated with a lower risk of ovarian hyperstimulation syndrome, which can lead to cycle cancellation. On the other hand, because their antagonist effects reverse more quickly after their discontinuation, adherence to the treatment regimen is critical. The antagonists produce a more complete suppression of gonadotropin secretion than agonists. There is concern that the suppression of LH may inhibit ovarian steroidogenesis to an extent that impairs follicular development when recombinant or the purified form of FSH is used during the follicular phase of an in vitro fertilization cycle. Clinical trials have shown a slightly lower rate of pregnancy in in vitro fertilization cycles that used GnRH antagonist treatment compared with cycles that used GnRH agonist treatment.

B. Advanced Prostate Cancer

Degarelix is approved for the treatment of symptomatic advanced prostate cancer. This GnRH antagonist reduces concentrations of gonadotropins and androgens more rapidly than GnRH agonists and avoids the testosterone surge seen with GnRH agonist therapy.

Toxicity

When used for controlled ovarian hyperstimulation, ganirelix and cetrorelix are well tolerated. The most common adverse effects are

nausea and headache. During the treatment of men with prostate cancer, degarelix caused injection-site reactions and increases in liver enzymes. Like continuous treatment with a GnRH agonist, degarelix leads to signs and symptoms of androgen deprivation, including hot flushes and weight gain.

PROLACTIN

Prolactin is a 198-amino-acid peptide hormone produced in the anterior pituitary. Its structure resembles that of GH. Prolactin is the principal hormone responsible for lactation. Milk production is stimulated by prolactin when appropriate circulating levels of estrogens, progestins, corticosteroids, and insulin are present. A deficiency of prolactin—which can occur in rare states of pituitary deficiency—is manifested by failure to lactate or by a luteal phase defect. In rare cases of hypothalamic destruction, prolactin levels may be elevated as a result of impaired transport of dopamine (prolactin-inhibiting hormone) to the pituitary. Much more commonly, however, prolactin is elevated as a result of prolactin-secreting adenomas. Hyperprolactinemia produces a syndrome of amenorrhea and galactorrhea in women, and loss of libido and infertility in men. In the case of large tumors (macroadenomas), it can be associated with symptoms of a pituitary mass, including visual changes due to compression of the optic nerves. The hypogonadism and infertility associated with hyperprolactinemia result from inhibition of GnRH release.

No preparation of prolactin is available for use in prolactin-deficient patients. For patients with symptomatic hyperprolactinemia, inhibition of prolactin secretion can be achieved with dopamine agonists, which act in the pituitary to inhibit prolactin release.

DOPAMINE AGONISTS

Adenomas that secrete excess prolactin usually retain the sensitivity to inhibition by dopamine exhibited by the normal pituitary. **Bromocriptine** and **cabergoline** are ergot derivatives (see Chapters 16 and 28) with a high affinity for dopamine D_2 receptors. **Quinagolide,** a drug approved in Europe, is a nonergot agent with similarly high D_2 receptor affinity. The chemical structure and pharmacokinetic features of ergot alkaloids are presented in Chapter 16.

Dopamine agonists suppress prolactin release very effectively in patients with hyperprolactinemia. GH release is reduced in patients with acromegaly, although not as effectively. Bromocriptine has also been used in Parkinson's disease to improve motor function and reduce levodopa requirements (see Chapter 28). Newer, nonergot D_2 agonists used in Parkinson's disease (pramipexole and ropinirole; see Chapter 28) have been reported to interfere with lactation, but they are not approved for use in hyperprolactinemia.

Pharmacokinetics

All available dopamine agonists are active as oral preparations, and all are eliminated by metabolism. They can also be absorbed systemically after vaginal insertion of tablets. Cabergoline, with a half-life of approximately 65 hours, has the longest duration of action. Quinagolide has a half-life of about 20 hours, whereas the half-life of bromocriptine is about 7 hours. After vaginal administration, serum levels peak more slowly.

Clinical Pharmacology

A. Hyperprolactinemia

A dopamine agonist is the standard medical treatment for hyperprolactinemia. These drugs shrink pituitary prolactin-secreting tumors, lower circulating prolactin levels, and restore ovulation in approximately 70% of women with microadenomas and 30% of women with macroadenomas (Figure 37–4). Cabergoline is initiated at 0.25 mg twice weekly orally or vaginally. It can be increased gradually, according to serum prolactin determinations, up to a maximum of 1 mg twice weekly. Bromocriptine is generally taken daily after the evening meal at the initial dose of 1.25 mg; the dose

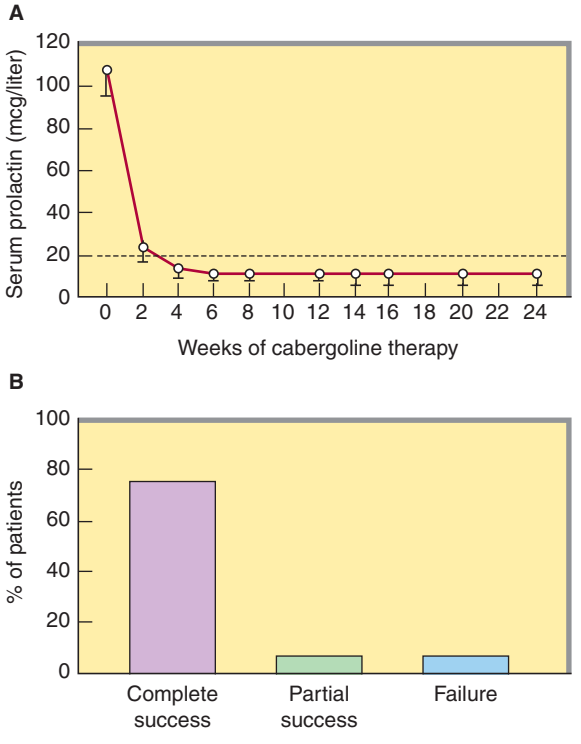

FIGURE 37–4 Results from a clinical trial of cabergoline in women with hyperprolactinemia and anovulation. **A:** The dotted line indicates the upper limit of normal serum prolactin concentrations. **B:** Complete success was defined as pregnancy or at least two consecutive menses with evidence of ovulation at least once. Partial success was two menstrual cycles without evidence of ovulation or just one ovulatory cycle. The most common reasons for withdrawal from the trial were nausea, headache, dizziness, abdominal pain, and fatigue. (Modified and reproduced, with permission, from Webster J et al: A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med 1994;331:904.)

is then increased as tolerated. Most patients require 2.5–7.5 mg daily. Long-acting oral bromocriptine formulations (Parlodel SRO) and intramuscular formulations (Parlodel L.A.R.) are available outside the United States.

B. Physiologic Lactation

Dopamine agonists were used in the past to prevent breast engorgement when breast-feeding was not desired. Their use for this purpose has been discouraged because of toxicity (see Toxicity & Contraindications).

C. Acromegaly

A dopamine agonist alone or in combination with pituitary surgery, radiation therapy, or octreotide administration can be used to treat acromegaly. The doses required are higher than those used to treat hyperprolactinemia. For example, patients with acromegaly require 20–30 mg/d of bromocriptine and seldom respond adequately to bromocriptine alone unless the pituitary tumor secretes prolactin as well as GH.

Toxicity & Contraindications

Dopamine agonists can cause nausea, headache, light-headedness, orthostatic hypotension, and fatigue. Psychiatric manifestations occasionally occur, even at lower doses, and may take months to resolve. Erythromelalgia occurs rarely. High dosages of ergot-derived preparations can cause cold-induced peripheral digital vasospasm. Pulmonary infiltrates have occurred with chronic high-dosage therapy. Cabergoline appears to cause nausea less often than bromocriptine. Vaginal administration can reduce nausea, but may cause local irritation.

Dopamine agonist therapy during the early weeks of pregnancy has not been associated with an increased risk of spontaneous abortion or congenital malformations. Although there has been a longer experience with the safety of bromocriptine during early pregnancy, there is growing evidence that cabergoline is also safe in women with macroadenomas who must continue a dopamine agonist during pregnancy. In patients with small pituitary adenomas, dopamine agonist therapy is discontinued upon conception because growth of microadenomas during pregnancy is rare. Patients with very large adenomas require vigilance for tumor progression and often require a dopamine agonist throughout pregnancy. There have been rare reports of stroke or coronary thrombosis in postpartum women taking bromocriptine to suppress postpartum lactation.

POSTERIOR PITUITARY HORMONES

The two posterior pituitary hormones—vasopressin and oxytocin—are synthesized in neuronal cell bodies in the hypothalamus and transported via their axons to the posterior pituitary, where they are stored and then released into the circulation. Each has limited but important clinical uses.

OXYTOCIN

Oxytocin is a peptide hormone secreted by the posterior pituitary that participates in labor and delivery and elicits milk ejection in lactating women. During the second half of pregnancy, uterine smooth muscle shows an increase in the expression of oxytocin receptors and becomes increasingly sensitive to the stimulant action of endogenous oxytocin. Pharmacologic concentrations of oxytocin powerfully stimulate uterine contraction.

Chemistry & Pharmacokinetics

A. Structure

Oxytocin is a 9-amino-acid peptide with an intrapeptide disulfide cross-link (Figure 37–5). Its amino acid sequence differs from that of vasopressin at positions 3 and 8.

B. Absorption, Metabolism, and Excretion

Oxytocin is administered intravenously for initiation and augmentation of labor. It also can be administered intramuscularly for control of postpartum bleeding. Oxytocin is not bound to plasma proteins and is eliminated by the kidneys and liver, with a circulating half-life of 5 minutes.

Pharmacodynamics

Oxytocin acts through G protein-coupled receptors and the phosphoinositide-calcium second-messenger system to contract uterine smooth muscle. Oxytocin also stimulates the release of prostaglandins and leukotrienes that augment uterine contraction. Oxytocin in small doses increases both the frequency and the force of uterine contractions. At higher doses, it produces sustained contraction.

Oxytocin also causes contraction of myoepithelial cells surrounding mammary alveoli, which leads to milk ejection. Without

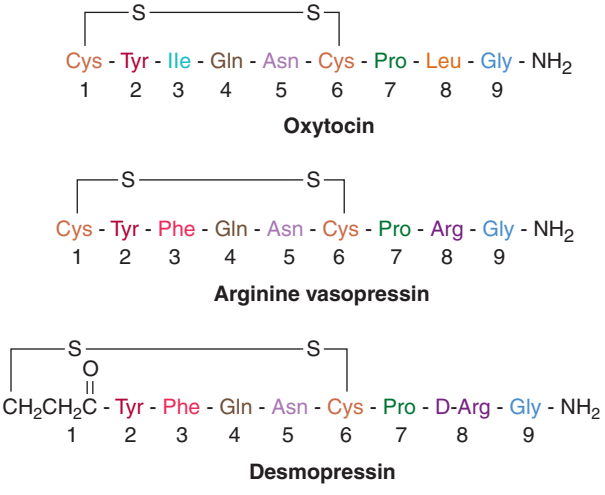

FIGURE 37–5 Posterior pituitary hormones and desmopressin. (Modified and reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 21st ed. McGraw-Hill, 2003.)

oxytocin-induced contraction, normal lactation cannot occur. At high concentrations, oxytocin has weak antidiuretic and pressor activity due to activation of vasopressin receptors.

Clinical Pharmacology

Oxytocin is used to induce labor for conditions requiring early vaginal delivery such as Rh problems, maternal diabetes, preeclampsia, or ruptured membranes. It is also used to augment abnormal labor that is protracted or displays an arrest disorder. Oxytocin has several uses in the immediate postpartum period, including the control of uterine hemorrhage after vaginal or cesarean delivery. It is sometimes used during second-trimester abortions.

Before delivery, oxytocin is usually administered intravenously via an infusion pump with appropriate fetal and maternal monitoring. For induction of labor, an initial infusion rate of 0.5–2 mU/min is increased every 30–60 minutes until a physiologic contraction pattern is established. The maximum infusion rate is 20 mU/min. For postpartum uterine bleeding, 10–40 units are added to 1 L of 5% dextrose, and the infusion rate is titrated to control uterine atony. Alternatively, 10 units of oxytocin can be administered by intramuscular injection after delivery of the placenta.

During the antepartum period, oxytocin induces uterine contractions that transiently reduce placental blood flow to the fetus. The oxytocin challenge test measures the fetal heart rate response to a standardized oxytocin infusion and provides information about placental circulatory reserve. An abnormal response, seen as late decelerations in the fetal heart rate, indicates fetal hypoxia and may warrant immediate cesarean delivery.

Toxicity & Contraindications

When oxytocin is used judiciously, serious toxicity is rare. The toxicity that does occur is due either to excessive stimulation of uterine contractions or to inadvertent activation of vasopressin receptors. Excessive stimulation of uterine contractions before delivery can cause fetal distress, placental abruption, or uterine rupture. These complications can be detected early by means of standard fetal monitoring equipment. High concentrations of oxytocin with activation of vasopressin receptors can cause excessive fluid retention, or water intoxication, leading to hyponatremia, heart failure, seizures, and death. Bolus injections of oxytocin can cause hypotension. To avoid hypotension, oxytocin is administered intravenously as dilute solutions at a controlled rate.

Contraindications to oxytocin include fetal distress, prematurity, abnormal fetal presentation, cephalopelvic disproportion, and other predispositions for uterine rupture.

OXYTOCIN ANTAGONIST

Atosiban is an antagonist of the oxytocin receptor that has been approved outside the United States as a treatment for preterm labor (tocolysis). Atosiban is a modified form of oxytocin that is administered by IV infusion for 2–48 hours. In a small number of published clinical trials, atosiban appears to be as effective as β-adrenoceptor-agonist tocolytics and to produce fewer adverse effects. In 1998, however, the FDA decided not to approve atosiban based on concerns about efficacy and safety.

VASOPRESSIN (ANTIDIURETIC HORMONE, ADH)

Vasopressin is a peptide hormone released by the posterior pituitary in response to rising plasma tonicity or falling blood pressure. Vasopressin possesses antidiuretic and vasopressor properties. A deficiency of this hormone results in diabetes insipidus (see Chapters 15 and 17).

Chemistry & Pharmacokinetics

A. Structure

Vasopressin is a nonapeptide with a 6-amino-acid ring and a 3-amino-acid side chain. The residue at position 8 is arginine in humans and in most other mammals except pigs and related species, whose vasopressin contains lysine at position 8 (Figure 37–5). Desmopressin acetate (DDAVP, 1-desamino-8-D-arginine vasopressin) is a long-acting synthetic analog of vasopressin with minimal pressor activity and an antidiuretic-to-pressor ratio 4000 times that of vasopressin. **Desmopressin** is modified at position 1 and contains a D-amino acid at position 8. Like vasopressin and oxytocin, desmopressin has a disulfide linkage between positions 1 and 6.

B. Absorption, Metabolism, and Excretion

Vasopressin is administered by intravenous or intramuscular injection. The half-life of circulating vasopressin is approximately 15 minutes, with renal and hepatic metabolism via reduction of the disulfide bond and peptide cleavage.

Desmopressin can be administered intravenously, subcutaneously, intranasally, or orally. The half-life of circulating desmopressin is 1.5–2.5 hours. Nasal desmopressin is available as a unit dose spray that delivers 0.1 mL per spray; it is also available with a calibrated nasal tube that can be used to deliver a more precise dose. Nasal bioavailability of desmopressin is 3–4%, whereas oral bioavailability is less than 1%.

Pharmacodynamics

Vasopressin activates two subtypes of G protein-coupled receptors (see Chapter 17). V_1 receptors are found on vascular smooth muscle cells and mediate vasoconstriction via the coupling protein G_q. V_2 receptors are found on renal tubule cells and reduce diuresis through increased water permeability and water resorption in the collecting tubules via G_s. Extrarenal V_2-like receptors regulate the release of coagulation factor VIII and von Willebrand factor.

Clinical Pharmacology

Vasopressin and desmopressin are treatments of choice for pituitary diabetes insipidus. The dosage of desmopressin is 10–40 mcg

(0.1–0.4 mL) in two to three divided doses as a nasal spray or, as an oral tablet, 0.1–0.2 mg two to three times daily. The dosage by injection is 1–4 mcg (0.25–1 mL) every 12–24 hours as needed for polyuria, polydipsia, or hypernatremia. Bedtime desmopressin therapy, by intranasal or oral administration, ameliorates nocturnal enuresis by decreasing nocturnal urine production. Vasopressin infusion is effective in some cases of esophageal variceal bleeding and colonic diverticular bleeding.

Desmopressin is also used for the treatment of coagulopathy in hemophilia A and von Willebrand's disease (see Chapter 34).

Toxicity & Contraindications

Headache, nausea, abdominal cramps, agitation, and allergic reactions occur rarely. Overdosage can result in hyponatremia and seizures.

Vasopressin (but not desmopressin) can cause vasoconstriction and should be used cautiously in patients with coronary artery disease. Nasal insufflation of desmopressin may be less effective when nasal congestion is present.

VASOPRESSIN ANTAGONISTS

A group of nonpeptide antagonists of vasopressin receptors is being investigated for use in patients with hyponatremia or acute heart failure, which is often associated with elevated concentrations of vasopressin. **Conivaptan** has high affinity for both V_{1a} and V_2 receptors. **Tolvaptan** has a 30-fold higher affinity for V_2 than for V_1 receptors. In several clinical trials, both agents relieved symptoms and reduced objective signs of hyponatremia and heart failure. Conivaptan and tolvaptan are approved by the FDA for intravenous administration in hyponatremia. Several other nonselective nonpeptide vasopressin receptor antagonists are being investigated for these conditions (see Chapter 15).

SUMMARY Hypothalamic & Pituitary Hormones[1]

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GROWTH HORMONE (GH)				
• Somatropin	Recombinant form of human GH • acts through GH receptors to increase production of IGF-I	Restores normal growth and metabolic GH effects in GH-deficient individuals • increases final adult height in some children with short stature not due to GH deficiency	Replacement in GH deficiency • increased final adult height in children with certain conditions associated with short stature (see Table 37–4) • wasting in HIV infection • short bowel syndrome	SC injection • *Toxicity:* Pseudotumor cerebri, slipped capital femoral epiphysis, edema, hyperglycemia, progression of scoliosis, risk of asphyxia in severely obese patients with Prader-Willi syndrome and upper airway obstruction or sleep apnea
IGF-I AGONIST				
• Mecasermin	Recombinant form of IGF-I that stimulates IGF-I receptors	Improves growth and metabolic IGF-I effects in individuals with IGF-I deficiency due to severe GH resistance	Replacement in IGF-I deficiency that is not responsive to exogenous GH	SC injection • *Toxicity:* Hypoglycemia, intracranial hypertension, increased liver enzymes
SOMATOSTATIN ANALOGS				
• Octreotide	Agonist at somatostatin receptors	Inhibits production of GH and, to a lesser extent, of TSH, glucagon, insulin, and gastrin	Acromegaly and several other hormone-secreting tumors • acute control of bleeding from esophageal varices	SC or IV injection • long-acting formulation injected IM monthly • *Toxicity:* Gastrointestinal disturbances, gallstones, bradycardia, cardiac conduction problems
• *Lanreotide: Similar to octreotide; available as a long-acting formulation for acromegaly*				
GH RECEPTOR ANTAGONIST				
• Pegvisomant	Blocks GH receptors	Ameliorates effects of excess GH production	Acromegaly	SC injection • *Toxicity:* Increased liver enzymes

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
GONADOTROPINS: FOLLICLE-STIMULATING HORMONE (FSH) ANALOGS				
• Follitropin alfa	Activates FSH receptors	Mimics effects of endogenous FSH	Controlled ovulation hyperstimulation in women • infertility due to hypogonadotropic hypogonadism in men	SC injection • *Toxicity:* Ovarian hyperstimulation syndrome and multiple pregnancies in women • gynecomastia in men • headache, depression, edema in both sexes
• *Follitropin beta: A recombinant product with the same peptide sequence as follitropin alfa but differs in its carbohydrate side chains*				
• *Urofollitropin: Human FSH purified from the urine of postmenopausal women*				
• *Menotropins (hMG): Extract of the urine of postmenopausal women; contains both FSH and LH activity*				
GONADOTROPINS: LUTEINIZING HORMONE (LH) ANALOGS				
• Human chorionic gonadotropin (hCG)	Agonist at LH receptors	Mimics effects of endogenous LH	Initiation of ovulation during controlled ovulation hyperstimulation • ovarian follicle development in women with hypogonadotropic hypogonadism • male hypogonadotropic hypogonadism	IM injection • *Toxicity:* Ovarian hyperstimulation syndrome and multiple pregnancies in women • gynecomastia in men • headache, depression, edema in both sexes
• *Choriogonadotropin alfa: Recombinant form of hCG*				
• *Lutropin: Recombinant form of human LH*				
• *Menotropins (hMG): Extract of the urine of postmenopausal women that contains both FSH and LH activity*				
GONADOTROPIN-RELEASING HORMONE (GNRH) ANALOGS				
• Leuprolide	Agonist of GnRH receptors	Increased LH and FSH secretion with intermittent administration • reduced LH and FSH secretion with prolonged continuous administration	Ovarian suppression • controlled ovarian hyperstimulation • central precocious puberty • block of endogenous puberty in some transgender/gender variant early pubertal adolescents • advanced prostate cancer	Administered IV, SC, IM, or intranasally • depot formulations are available • *Toxicity:* Headache, light-headedness, nausea, injection site reactions • symptoms of hypogonadism with continuous treatment
• *Gonadorelin: Synthetic human GnRH*				
• *Other GnRH analogs: Goserelin, histrelin, nafarelin, and triptorelin*				
GONADOTROPIN-RELEASING HORMONE (GNRH) RECEPTOR ANTAGONISTS				
• Ganirelix	Blocks GnRH receptors	Reduces endogenous production of LH and FSH	Prevention of premature LH surges during controlled ovulation hyperstimulation	SC injection • *Toxicity:* Nausea, headache
• *Cetrorelix: Similar to ganirelix, approved for controlled ovarian hyperstimulation*				
• *Degarelix: Approved for advanced prostate cancer*				
DOPAMINE AGONISTS				
• Bromocriptine	Activates dopamine D_2 receptors	Suppresses pituitary secretion of prolactin and, less effectively, GH • dopaminergic effects on CNS motor control and behavior	Treatment of hyperprolactinemia • acromegaly • Parkinson's disease (see Chapter 28)	Administered orally or, for hyperprolactinemia, vaginally • *Toxicity:* Gastrointestinal disturbances, orthostatic hypotension, headache, psychiatric disturbances, vasospasm and pulmonary infiltrates in high doses
• *Cabergoline: Another ergot derivative with similar effects*				
OXYTOCIN	Activates oxytocin receptors	Increased uterine contractions	Induction and augmentation of labor • control of uterine hemorrhage after delivery	IV infusion or IM injection • *Toxicity:* Fetal distress, placental abruption, uterine rupture, fluid retention, hypotension
OXYTOCIN RECEPTOR ANTAGONIST				
• Atosiban	Blocks oxytocin receptors	Decreased uterine contractions	Tocolysis for preterm labor	IV infusion • *Toxicity:* Concern about increased rates of infant death; not FDA approved

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
VASOPRESSIN RECEPTOR AGONISTS				
• Desmopressin	Relatively selective vasopressin V_2 receptor agonist	Acts in the kidney collecting duct cells to decrease the excretion of water • acts on extrarenal V_2 receptors to increase factor VIII and von Willebrand factor	Pituitary diabetes insipidus • pediatric primary nocturnal enuresis • hemophilia A and von Willebrand disease	Oral, IV, SC, or intranasal • *Toxicity:* Gastrointestinal disturbances, headache, hyponatremia, allergic reactions
• *Vasopressin: Available for treatment of diabetes insipidus and sometimes used to control bleeding from esophageal varices*				
VASOPRESSIN RECEPTOR ANTAGONIST				
• Conivaptan	Antagonist of vasopressin V_{1a} and V_2 receptors	Reduced renal excretion of water in conditions associated with increased vasopressin	Hyponatremia in hospitalized patients	IV infusion • *Toxicity:* Infusion site reactions
• *Tolvaptan: Similar but more selective for vasopressin V_2 receptors; oral administration*				

[1]See Tables 37-2 and 37-3 for summaries of the clinical uses of the rarely used hypothalamic and pituitary hormones not described in this table.

PREPARATIONS AVAILABLE

GROWTH FACTOR AGONISTS & ANTAGONISTS

Lanreotide acetate (Somatuline Depot)
Parenteral: 60, 90, 120 mg in single-use prefilled syringe for SC injection

Mecasermin (Increlex)
Parenteral: 10 mg/mL solution for SC injection

Octreotide acetate (generic, Sandostatin)
Parenteral: 0.05, 0.1, 0.2, 0.5, 1.0 mg/mL solution for SC or IV injection
Parenteral depot injection (Sandostatin LAR Depot): 10, 20, 30 mg powder in single-use vials to reconstitute for IM injection

Pegvisomant (Somavert)
Parenteral: 10, 15, 20 mg powder in single-use vials to reconstitute for SC injection

Somatropin (various)
Parenteral: many dose strengths between 0.2 to 24 mg available to reconstitute for SC or IM injection

GONADOTROPIN AGONISTS & ANTAGONISTS

Cetrorelix acetate (Cetrotide)
Parenteral: 0.25, 3.0 mg in single-use vials for SC injection

Choriogonadotropin alfa [rhCG] (Ovidrel)
Parenteral: 250 mcg in single-dose prefilled syringes for SC injection

Chorionic gonadotropin [hCG] (generic, Profasi, Pregnyl)
Parenteral: 10,000 unit powder to reconstitute for IM injection

Degarelix (Firmagon)
Parenteral: 80, 120 mg powder to reconstitute for SC injection

Follitropin alfa [rFSH] (Gonal-f)
Parenteral: 75, 450, 1050 unit powder in vials to reconstitute or 300, 450, 900 units in prefilled pens with needles for SC injection

Follitropin beta [rFSH] (Follistim)
Parenteral: 37.5, 150 units/mL solution in single-use vials for 175, 350, 650, 975 units in cartridges for SC injection

Ganirelix acetate (Antagon)
Parenteral: 500 mcg/mL solution in prefilled syringes for SC injection

Gonadorelin hydrochloride [GnRH] (Factrel)
Parenteral: 100, 500 mcg powder to reconstitute for SC or intravenous injection

Goserelin acetate (Zoladex)
Parenteral: 3.6, 10.8 mg in prefilled syringes for SC implantation

Histrelin acetate (Supprelin LA, Vantas)
Parenteral: 50 mg SC implant

Leuprolide acetate (generic, Eligard, Lupron)
Parenteral: 5 mg/mL solution in multiple-dose vials for SC injection
Parenteral depot polymeric delivery system: 7.5, 22.5, 30, 45 mg in a single-dose kit for SC injection
Parenteral depot microsphere suspension: 3.75, 7.5, 11.25, 15, 22.5, 30 mg in a single-dose kit for IM injection

Lutropin alfa [rLH] (Luveris)
Parenteral: 75 unit powder to reconstitute for SC injection

Menotropins [hMG] (Menopur, Repronex)
Parenteral: 75 IU FSH and 75 IU LH powder to reconstitute for SC or IM injection

Nafarelin acetate (Synarel)
Nasal: 2 mg/mL solution

Triptorelin pamoate (Trelstar)
Parenteral: 3.75, 11.25, 22.5 mg powder to reconstitute for IM injection

Urofollitropin (Bravelle)
Parenteral: 75 IU FSH powder to reconstitute for SC injection

PROLACTIN ANTAGONISTS (DOPAMINE AGONISTS)

Bromocriptine mesylate (generic, Parlodel)
Oral: 2.5 mg tablets, 5 mg capsules

Cabergoline (generic, Dostinex)
Oral: 0.5 mg tablets

OXYTOCIN

Oxytocin (generic, Pitocin)
Parenteral: 10 units/mL solution for intravenous or IM injection

VASOPRESSIN AGONISTS AND ANTAGONISTS

Conivaptan HCl (Vaprisol)
Parenteral: 0.2 mg/mL solution for IV injection

Desmopressin acetate (DDAVP, generic, Minirin, Stimate)
Nasal: 0.1, 1.5 mg/mL solution
Parenteral: 4 mcg/mL solution for IV or SC injection
Oral: 0.1, 0.2 mg tablets

Tolvaptan (Samsca)
Oral: 15, 30 mg tablets

Vasopressin (generic, Pitressin)
Parenteral: 20 IU/mL solution for IM, SC or nasal administration

OTHER

Corticorelin ovine triflutate (Acthrel)
Parenteral: 100 mcg powder to reconstitute for IV injection

Corticotropin (H.P. Acthar Gel)
Parenteral: 80 units/mL gelatin for IM or SC administration

Cosyntropin (generic, Cortrosyn)
Parenteral: 0.25 mg powder to reconstitute or 0.25 mg/mL solution for IV or IM injection

Thyrotropin alfa (Thyrogen)
Parenteral: 1.1 mg powder to reconstitute for IM injection

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CASE STUDY ANSWER

While GH may have some direct growth-promoting effects, GH is thought to mediate skeletal growth principally through epiphyseal production of insulin-like growth factor-I (IGF-I), which acts principally in an autocrine/paracrine manner. IGF-I may also promote statural growth through endocrine mechanisms. The findings of small testes and a microphallus in this patient suggest a diagnosis of hypogonadism, likely as a consequence of gonadotropin deficiency. This patient is at risk for multiple hypothalamic/pituitary deficiencies. This patient may already have or may subsequently develop ACTH/cortisol and TSH/thyroid hormone deficiencies and thus may require supplementation with hydrocortisone and levothyroxine, in addition to supplementation with GH and testosterone. The patient should also be evaluated for the presence of central diabetes insipidus and, if present, treated with desmopressin, a V_2 vasopressin receptor-selective analog.

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CHAPTER

38

Thyroid & Antithyroid Drugs

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CASE STUDY

A 33-year-old woman presents with complaints of fatigue, sluggishness, weight gain, cold intolerance, dry skin, and muscle weakness for the last 2 months. She is so tired that she has to take several naps during the day to complete her tasks. These complaints are new for her since she used to feel warm all the time, had boundless energy causing her some insomnia, and states she felt like her heart was going to jump out of her chest. She also states that she would like to become pregnant in the near future. Her past medical history is significant for radioactive iodine therapy (RAI) about 1 year ago after a short trial of methimazole and propranolol therapy. She underwent RAI due to her poor medication adherence and did not attend routine scheduled appointments afterward. On physical examination, her blood pressure is 130/89 mm Hg with a pulse of 50 bpm. Her weight is 136 lb (61.8 kg), an increase of 10 lb (4.5 kg) in the last year. Her thyroid gland is not palpable and her reflexes are delayed. Laboratory findings include a thyroid-stimulating hormone (TSH) level of 24.9 μIU/mL and a free thyroxine level of 8 pmol/L. Evaluate the management of her past history of hyperthyroidism. Identify the available treatment options for control of her current thyroid status.

THYROID PHYSIOLOGY

The normal thyroid gland secretes sufficient amounts of the thyroid hormones—**triiodothyronine (T_3)** and **tetraiodothyronine (T_4, thyroxine)**—to normalize growth and development, body temperature, and energy levels. These hormones contain 59% and 65% (respectively) of iodine as an essential part of the molecule. Calcitonin, the second type of thyroid hormone, is important in the regulation of calcium metabolism and is discussed in Chapter 42.

Iodide Metabolism

The recommended daily adult iodide (I^-)* intake is 150 mcg (200 mcg during pregnancy).

Iodide, ingested from food, water, or medication, is rapidly absorbed and enters an extracellular fluid pool. The thyroid gland removes about 75 mcg a day from this pool for hormone synthesis, and the balance is excreted in the urine. If iodide intake is increased, the fractional iodine uptake by the thyroid is diminished.

Biosynthesis of Thyroid Hormones

Once taken up by the thyroid gland, iodide undergoes a series of enzymatic reactions that incorporate it into active thyroid hormone (Figure 38–1). The first step is the transport of iodide into the thyroid gland by an intrinsic follicle cell basement membrane protein called the sodium/iodide symporter (NIS). This can be inhibited by such anions as thiocyanate (SCN^-), pertechnetate (TcO_4^-), and perchlorate (ClO_4^-). At the apical cell membrane a second I^- transport enzyme called pendrin controls the flow of iodide across the membrane. Pendrin is also found in the cochlea of the inner ear. If pendrin is deficient or absent, a hereditary syndrome of goiter and

*In this chapter, the term "iodine" denotes all forms of the element; the term "iodide" denotes only the ionic form, I^-.

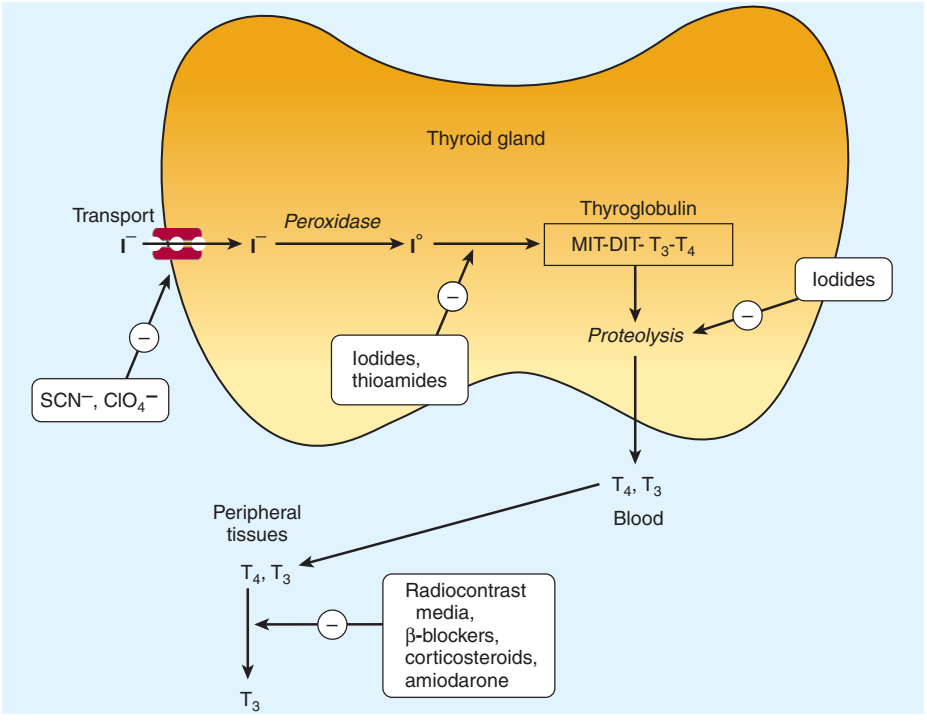

FIGURE 38–1 Biosynthesis of thyroid hormones. The sites of action of various drugs that interfere with thyroid hormone biosynthesis are shown.

deafness, called Pendred's syndrome, ensues. At the apical cell membrane, iodide is oxidized by thyroidal peroxidase to iodine, in which form it rapidly iodinates tyrosine residues within the thyroglobulin molecule to form **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT).** This process is called **iodide organification.** Thyroidal peroxidase is transiently blocked by high levels of intrathyroidal iodide and blocked more persistently by thioamide drugs.

Two molecules of DIT combine within the thyroglobulin molecule to form L-thyroxine (T_4). One molecule of MIT and one molecule of DIT combine to form T_3. In addition to thyroglobulin, other proteins within the gland may be iodinated, but these iodoproteins do not have hormonal activity. Thyroxine, T_3, MIT, and DIT are released from thyroglobulin by exocytosis and proteolysis of thyroglobulin at the apical colloid border. The MIT and DIT are then deiodinated within the gland, and the iodine is reutilized. This process of proteolysis is also blocked by high levels of intrathyroidal iodide. The ratio of T_4 to T_3 within thyroglobulin is approximately 5:1, so that most of the hormone released is thyroxine. Most of the T_3 circulating in the blood is derived from peripheral metabolism of thyroxine (see below, Figure 38–2).

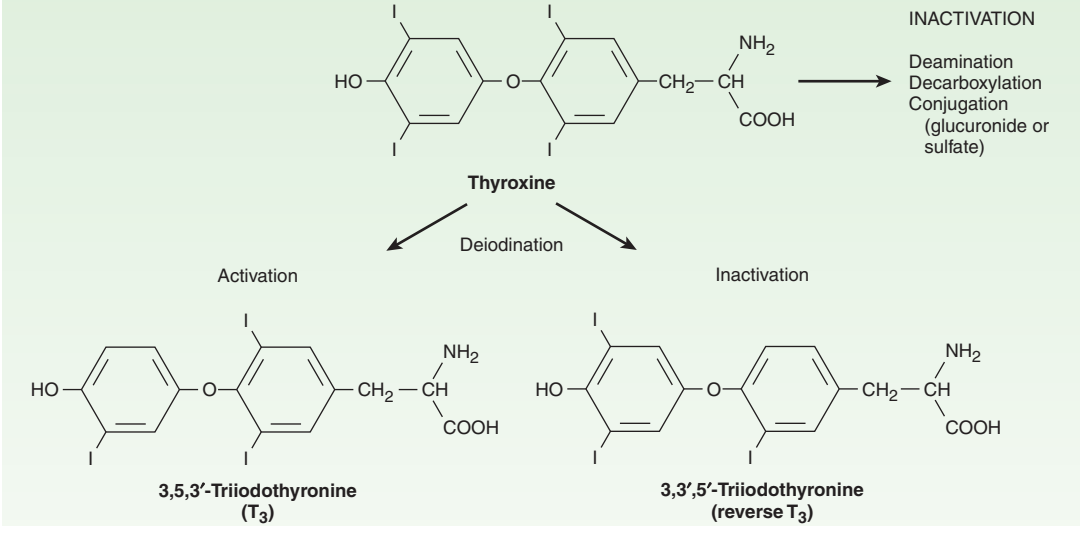

FIGURE 38–2 Peripheral metabolism of thyroxine. (Modified and reproduced, with permission, from Gardner DG, Shoback D [editors]: *Greenspan's Basic & Clinical Endocrinology*, 8th ed. McGraw-Hill, 2007.)

TABLE 38–1 Summary of thyroid hormone kinetics.

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	4.8–10.4 mcg/dL	60–181 ng/dL
	(62–134 nmol/L)	(0.92–2.79 nmol/L)
Free	0.8–2.7 ng/dL	230–420 pg/dL
	(10.3–34.7 pmol/L)	(3.5–6.47 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	80%	95%

Transport of Thyroid Hormones

T_4 and T_3 in plasma are reversibly bound to protein, primarily thyroxine-binding globulin (TBG). Only about 0.04% of total T_4 and 0.4% of T_3 exist in the free form. Many physiologic and pathologic states and drugs affect T_4, T_3, and thyroid transport. However, the actual levels of free hormone generally remain normal, reflecting feedback control.

Peripheral Metabolism of Thyroid Hormones

The primary pathway for the peripheral metabolism of thyroxine is deiodination. Deiodination of T_4 may occur by monodeiodination of the outer ring, producing 3,5,3'-triiodothyronine (T_3), which is three to four times more potent than T_4. Alternatively, deiodination may occur in the inner ring, producing 3,3',5'-triiodothyronine (reverse T_3, or rT_3), which is metabolically inactive (Figure 38–2). Drugs such as amiodarone, iodinated contrast media, β blockers, and corticosteroids, and severe illness or starvation inhibit the 5'-deiodinase necessary for the conversion of T_4 to T_3, resulting in low T_3 and high rT_3 levels in the serum. The pharmacokinetics of thyroid hormones are listed in Table 38–1. The low serum levels of T_3 and rT_3 in normal individuals are due to the high metabolic clearances of these two compounds.

Evaluation of Thyroid Function

The tests used to evaluate thyroid function are listed in Table 38–2.

A. Thyroid-Pituitary Relationships

Control of thyroid function via thyroid-pituitary feedback is also discussed in Chapter 37. Briefly, hypothalamic cells secrete thyrotropin-releasing hormone (TRH) (Figure 38–3). TRH is secreted into capillaries of the pituitary portal venous system, and in the pituitary gland, TRH stimulates the synthesis and release of thyrotropin (thyroid-stimulating hormone, TSH). TSH in turn stimulates an adenylyl cyclase–mediated mechanism in the thyroid cell to increase the synthesis and release of T_4 and T_3. These thyroid hormones act in a negative feedback fashion in the

TABLE 38–2 Typical values for thyroid function tests.

Name of Test	Normal Value[1]	Results in Hypothyroidism	Results in Hyperthyroidism
Total thyroxine (T_4)	4.8–10.4 mcg/dL (62–134 nmol/L)	Low	High
Total triiodothyronine (T_3)	60–181 ng/dL (0.92–2.79 nmol/L)	Normal or low	High
Free T_4 (FT_4)	0.8–2.7 ng/dL (10.3–34.7 pmol/L)	Low	High
Free T_3 (FT_3)	230–420 pg/dL (3.5–6.47 pmol/L)	Low	High
Thyrotropic hormone (TSH)	0.4–4 μIU/mL (0.4–4 mIU/L)	High[2]	Low
^{123}I uptake at 24 hours	5–35%	Low	High
Thyroglobulin autoantibodies (Tg-ab)	< 20 IU/mL	Often present	Usually present
Thyroid peroxidase antibodies (TPA)	< 0.8 IU/mL	Often present	Usually present
Isotope scan with ^{123}I or $^{99m}TcO_4$	Normal pattern	Test not indicated	Diffusely enlarged gland
Fine-needle aspiration biopsy (FNA)	Normal pattern	Test not indicated	Test not indicated
Serum thyroglobulin	< 56 ng/mL	Test not indicated	Test not indicated
Serum calcitonin	Men: < 8 ng/L (< 2.3 pmol/L); women: < 4 ng/L (< 1.17 pmol/L)	Test not indicated	Test not indicated
TSH receptor-stimulating antibody or thyroid-stimulating immunoglobulin (TSI)	< 125%	Test not indicated	Elevated in Graves' disease

[1]Results may vary with different laboratories.

[2]Exception is central hypothyroidism.

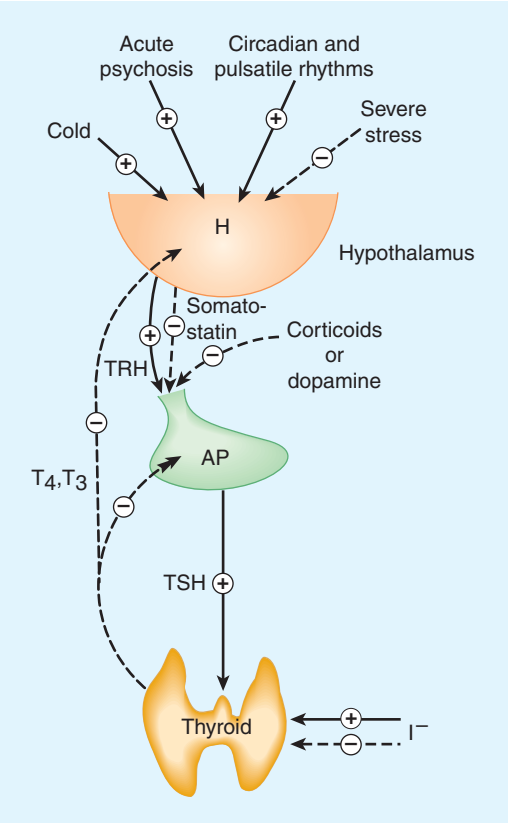

FIGURE 38–3 The hypothalamic-pituitary-thyroid axis. Acute psychosis or prolonged exposure to cold may activate the axis. Hypothalamic thyroid-releasing hormone (TRH) stimulates pituitary thyroid-stimulating hormone (TSH) release, while somatostatin and dopamine inhibit it. TSH stimulates T_4 and T_3 synthesis and release from the thyroid, and they in turn inhibit both TRH and TSH synthesis and release. Small amounts of iodide are necessary for hormone production, but large amounts inhibit T_3 and T_4 production and release. Solid arrows, stimulatory influence; dashed arrows, inhibitory influence. H, hypothalamus; AP, anterior pituitary.

pituitary to block the action of TRH and in the hypothalamus to inhibit the synthesis and secretion of TRH. Other hormones or drugs may also affect the release of TRH or TSH.

B. Autoregulation of the Thyroid Gland

The thyroid gland also regulates its uptake of iodide and thyroid hormone synthesis by intrathyroidal mechanisms that are independent of TSH. These mechanisms are primarily related to the level of iodine in the blood. Large doses of iodine inhibit iodide organification (Wolff-Chaikoff block, see Figure 38–1). In certain disease states (eg, Hashimoto's thyroiditis), this can inhibit thyroid hormone synthesis and result in hypothyroidism. Hyperthyroidism can result from the loss of the Wolff-Chaikoff block in susceptible individuals (eg, multinodular goiter).

C. Abnormal Thyroid Stimulators

In Graves' disease (see below), lymphocytes secrete a TSH receptor-stimulating antibody (TSH-R Ab [stim]), also known as thyroid-stimulating immunoglobulin (TSI). This immunoglobulin binds to the TSH receptor and stimulates the gland in the same fashion as TSH itself. The duration of its effect, however, is much longer than that of TSH. TSH receptors are also found in orbital fibrocytes, which may be stimulated by high levels of TSH-R Ab [stim] and can cause ophthalmopathy.

BASIC PHARMACOLOGY OF THYROID & ANTITHYROID DRUGS

THYROID HORMONES

Chemistry

The structural formulas of thyroxine and triiodothyronine as well as reverse triiodothyronine (rT_3) are shown in Figure 38–2. All of these naturally occurring molecules are levo (L) isomers. The synthetic dextro (D) isomer of thyroxine, dextrothyroxine, has approximately 4% of the biologic activity of the L-isomer as evidenced by its lesser ability to suppress TSH secretion and correct hypothyroidism.

Pharmacokinetics

Thyroxine is absorbed best in the duodenum and ileum; absorption is modified by intraluminal factors such as food, drugs, gastric acidity, and intestinal flora. Oral bioavailability of current preparations of L-thyroxine averages 80% (Table 38–1). In contrast, T_3 is almost completely absorbed (95%). T_4 and T_3 absorption appears not to be affected by mild hypothyroidism but may be impaired in severe myxedema with ileus. These factors are important in switching from oral to parenteral therapy. For parenteral use, the intravenous route is preferred for both hormones.

In patients with hyperthyroidism, the metabolic clearances of T_4 and T_3 are increased and the half-lives decreased; the opposite is true in patients with hypothyroidism. Drugs that induce hepatic microsomal enzymes (eg, rifampin, phenobarbital, carbamazepine, phenytoin, tyrosine kinase inhibitors, HIV protease inhibitors) increase the metabolism of both T_4 and T_3 (Table 38–3). Despite this change in clearance, the normal hormone concentration is maintained in the majority of euthyroid patients as a result of compensatory hyperfunction of the thyroid. However, patients dependent on T_4 replacement medication may require increased dosages to maintain clinical effectiveness. A similar compensation occurs if binding sites are altered. If TBG sites are increased by pregnancy, estrogens, or oral contraceptives, there is an initial shift of hormone from the free to the bound state and a decrease in its rate of elimination until the normal free hormone concentration is restored. Thus, the concentration of total and bound hormone will increase, but the concentration of free hormone and the steady-state elimination will remain normal. The reverse occurs when thyroid binding sites are decreased.

Mechanism of Action

A model of thyroid hormone action is depicted in Figure 38–4, which shows the free forms of thyroid hormones, T_4 and T_3,

TABLE 38–3 Drug effects and thyroid function.

Drug Effect	Drugs
Change in thyroid hormone synthesis	
Inhibition of TRH or TSH secretion without induction of hypothyroidism or hyperthyroidism	Dopamine, bromocriptine, levodopa, corticosteroids, somatostatin, metformin
Inhibition of thyroid hormone synthesis or release with the induction of hypothyroidism (or occasionally hyperthyroidism)	Iodides (including amiodarone), lithium, aminoglutethimide, thioamides, ethionamide, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib), HIV protease inhibitors
Alteration of thyroid hormone transport and serum total T_3 and T_4 levels, but usually no modification of FT_4 or TSH	
Increased TBG	Estrogens, tamoxifen, heroin, methadone, mitotane, fluorouracil
Decreased TBG	Androgens, glucocorticoids
Displacement of T_3 and T_4 from TBG with transient hyperthyroxinemia	Salicylates, fenclofenac, mefenamic acid, furosemide
Alteration of T_4 and T_3 metabolism with modified serum T_3 and T_4 levels but not TSH levels (unless receiving thyroxine replacement therapy)	
Increased hepatic metabolism, enhanced degradation of thyroid hormone	Nicardipine, bexarotene, phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Inhibition of 5'-deiodinase with decreased T_3, increased rT_3	Iopanoic acid, ipodate, amiodarone, β blockers, corticosteroids, propylthiouracil, flavonoids
Other interactions	
Interference with T_4 absorption	Cholestyramine, chromium picolinate, colestipol, ciprofloxacin, proton pump inhibitors, sucralfate, sodium polystyrene sulfonate, raloxifene, sevelamer hydrochloride, aluminum hydroxide, ferrous sulfate, calcium carbonate, bran, soy, coffee
Induction of autoimmune thyroid disease with hypothyroidism or hyperthyroidism	Interferon-α, interleukin-2, interferon-β, lithium, amiodarone, tyrosine kinase inhibitors (eg, sunitinib, sorafenib, imatinib)
Effect of thyroid function on drug effects	
Anticoagulation	Lower doses of warfarin required in hyperthyroidism, higher doses in hypothyroidism
Glucose control	Increased hepatic glucose production and glucose intolerance in hyperthyroidism; impaired insulin action and glucose disposal in hypothyroidism
Cardiac drugs	Higher doses of digoxin required in hyperthyroidism; lower doses in hypothyroidism
Sedatives; analgesics	Increased sedative and respiratory depressant effects from sedatives and opioids in hypothyroidism; converse in hyperthyroidism

dissociated from thyroid-binding proteins, entering the cell by active transport. Within the cell, T_4 is converted to T_3 by 5'-deiodinase, and the T_3 enters the nucleus, where T_3 binds to a specific T_3 receptor protein, a member of the c-*erb* oncogene family. (This family also includes the steroid hormone receptors and receptors for vitamins A and D.) The T_3 receptor exists in two forms, α and β. Differing concentrations of receptor forms in different tissues may account for variations in T_3 effect on different tissues.

Most of the effects of thyroid on metabolic processes appear to be mediated by activation of nuclear receptors that lead to increased formation of RNA and subsequent protein synthesis, eg, increased formation of Na^+/K^+-ATPase. This is consistent with the observation that the action of thyroid is manifested in vivo with a time lag of hours or days after its administration.

Large numbers of thyroid hormone receptors are found in the most hormone-responsive tissues (pituitary, liver, kidney, heart, skeletal muscle, lung, and intestine), while few receptor sites occur in hormone-unresponsive tissues (spleen, testes). The brain, which lacks an anabolic response to T_3, contains an intermediate number of receptors. In congruence with their biologic potencies, the affinity of the receptor site for T_4 is about ten times lower than that for T_3. Under some conditions, the number of nuclear receptors may be altered to preserve body homeostasis. For example, starvation lowers both circulating T_3 hormone and cellular T_3 receptors.

Effects of Thyroid Hormones

The thyroid hormones are responsible for optimal growth, development, function, and maintenance of all body tissues. Excess or inadequate amounts result in the signs and symptoms of hyperthyroidism or hypothyroidism, respectively (Table 38–4). Since T_3 and T_4 are qualitatively similar, they may be considered as one hormone in the discussion that follows.

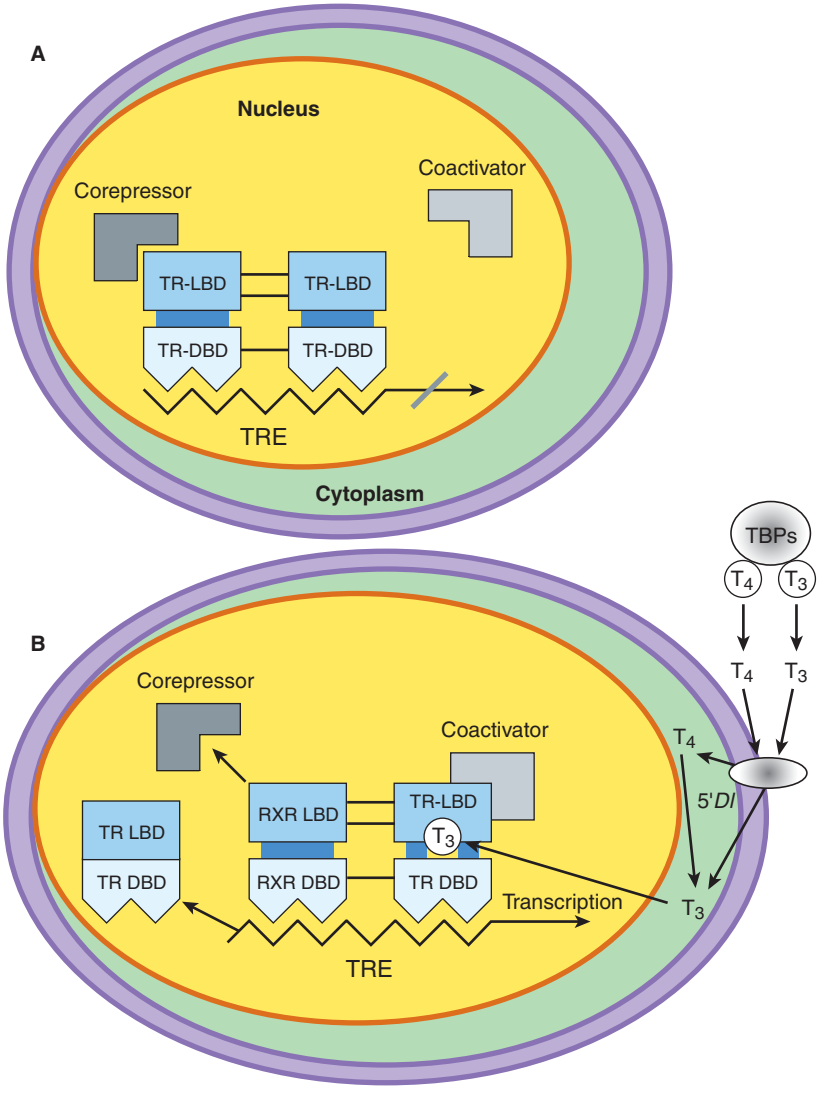

FIGURE 38–4 Model of the interaction of T_3 with the T_3 receptor. **A:** *Inactive phase*—the unliganded T_3 receptor dimer bound to the thyroid hormone response element (TRE) along with corepressors acts as a suppressor of gene transcription. **B:** *Active phase*—T_3 and T_4 circulate bound to thyroid-binding proteins (TBPs). The free hormones are transported into the cell by a specific transport system. Within the cytoplasm, T_4 is converted to T_3 by 5′-deiodinase (5′DI); T_3 then moves into the nucleus. There it binds to the ligand-binding domain of the thyroid receptor (TR) monomer. This promotes disruption of the TR homodimer and heterodimerization with retinoid X receptor (RXR) on the TRE, displacement of corepressors, and binding of coactivators. The TR-coactivator complex activates gene transcription, which leads to alteration in protein synthesis and cellular phenotype. TR-LBD, T_3 receptor ligand-binding domain; TR-DBD, T_3 receptor DNA-binding domain; RXR-LBD, retinoid X receptor ligand-binding domain; RXR-DBD, retinoid X receptor DNA-binding domain; T_3, triiodothyronine; T_4, tetraiodothyronine, L-thyroxine. (Modified and reproduced, with permission, from Gardner DG, Shoback D [editors]: *Greenspan's Basic & Clinical Endocrinology,* 8th ed. McGraw-Hill, 2007.)

Thyroid hormone is critical for the development and functioning of nervous, skeletal, and reproductive tissues. Its effects depend on protein synthesis as well as potentiation of the secretion and action of growth hormone. Thyroid deprivation in early life results in irreversible mental retardation and dwarfism—typical of congenital cretinism.

Effects on growth and calorigenesis are accompanied by a pervasive influence on metabolism of drugs as well as carbohydrates, fats, proteins, and vitamins. Many of these changes are dependent upon or modified by activity of other hormones. Conversely, the secretion and degradation rates of virtually all other hormones, including catecholamines, cortisol, estrogens, testosterone, and insulin, are affected by thyroid status.

Many of the manifestations of thyroid hyperactivity resemble sympathetic nervous system overactivity (especially in the cardiovascular system), although catecholamine levels are not increased. Changes in catecholamine-stimulated adenylyl cyclase activity as measured by cAMP are found with changes in thyroid activity.

TABLE 38–4 Manifestations of thyrotoxicosis and hypothyroidism.

System	Thyrotoxicosis	Hypothyroidism
Skin and appendages	Warm, moist skin; sweating; heat intolerance; fine, thin hair; Plummer's nails; pretibial dermopathy (Graves' disease)	Pale, cool, puffy skin; dry and brittle hair; brittle nails
Eyes, face	Retraction of upper lid with wide stare; periorbital edema; exophthalmos; diplopia (Graves' disease)	Drooping of eyelids; periorbital edema; loss of temporal aspects of eyebrows; puffy, nonpitting facies; large tongue
Cardiovascular system	Decreased peripheral vascular resistance; increased heart rate, stroke volume, cardiac output, pulse pressure; high-output heart failure; increased inotropic and chronotropic effects; arrhythmias; angina	Increased peripheral vascular resistance; decreased heart rate, stroke volume, cardiac output, pulse pressure; low-output heart failure; ECG: bradycardia, prolonged PR interval, flat T wave, low voltage; pericardial effusion
Respiratory system	Dyspnea; decreased vital capacity	Pleural effusions; hypoventilation and CO_2 retention
Gastrointestinal system	Increased appetite; increased frequency of bowel movements; hypoproteinemia	Decreased appetite; decreased frequency of bowel movements; ascites
Central nervous system	Nervousness; hyperkinesia; emotional lability	Lethargy; general slowing of mental processes; neuropathies
Musculoskeletal system	Weakness and muscle fatigue; increased deep tendon reflexes; hypercalcemia; osteoporosis	Stiffness and muscle fatigue; decreased deep tendon reflexes; increased alkaline phosphatase, LDH, AST
Renal system	Mild polyuria; increased renal blood flow; increased glomerular filtration rate	Impaired water excretion; decreased renal blood flow; decreased glomerular filtration rate
Hematopoietic system	Increased erythropoiesis; anemia[1]	Decreased erythropoiesis; anemia[1]
Reproductive system	Menstrual irregularities; decreased fertility; increased gonadal steroid metabolism	Hypermenorrhea; infertility; decreased libido; impotence; oligospermia; decreased gonadal steroid metabolism
Metabolic system	Increased basal metabolic rate; negative nitrogen balance; hyperglycemia; increased free fatty acids; decreased cholesterol and triglycerides; increased hormone degradation; increased requirements for fat- and water-soluble vitamins; increased drug metabolism; decreased warfarin requirement	Decreased basal metabolic rate; slight positive nitrogen balance; delayed degradation of insulin with increased sensitivity; increased cholesterol and triglycerides; decreased hormone degradation; decreased requirements for fat- and water-soluble vitamins; decreased drug metabolism; increased warfarin requirement

[1]The anemia of hyperthyroidism is usually normochromic and caused by increased red blood cell turnover. The anemia of hypothyroidism may be normochromic, hyperchromic, or hypochromic and may be due to decreased production rate, decreased iron absorption, decreased folic acid absorption, or to autoimmune pernicious anemia. LDH, lactic dehydrogenase; AST, aspartate aminotransferase.

Possible explanations include increased numbers of β receptors or enhanced amplification of the β-receptor signal. Other clinical symptoms reminiscent of excessive epinephrine activity (and partially alleviated by adrenoceptor antagonists) include lid lag and retraction, tremor, excessive sweating, anxiety, and nervousness. The opposite constellation of effects is seen in hypothyroidism (Table 38–4).

Thyroid Preparations

See the Preparations Available section at the end of this chapter for a list of available preparations. These preparations may be synthetic (levothyroxine, liothyronine, liotrix) or of animal origin (desiccated thyroid).

Thyroid hormones are not effective and can be detrimental in the management of obesity, abnormal vaginal bleeding, or depression if thyroid hormone levels are normal. Anecdotal reports of a beneficial effect of T_3 administered with antidepressants were not confirmed in a controlled study.

Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its stability, content uniformity, low cost, lack of allergenic foreign protein, easy laboratory measurement of serum levels, and long half-life (7 days), which permits once-daily administration. In addition, T_4 is converted to T_3 intracellularly; thus, administration of T_4 produces both hormones. Generic levothyroxine preparations provide comparable efficacy and are more cost-effective than branded preparations.

Although liothyronine (T_3) is three to four times more potent than levothyroxine, it is not recommended for routine replacement therapy because of its shorter half-life (24 hours), which requires multiple daily doses; its higher cost; and the greater difficulty of monitoring its adequacy of replacement by conventional laboratory tests. Furthermore, because of its greater hormone activity and consequent greater risk of cardiotoxicity, T_3 should be avoided in patients with cardiac disease. It is best used for short-term suppression of TSH. Because oral administration of T_3 is unnecessary, use of the more expensive mixture of thyroxine and liothyronine (liotrix) instead of levothyroxine is never required.

The use of desiccated thyroid rather than synthetic preparations is never justified, since the disadvantages of protein antigenicity, product instability, variable hormone concentrations, and

difficulty in laboratory monitoring far outweigh the advantage of lower cost. Significant amounts of T_3 found in some thyroid extracts and liotrix may produce significant elevations in T_3 levels and toxicity. Equi-effective doses are 100 mg of desiccated thyroid, 100 mcg of levothyroxine, and 37.5 mcg of liothyronine.

The shelf life of synthetic hormone preparations is about 2 years, particularly if they are stored in dark bottles to minimize spontaneous deiodination. The shelf life of desiccated thyroid is not known with certainty, but its potency is better preserved if it is kept dry.

ANTITHYROID AGENTS

Reduction of thyroid activity and hormone effects can be accomplished by agents that interfere with the production of thyroid hormones, by agents that modify the tissue response to thyroid hormones, or by glandular destruction with radiation or surgery. Goitrogens are agents that suppress secretion of T_3 and T_4 to subnormal levels and thereby increase TSH, which in turn produces glandular enlargement (goiter). The antithyroid compounds used clinically include the thioamides, iodides, and radioactive iodine.

THIOAMIDES

The thioamides methimazole and propylthiouracil are major drugs for treatment of thyrotoxicosis. In the United Kingdom, carbimazole, which is converted to methimazole in vivo, is widely used. Methimazole is about ten times more potent than propylthiouracil and is the drug of choice in adults and children. Due to a black box warning about severe hepatitis, propylthiouracil should be reserved for use during the first trimester of pregnancy, in thyroid storm, and in those experiencing adverse reactions to methimazole (other than agranulocytosis or hepatitis). The chemical structures of these compounds are shown in Figure 38–5. The thiocarbamide group is essential for antithyroid activity.

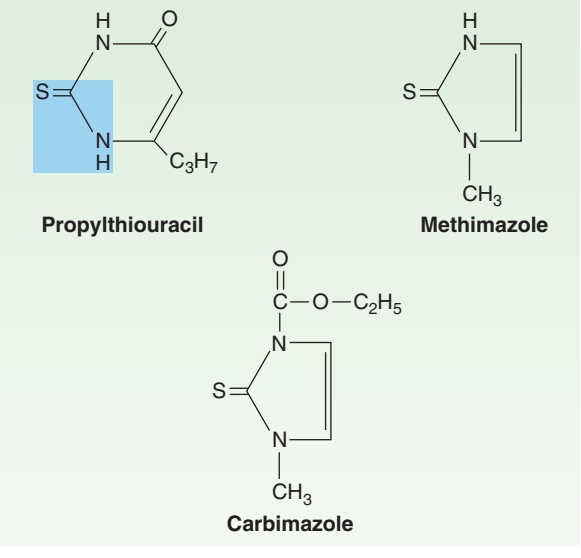

FIGURE 38–5 Structure of thioamides. The thiocarbamide moiety is shaded in color.

Pharmacokinetics

Methimazole is completely absorbed but at variable rates. It is readily accumulated by the thyroid gland and has a volume of distribution similar to that of propylthiouracil. Excretion is slower than with propylthiouracil; 65–70% of a dose is recovered in the urine in 48 hours.

In contrast, propylthiouracil is rapidly absorbed, reaching peak serum levels after 1 hour. The bioavailability of 50–80% may be due to incomplete absorption or a large first-pass effect in the liver. The volume of distribution approximates total body water with accumulation in the thyroid gland. Most of an ingested dose of propylthiouracil is excreted by the kidney as the inactive glucuronide within 24 hours.

The short plasma half-life of these agents (1.5 hours for propylthiouracil and 6 hours for methimazole) has little influence on the duration of the antithyroid action or the dosing interval because both agents are accumulated by the thyroid gland. For propylthiouracil, giving the drug every 6–8 hours is reasonable since a single 100 mg dose can inhibit iodine organification by 60% for 7 hours. Since a single 30 mg dose of methimazole exerts an antithyroid effect for longer than 24 hours, a single daily dose is effective in the management of mild to severe hyperthyroidism.

Both thioamides cross the placental barrier and are concentrated by the fetal thyroid, so that caution must be employed when using these drugs in pregnancy. Because of the risk of fetal hypothyroidism, both thioamides are classified as Food and Drug Administration pregnancy category D (evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, see Chapter 59). Of the two, propylthiouracil is preferable during the first trimester of pregnancy because it is more strongly protein-bound and, therefore, crosses the placenta less readily. In addition, methimazole has been, albeit rarely, associated with congenital malformations. Both thioamides are secreted in low concentrations in breast milk but are considered safe for the nursing infant.

Pharmacodynamics

The thioamides act by multiple mechanisms. The major action is to prevent hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions and blocking iodine organification. In addition, they block coupling of the iodotyrosines. They do not block uptake of iodide by the gland. Propylthiouracil and (to a much lesser extent) methimazole inhibit the peripheral deiodination of T_4 and T_3 (Figure 38–1). Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3–4 weeks before stores of T_4 are depleted.

Toxicity

Adverse reactions to the thioamides occur in 3–12% of treated patients. Most reactions occur early, especially nausea and gastrointestinal distress. An altered sense of taste or smell may occur with methimazole. The most common adverse effect is a maculopapular pruritic rash (4–6%), at times accompanied by systemic signs such as fever. Rare adverse effects include an urticarial rash,

vasculitis, a lupus-like reaction, lymphadenopathy, hypoprothrombinemia, exfoliative dermatitis, polyserositis, and acute arthralgia. An increased risk of severe hepatitis, sometimes resulting in death, has been reported with propylthiouracil (black box warning), so it should be avoided in children and adults unless no other options are available. Cholestatic jaundice is more common with methimazole than propylthiouracil. Asymptomatic elevations in transaminase levels can also occur.

The most dangerous complication is agranulocytosis (granulocyte count < 500 cells/mm^3), an infrequent but potentially fatal adverse reaction. It occurs in 0.1–0.5% of patients taking thioamides, but the risk may be increased in older patients and in those receiving more than 40 mg/d of methimazole. The reaction is usually rapidly reversible when the drug is discontinued, but broad-spectrum antibiotic therapy may be necessary for complicating infections. Colony-stimulating factors (eg, G-CSF; see Chapter 33) may hasten recovery of the granulocytes. The cross-sensitivity between propylthiouracil and methimazole is about 50%; therefore, switching drugs in patients with severe reactions is not recommended.

ANION INHIBITORS

Monovalent anions such as perchlorate (ClO_4^-), pertechnetate (TcO_4^-), and thiocyanate (SCN^-) can block uptake of iodide by the gland through competitive inhibition of the iodide transport mechanism. Since these effects can be overcome by large doses of iodides, their effectiveness is somewhat unpredictable.

The major clinical use for potassium perchlorate is to block thyroidal reuptake of I^- in patients with iodide-induced hyperthyroidism (eg, amiodarone-induced hyperthyroidism). However, potassium perchlorate is rarely used clinically because it is associated with aplastic anemia.

IODIDES

Prior to the introduction of the thioamides in the 1940s, iodides were the major antithyroid agents; today they are rarely used as sole therapy.

Pharmacodynamics

Iodides have several actions on the thyroid. They inhibit organification and hormone release and decrease the size and vascularity of the hyperplastic gland. In susceptible individuals, iodides can induce hyperthyroidism (Jod-Basedow phenomenon) or precipitate hypothyroidism.

In pharmacologic doses (> 6 mg/d), the major action of iodides is to inhibit hormone release, possibly through inhibition of thyroglobulin proteolysis. Improvement in thyrotoxic symptoms occurs rapidly—within 2–7 days—hence the value of iodide therapy in thyroid storm. In addition, iodides decrease the vascularity, size, and fragility of a hyperplastic gland, making the drugs valuable as preoperative preparation for surgery.

Clinical Use of Iodide

Disadvantages of iodide therapy include an increase in intraglandular stores of iodine, which may delay onset of thioamide therapy or prevent use of radioactive iodine therapy for several weeks. Thus, iodides should be initiated after onset of thioamide therapy and avoided if treatment with radioactive iodine seems likely. Iodide should not be used alone, because the gland will escape from the iodide block in 2–8 weeks, and its withdrawal may produce severe exacerbation of thyrotoxicosis in an iodine-enriched gland. Chronic use of iodides in pregnancy should be avoided, since they cross the placenta and can cause fetal goiter. In radiation emergencies involving release of radioactive iodine isotopes, the thyroid-blocking effects of potassium iodide can protect the gland from subsequent damage if administered before radiation exposure.

Toxicity

Adverse reactions to iodine (iodism) are uncommon and in most cases reversible upon discontinuance. They include acneiform rash (similar to that of bromism), swollen salivary glands, mucous membrane ulcerations, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding disorders, and rarely, anaphylactoid reactions.

RADIOACTIVE IODINE

^{131}I is the only isotope used for treatment of thyrotoxicosis (others are used in diagnosis). Administered orally in solution as sodium ^{131}I, it is rapidly absorbed, concentrated by the thyroid, and incorporated into storage follicles. Its therapeutic effect depends on emission of β rays with an effective half-life of 5 days and a penetration range of 400–2000 μm. Within a few weeks after administration, destruction of the thyroid parenchyma is evidenced by epithelial swelling and necrosis, follicular disruption, edema, and leukocyte infiltration. Advantages of radioiodine include easy administration, effectiveness, low expense, and absence of pain. Fears of radiation-induced genetic damage, leukemia, and neoplasia have not been realized after more than 50 years of clinical experience with radioiodine therapy for hyperthyroidism. Radioactive iodine should not be administered to pregnant women or nursing mothers, since it crosses the placenta to destroy the fetal thyroid gland and is excreted in breast milk.

ADRENOCEPTOR-BLOCKING AGENTS

Beta blockers without intrinsic sympathomimetic activity (eg, metoprolol, propranolol, atenolol) are effective therapeutic adjuncts in the management of thyrotoxicosis since many of these symptoms mimic those associated with sympathetic stimulation. Propranolol has been the β blocker most widely studied and used in the therapy of thyrotoxicosis. Beta blockers cause clinical improvement of hyperthyroid symptoms but do not typically alter thyroid hormone levels. Propranolol at doses greater than 160 mg/d may also reduce T_3 levels approximately 20% by inhibiting the peripheral conversion of T_4 to T_3.

TABLE 38–5 Etiology and pathogenesis of hypothyroidism.

Cause	Pathogenesis	Goiter	Degree of Hypothyroidism
Hashimoto's thyroiditis	Autoimmune destruction of thyroid	Present early, absent later	Mild to severe
Drug-induced[1]	Blocked hormone formation[2]	Present	Mild to moderate
Dyshormonogenesis	Impaired synthesis of T_4 due to enzyme deficiency	Present	Mild to severe
Radiation, ^{131}I, x-ray, thyroidectomy	Destruction or removal of gland	Absent	Severe
Congenital (cretinism)	Athyreosis or ectopic thyroid, iodine deficiency; TSH receptor-blocking antibodies	Absent or present	Severe
Secondary (TSH deficit)	Pituitary or hypothalamic disease	Absent	Mild

[1]Iodides, lithium, fluoride, thioamides, aminosalicylic acid, phenylbutazone, amiodarone, perchlorate, ethionamide, thiocyanate, cytokines (interferons, interleukins), bexarotene, tyrosine kinase inhibitors, etc. See Table 38–3.

[2]See Table 38–3 for specific pathogenesis.

■ CLINICAL PHARMACOLOGY OF THYROID & ANTITHYROID DRUGS

HYPOTHYROIDISM

Hypothyroidism is a syndrome resulting from deficiency of thyroid hormones and is manifested largely by a reversible slowing down of all body functions (Table 38–4). In infants and children, there is striking retardation of growth and development that results in dwarfism and irreversible mental retardation.

The etiology and pathogenesis of hypothyroidism are outlined in Table 38–5. Hypothyroidism can occur with or without thyroid enlargement (goiter). The laboratory diagnosis of hypothyroidism in the adult is easily made by the combination of a low free thyroxine and elevated serum TSH (Table 38–2).

The most common cause of hypothyroidism in the USA at this time is probably Hashimoto's thyroiditis, an immunologic disorder in genetically predisposed individuals. In this condition, there is evidence of humoral immunity in the presence of antithyroid antibodies and lymphocyte sensitization to thyroid antigens. Certain medications can also cause hypothyroidism (Table 38–5).

MANAGEMENT OF HYPOTHYROIDISM

Except for hypothyroidism caused by drugs, which can be treated in some cases by simply removing the depressant agent, the general strategy of replacement therapy is appropriate. The most satisfactory preparation is levothyroxine, administered as either a branded or generic preparation. Treatment with combination levothyroxine plus liothyronine has not been found to be superior to levothyroxine alone. Infants and children require more T_4 per kilogram of body weight than adults. The average dosage for an infant 1–6 months of age is 10–15 mcg/kg/d, whereas the average dosage for an adult is about 1.7 mcg/kg/d. Older adults (> 65 years of age) may require less thyroxine for replacement. There is some variability in the absorption of thyroxine, so this dosage will vary from patient to patient. Since interactions with certain foods (eg, bran, soy, coffee) and drugs (Table 38–3) can impair its absorption, thyroxine should be administered on an empty stomach (eg, 30 minutes before meals or 1 hour after meals or at bedtime). Its long half-life of 7 days permits once-daily dosing. Children should be monitored for normal growth and development. Serum TSH and free thyroxine should be measured at regular intervals and TSH maintained within an optimal range of 0.5–2.5 mU/L. It takes 6–8 weeks after starting a given dose of thyroxine to reach steady-state levels in the bloodstream. Thus, dosage changes should be made slowly.

In long-standing hypothyroidism, in older patients, and in patients with underlying cardiac disease, it is imperative to start treatment with reduced dosages. In such adult patients, levothyroxine is given in a dosage of 12.5–25 mcg/d for 2 weeks, increasing the daily dose by 12.5–25 mcg every 2 weeks until euthyroidism or drug toxicity is observed. In older patients, the heart is very sensitive to the level of circulating thyroxine, and if angina pectoris or cardiac arrhythmia develops, it is essential to stop or reduce the dose of thyroxine immediately. In younger patients or those with very mild disease, full replacement therapy may be started immediately.

The toxicity of thyroxine is directly related to the hormone level. In children, restlessness, insomnia, and accelerated bone maturation and growth may be signs of thyroxine toxicity. In adults, increased nervousness, heat intolerance, episodes of palpitation and tachycardia, or unexplained weight loss may be the presenting symptoms. If these symptoms are present, it is important to monitor serum TSH (Table 38–2), which will determine whether the symptoms are due to excess thyroxine blood levels. Chronic overtreatment with T_4, particularly in elderly patients, can increase the risk of atrial fibrillation and accelerated osteoporosis.

Special Problems in Management of Hypothyroidism

A. Myxedema and Coronary Artery Disease

Since myxedema frequently occurs in older persons, it is often associated with underlying coronary artery disease. In this situation, the

low levels of circulating thyroid hormone actually protect the heart against increasing demands that could result in angina pectoris or myocardial infarction. Correction of myxedema must be done cautiously to avoid provoking arrhythmia, angina, or acute myocardial infarction. If coronary artery surgery is indicated, it should be done first, prior to correction of the myxedema by thyroxine administration.

B. Myxedema Coma

Myxedema coma is an end state of untreated hypothyroidism. It is associated with progressive weakness, stupor, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock, and death.

Myxedema coma is a medical emergency. The patient should be treated in the intensive care unit, since tracheal intubation and mechanical ventilation may be required. Associated illnesses such as infection or heart failure must be treated by appropriate therapy. It is important to give all preparations intravenously, because patients with myxedema coma absorb drugs poorly from other routes. Intravenous fluids should be administered with caution to avoid excessive water intake. These patients have large pools of empty T_3 and T_4 binding sites that must be filled before there is adequate free thyroxine to affect tissue metabolism. Accordingly, the treatment of choice in myxedema coma is to give a loading dose of levothyroxine intravenously—usually 300–400 mcg initially, followed by 50–100 mcg daily. Intravenous T_3 can also be used but may be more cardiotoxic and more difficult to monitor. Intravenous hydrocortisone is indicated if the patient has associated adrenal or pituitary insufficiency but is probably not necessary in most patients with primary myxedema. Opioids and sedatives must be used with extreme caution.

C. Hypothyroidism and Pregnancy

Hypothyroid women frequently have anovulatory cycles and are therefore relatively infertile until restoration of the euthyroid state. This has led to the widespread use of thyroid hormone for infertility, although there is no evidence for its usefulness in infertile euthyroid patients. In a pregnant hypothyroid patient receiving thyroxine, it is extremely important that the daily dose of thyroxine be adequate because early development of the fetal brain depends on maternal thyroxine. In many hypothyroid patients, an increase in the thyroxine dose (about 30–50%) is required to normalize the serum TSH level during pregnancy. It is reasonable to counsel women to take an extra 25 mcg thyroxine tablet as soon as they are pregnant and to separate thyroxine from prenatal vitamins by at least 4 hours. Because of the elevated maternal TBG levels and, therefore, elevated total T_4 levels, adequate maternal thyroxine dosages warrant maintenance of TSH between 0.5 and 3.0 mU/L and the total T_4 at or above the upper range of normal.

D. Subclinical Hypothyroidism

Subclinical hypothyroidism, defined as an elevated TSH level and normal thyroid hormone levels, is found in 4–10% of the general population but increases to 20% in women older than age 50. The consensus of expert thyroid organizations concluded that thyroid hormone therapy should be considered for patients with TSH levels greater than 10 mIU/L while close TSH monitoring is appropriate for those with lower TSH elevations.

E. Drug-Induced Hypothyroidism

Drug-induced hypothyroidism (Table 38–3) can be satisfactorily managed with levothyroxine therapy if the offending agent cannot be stopped. In the case of amiodarone-induced hypothyroidism, levothyroxine therapy may be necessary even after discontinuance because of amiodarone's very long half-life.

HYPERTHYROIDISM

Hyperthyroidism (thyrotoxicosis) is the clinical syndrome that results when tissues are exposed to high levels of thyroid hormone (Table 38–4).

GRAVES' DISEASE

The most common form of hyperthyroidism is Graves' disease, or diffuse toxic goiter. The presenting signs and symptoms of Graves' disease are set forth in Table 38–4.

Pathophysiology

Graves' disease is considered to be an autoimmune disorder in which helper T lymphocytes stimulate B lymphocytes to synthesize antibodies to thyroidal antigens. The antibody described previously (TSH-R Ab [stim]) is directed against the TSH receptor site in the thyroid cell membrane and has the capacity to stimulate growth and biosynthetic activity of the thyroid cell. Spontaneous remission occurs but some patients require years of antithyroid therapy.

Laboratory Diagnosis

In most patients with hyperthyroidism, T_3, T_4, FT_4, and FT_3 are elevated and TSH is suppressed (Table 38–2). Radioiodine uptake is usually markedly elevated as well. Antithyroglobulin, thyroid peroxidase, and TSH-R Ab [stim] antibodies are usually present.

Management of Graves' Disease

The three primary methods for controlling hyperthyroidism are antithyroid drug therapy, surgical thyroidectomy, and destruction of the gland with radioactive iodine.

A. Antithyroid Drug Therapy

Drug therapy is most useful in young patients with small glands and mild disease. Methimazole or propylthiouracil is administered until the disease undergoes spontaneous remission. This is the only therapy that leaves an intact thyroid gland, but it does require a long period of treatment and observation (12–18 months), and there is a 50–70% incidence of relapse.

Methimazole is preferable to propylthiouracil (except in pregnancy and thyroid storm) because it has a lower risk of serious liver injury and can be administered once daily, which may enhance adherence. Antithyroid drug therapy is usually begun with divided doses, shifting to maintenance therapy with single daily doses when the patient becomes clinically euthyroid. However, mild to moderately severe thyrotoxicosis can often be controlled with methimazole given in a single morning dose of 20–40 mg initially for 4–8 weeks to normalize hormone levels. Maintenance therapy requires 5–15 mg once daily. Alternatively, therapy is started with propylthiouracil, 100–150 mg every 6 or 8 hours until the patient is euthyroid, followed by gradual reduction of the dose to the maintenance level of 50–150 mg once daily. In addition to inhibiting iodine organification, propylthiouracil also inhibits the conversion of T_4 to T_3, so it brings the level of activated thyroid hormone down more quickly than does methimazole. The best clinical guide to remission is reduction in the size of the goiter. Laboratory tests most useful in monitoring the course of therapy are serum FT_3, FT_4, and TSH levels.

Reactions to antithyroid drugs have been described above. A minor rash can often be controlled by antihistamine therapy. Because the more severe reaction of agranulocytosis is often heralded by sore throat or high fever, patients receiving antithyroid drugs must be instructed to discontinue the drug and seek immediate medical attention if these symptoms develop. White cell and differential counts and a throat culture are indicated in such cases, followed by appropriate antibiotic therapy. Treatment should also be stopped if significant elevations in transaminases occur.

B. Thyroidectomy

A near-total thyroidectomy is the treatment of choice for patients with very large glands or multinodular goiters. Patients are treated with antithyroid drugs until euthyroid (about 6 weeks). In addition, for 10–14 days prior to surgery, they receive saturated solution of potassium iodide, 5 drops twice daily, to diminish vascularity of the gland and simplify surgery. About 80–90% of patients will require thyroid supplementation following near-total thyroidectomy.

C. Radioactive Iodine

Radioiodine therapy utilizing ^{131}I is the preferred treatment for most patients over 21 years of age. In patients without heart disease, the therapeutic dose may be given immediately in a range of 80–120 μCi/g of estimated thyroid weight corrected for uptake. In patients with underlying heart disease or severe thyrotoxicosis and in elderly patients, it is desirable to treat with antithyroid drugs (preferably methimazole) until the patient is euthyroid. The medication is then stopped for 5–7 days before the appropriate dose of ^{131}I is administered. Iodides should be avoided to ensure maximal ^{131}I uptake. Six to 12 weeks following the administration of radioiodine, the gland will shrink in size and the patient will usually become euthyroid or hypothyroid. A second dose may be required in some patients. Hypothyroidism occurs in about 80% of patients following radioiodine therapy. Serum FT_4 and TSH levels should be monitored regularly. When hypothyroidism develops, prompt replacement with oral levothyroxine, 50–150 mcg daily, should be instituted.

D. Adjuncts to Antithyroid Therapy

During the acute phase of thyrotoxicosis, β-adrenoceptor–blocking agents without intrinsic sympathomimetic activity are extremely helpful. Propranolol, 20–40 mg orally every 6 hours, or metoprolol, 25–50 mg orally every 6–8 hours, will control tachycardia, hypertension, and atrial fibrillation. Beta-adrenoceptor–blocking agents are gradually withdrawn as serum thyroxine levels return to normal. Diltiazem, 90–120 mg three or four times daily, can be used to control tachycardia in patients in whom β blockers are contraindicated, eg, those with asthma. Other calcium channel blockers may not be as effective as diltiazem. Adequate nutrition and vitamin supplements are essential. Barbiturates accelerate T_4 breakdown (by hepatic enzyme induction) and may be helpful both as sedatives and to lower T_4 levels. Bile acid sequestrants (eg, cholestyramine) can also rapidly lower T_4 levels by increasing the fecal excretion of T_4.

TOXIC UNINODULAR GOITER & TOXIC MULTINODULAR GOITER

These forms of hyperthyroidism occur often in older women with nodular goiters. FT_4 is moderately elevated or occasionally normal, but FT_3 or T_3 is strikingly elevated. Single toxic adenomas can be managed with either surgical excision of the adenoma or with radioiodine therapy. Toxic multinodular goiter is usually associated with a large goiter and is best treated by preparation with methimazole (preferable) or propylthiouracil followed by subtotal thyroidectomy.

SUBACUTE THYROIDITIS

During the acute phase of a viral infection of the thyroid gland, there is destruction of thyroid parenchyma with transient release of stored thyroid hormones. A similar state may occur in patients with Hashimoto's thyroiditis. These episodes of transient thyrotoxicosis have been termed *spontaneously resolving hyperthyroidism.* Supportive therapy is usually all that is necessary, such as β-adrenoceptor–blocking agents without intrinsic sympathomimetic activity (eg, propranolol) for tachycardia and aspirin or nonsteroidal anti-inflammatory drugs to control local pain and fever. Corticosteroids may be necessary in severe cases to control the inflammation.

SPECIAL PROBLEMS

Thyroid Storm

Thyroid storm, or thyrotoxic crisis, is sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life-threatening syndrome. Vigorous management is mandatory. Propranolol, 1–2 mg slowly intravenously or 40–80 mg orally

every 6 hours, is helpful to control the severe cardiovascular manifestations. If propranolol is contraindicated by the presence of severe heart failure or asthma, hypertension and tachycardia may be controlled with diltiazem, 90–120 mg orally three or four times daily or 5–10 mg/h by intravenous infusion (asthmatic patients only). Release of thyroid hormones from the gland is retarded by the administration of saturated solution of potassium iodide, 10 drops orally daily. Hormone synthesis is blocked by the administration of propylthiouracil, 250 mg orally every 6 hours. If the patient is unable to take propylthiouracil by mouth, a rectal formulation* can be prepared and administered in a dosage of 400 mg every 6 hours as a retention enema. Methimazole may also be prepared for rectal administration in a dose of 60 mg daily. Hydrocortisone, 50 mg intravenously every 6 hours, will protect the patient against shock and will block the conversion of T_4 to T_3, rapidly bringing down the level of thyroactive material in the blood.

Supportive therapy is essential to control fever, heart failure, and any underlying disease process that may have precipitated the acute storm. In rare situations, where the above methods are not adequate to control the problem, plasmapheresis or peritoneal dialysis has been used to lower the levels of circulating thyroxine.

Ophthalmopathy

Although severe ophthalmopathy is rare, it is difficult to treat. Management requires effective treatment of the thyroid disease, usually by total surgical excision or ^{131}I ablation of the gland plus oral prednisone therapy (see below). In addition, local therapy may be necessary, eg, elevation of the head to diminish periorbital edema and artificial tears to relieve corneal drying due to exophthalmos. Smoking cessation should be advised to prevent progression of the ophthalmopathy. For the severe, acute inflammatory reaction, a short course of prednisone, 60–100 mg orally daily for about a week and then 60–100 mg every other day, tapering the dose over a period of 6–12 weeks, may be effective. If steroid therapy fails or is contraindicated, irradiation of the posterior orbit, using well-collimated high-energy x-ray therapy, will frequently result in marked improvement of the acute process. Threatened loss of vision is an indication for surgical decompression of the orbit. Eyelid or eye muscle surgery may be necessary to correct residual problems after the acute process has subsided.

Dermopathy

Dermopathy or pretibial myxedema will often respond to topical corticosteroids applied to the involved area and covered with an occlusive dressing.

Thyrotoxicosis during Pregnancy

Ideally, women in the childbearing period with severe disease should have definitive therapy with ^{131}I or subtotal thyroidectomy *prior* to pregnancy in order to avoid an acute exacerbation of the disease during pregnancy or following delivery. If thyrotoxicosis does develop during pregnancy, radioiodine is contraindicated because it crosses the placenta and may injure the fetal thyroid. Propylthiouracil (fewer teratogenic risks than methimazole) can be given in the first trimester, and then methimazole can be given for the remainder of the pregnancy in order to avoid potential liver damage. The dosage of propylthiouracil must be kept to the minimum necessary for control of the disease (ie, < 300 mg/d), because it may affect the function of the fetal thyroid gland. Alternatively, a subtotal thyroidectomy can be safely performed during the mid trimester. It is essential to give the patient a thyroid supplement during the balance of the pregnancy.

Neonatal Graves' Disease

Graves' disease may occur in the newborn infant, either due to passage of maternal TSH-R Ab [stim] through the placenta, stimulating the thyroid gland of the neonate, or to genetic transmission of the trait to the fetus. Laboratory studies reveal an elevated free T_4, a markedly elevated T_3, and a low TSH—in contrast to the normal infant, in whom TSH is elevated at birth. TSH-R Ab [stim] is usually found in the serum of both the child and the mother.

If caused by maternal TSH-R Ab [stim], the disease is usually self-limited and subsides over a period of 4–12 weeks, coinciding with the fall in the infant's TSH-R Ab [stim] level. However, treatment is necessary because of the severe metabolic stress the infant experiences. Therapy includes propylthiouracil in a dose of 5–10 mg/kg/d in divided doses at 8-hour intervals; Lugol's solution (8 mg of iodide per drop), 1 drop every 8 hours; and propranolol, 2 mg/kg/d in divided doses. Careful supportive therapy is essential. If the infant is very ill, oral prednisone, 2 mg/kg/d in divided doses, will help block conversion of T_4 to T_3. These medications are gradually reduced as the clinical picture improves and can be discontinued by 6–12 weeks.

SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism is defined as a suppressed TSH level (below the normal range) in conjunction with normal thyroid hormone levels. Cardiac toxicity (eg, atrial fibrillation), especially in older persons, is of greatest concern. The consensus of thyroid experts concluded that hyperthyroidism treatment is appropriate in those with TSH less than 0.1 mIU/L, while close monitoring of the TSH level is appropriate for those with less TSH suppression.

Amiodarone-Induced Thyrotoxicosis

In addition to those patients who develop hypothyroidism caused by amiodarone, approximately 3% of patients receiving this drug will develop hyperthyroidism instead. Two types of amiodarone-induced thyrotoxicosis have been reported: iodine-induced (type I), which often occurs in persons with underlying thyroid disease (eg, multinodular goiter); and an inflammatory thyroiditis

*To prepare a water suspension propylthiouracil enema, grind eight 50 mg tablets and suspend the powder in 90 mL of sterile water.

(type II) that occurs in patients without thyroid disease due to leakage of thyroid hormone into the circulation. Treatment of type I requires therapy with thioamides, while type II responds best to glucocorticoids. Since it is not always possible to differentiate between the two types, thioamides and glucocorticoids are often administered together. If possible, amiodarone should be discontinued; however, rapid improvement does not occur due to its long half-life.

NONTOXIC GOITER

Nontoxic goiter is a syndrome of thyroid enlargement without excessive thyroid hormone production. Enlargement of the thyroid gland is often due to TSH stimulation from inadequate thyroid hormone synthesis. The most common cause of nontoxic goiter worldwide is iodide deficiency, but in the USA, it is Hashimoto's thyroiditis. Other causes include germ-line or acquired mutations in genes involved in hormone synthesis, dietary goitrogens, and neoplasms (see below).

Goiter due to iodide deficiency is best managed by prophylactic administration of iodide. The optimal daily iodide intake is 150–200 mcg. Iodized salt and iodate used as preservatives in flour and bread are excellent sources of iodine in the diet. In areas where it is difficult to introduce iodized salt or iodate preservatives, a solution of iodized poppy-seed oil has been administered intramuscularly to provide a long-term source of inorganic iodine.

Goiter due to ingestion of goitrogens in the diet is managed by elimination of the goitrogen or by adding sufficient thyroxine to shut off TSH stimulation. Similarly, in Hashimoto's thyroiditis and dyshormonogenesis, adequate thyroxine therapy—150–200 mcg/d orally—will suppress pituitary TSH and result in slow regression of the goiter as well as correction of hypothyroidism.

THYROID NEOPLASMS

Neoplasms of the thyroid gland may be benign (adenomas) or malignant. The primary diagnostic test is a fine needle aspiration biopsy and cytologic examination. Benign lesions may be monitored for growth or symptoms of local obstruction, which would mandate surgical excision. Levothyroxine therapy is not recommended for the suppression of benign nodules, especially in iodine sufficient areas. Management of thyroid carcinoma requires a total thyroidectomy, postoperative radioiodine therapy in selected instances, and lifetime replacement with levothyroxine. The evaluation for recurrence of some thyroid malignancies often involves withdrawal of thyroxine replacement for 4–6 weeks—accompanied by the development of hypothyroidism. Tumor recurrence is likely if there is a rise in serum thyroglobulin (ie, a tumor marker) or a positive ^{131}I scan when TSH is elevated. Alternatively, administration of recombinant human TSH (Thyrogen) can produce comparable TSH elevations without discontinuing thyroxine and avoiding hypothyroidism. Recombinant human TSH is administered intramuscularly once daily for 2 days. A rise in serum thyroglobulin or a positive ^{131}I scan will indicate a recurrence of the thyroid cancer.

SUMMARY Drugs Used in the Management of Thyroid Disease

Class	Mechanism of Action and Effects	Indications	Pharmacokinetics, Toxicities, Interactions
Thyroid Preparations			
• Levothyroxine (T_4) • Liothyronine (T_3)	Activation of nuclear receptors results in gene expression with RNA formation and protein synthesis	Hypothyroidism	See Table 38–1• maximum effect seen after 6–8 weeks of therapy • *Toxicity:* See Table 38–4 for symptoms of thyroid excess
Antithyroid Agents			
THIOAMIDES			
• Methimazole • Propylthiouracil (PTU)	Inhibit thyroid peroxidase reactions • block iodine organification • inhibit peripheral deiodination of T_4 and T_3 (primarily PTU)	Hyperthyroidism	Oral • duration of action: 24 h (methimazole), 6–8 h (PTU) • delayed onset of action • *Toxicity:* Nausea, gastrointestinal distress, rash, agranulocytosis, hepatitis (PTU black box), hypothyroidism
IODIDES			
• Lugol solution • Potassium iodide	Inhibit organification and hormone release • reduce the size and vascularity of the gland	Preparation for surgical thyroidectomy	Oral • acute onset within 2–7 days • *Toxicity:* Rare (see text)
BETA BLOCKERS			
• Propranolol	Inhibition of β adrenoreceptors • inhibit T_4 to T_3 conversion (only propranolol)	Hyperthyroidism, especially thyroid storm • adjunct to control tachycardia, hypertension, and atrial fibrillation	Onset within hours • duration of 4–6 h (oral propranolol) • *Toxicity:* Asthma, AV blockade, hypotension, bradycardia
RADIOACTIVE IODINE ^{131}I (RAI)			
	Radiation destruction of thyroid parenchyma	Hyperthyroidism • patients should be euthyroid or on β blockers before RAI • avoid in pregnancy or in nursing mothers	Oral • half-life 5 days • onset of 6–12 weeks • maximum effect in 3–6 months • *Toxicity:* Sore throat, sialitis, hypothyroidism

PREPARATIONS AVAILABLE

THYROID AGENTS

Levothyroxine [T_4] (generic, Levoxyl, Levo-T, Levothroid, Levolet, Novothyrox, Synthroid, Tirosint, Unithroid)
Oral: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets; 13, 25, 50, 75, 88, 100, 112, 125, 137, 150 mcg capsules
Parenteral: 200, 500 mcg per vial (100 mcg/mL when reconstituted) for injection

Liothyronine [T_3] (generic, Cytomel)
Oral: 5, 25, 50 mcg tablets
Parenteral: 10 mcg/mL

Liotrix [a 4:1 ratio of T_4: T_3] (Thyrolar)
Oral: tablets containing 12.5, 25, 30, 50, 100, 150 mcg T_4 and one fourth as much T_3

Thyroid desiccated [USP] (generic, Armour, Nature-Throid, Westhroid)
Oral: tablets containing 15, 30, 60, 90, 120, 180, 240, 300 mg; capsules containing 120, 180, 300 mg

ANTITHYROID AGENTS

Radioactive iodine (^{131}I) sodium (Iodotope, Sodium Iodide I 131 Therapeutic)
Oral: available as capsules and solution

Methimazole (generic, Tapazole)
Oral: 5, 10 mg tablets

Potassium iodide
Oral solution (generic, SSKI): 1 g/mL; (Thyroshield) 65 mg/mL
Oral solution (Lugol's solution): 100 mg/mL potassium iodide plus 50 mg/mL iodine
Oral potassium iodide tablets (generic, IOSAT, Thyro-Block, Thyro-Safe): 65, 130 mg

Propylthiouracil [PTU] (generic)
Oral: 50 mg tablets

Thyrotropin; recombinant human TSH (Thyrogen)
Parenteral: 1.1 mg per vial

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CASE STUDY ANSWER

This patient presents with the typical signs and symptoms of hypothyroidism following radioactive iodine therapy. Radioactive iodine therapy and thyroidectomy are reasonable and effective strategies for definitive treatment of her hyperthyroidism, especially before becoming pregnant to avoid an acute exacerbation of the disease during pregnancy or following delivery. This patient's hypothyroid symptoms are easily corrected by the daily administration of levothyroxine, taken orally on an empty stomach. Thyroid function tests should be checked after 6–8 weeks and the dosage adjusted to achieve a normal TSH and resolution of hypothyroid symptoms.

CHAPTER 39

Adrenocorticosteroids & Adrenocortical Antagonists

George P. Chrousos, MD

CASE STUDY

A 19-year-old man complains of anorexia, fatigue, dizziness, and weight loss of 8 months' duration. The examining physician discovers postural hypotension and moderate vitiligo (depigmented areas of skin) and obtains routine blood tests. She finds hyponatremia, hyperkalemia, and acidosis and suspects Addison's disease. She performs a standard ACTH 1–24 stimulation test, which reveals an insufficient plasma cortisol response, compatible with primary adrenal insufficiency. The diagnosis of autoimmune Addison's disease is made, and the patient must start replacement of the hormones he cannot produce himself. How should this patient be treated? What precautions should he take?

The natural adrenocortical hormones are steroid molecules produced and released by the adrenal cortex. Both natural and synthetic corticosteroids are used for the diagnosis and treatment of disorders of adrenal function. They are also used—more often and in much larger doses—for treatment of a variety of inflammatory and immunologic disorders.

Secretion of adrenocortical steroids is controlled by the pituitary release of corticotropin (ACTH). Secretion of the salt-retaining hormone aldosterone is primarily under the influence of angiotensin. Corticotropin has some actions that do not depend on its effect on adrenocortical secretion. However, its pharmacologic value as an anti-inflammatory agent and its use in testing adrenal function depend on its secretory action. Its pharmacology is discussed in Chapter 37 and is reviewed only briefly here.

Inhibitors of the synthesis or antagonists of the action of the adrenocortical steroids are important in the treatment of several conditions. These agents are described at the end of this chapter.

ADRENOCORTICOSTEROIDS

The adrenal cortex releases a large number of steroids into the circulation. Some have minimal biologic activity and function primarily as precursors, and there are some for which no function has been established. The hormonal steroids may be classified as those having important effects on intermediary metabolism and immune function **(glucocorticoids)**, those having principally salt-retaining activity **(mineralocorticoids)**, and those having **androgenic** or **estrogenic** activity (see Chapter 40). In humans, the major glucocorticoid is **cortisol** and the most important mineralocorticoid is **aldosterone**. Quantitatively, dehydroepiandrosterone (DHEA) in its sulfated form (DHEAS) is the major adrenal androgen. However, DHEA and two other adrenal androgens, androstenediol and androstenedione, are weak androgens or (by conversion) estrogens. Adrenal androgens constitute the major endogenous precursors of estrogen in women after menopause and in younger patients in whom ovarian function is deficient or absent.

THE NATURALLY OCCURRING GLUCOCORTICOIDS; CORTISOL (HYDROCORTISONE)

Pharmacokinetics

Cortisol (also called hydrocortisone, compound F) exerts a wide range of physiologic effects, including regulation of intermediary metabolism, cardiovascular function, growth, and immunity. Its synthesis and secretion are tightly regulated by the central nervous system, which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids. Cortisol is synthesized from cholesterol (as shown in Figure 39–1). The mechanisms controlling its secretion are discussed in Chapter 37.

In the normal adult, in the absence of stress, 10–20 mg of cortisol is secreted daily. The rate of secretion follows a circadian rhythm governed by pulses of ACTH that peak in the early morning hours and after meals, especially after lunch (Figure 39–2). In plasma, cortisol is bound to circulating proteins. Corticosteroid-binding globulin (CBG), an α_2 globulin synthesized by the liver, binds about 90% of the circulating hormone under normal circumstances. The remainder is free (about 5–10%) or loosely bound to albumin (about 5%) and is available to exert its effect on target cells. When plasma cortisol levels exceed 20–30 mcg/dL, CBG is saturated, and the concentration of free cortisol rises rapidly. CBG is increased in pregnancy and with estrogen administration and in hyperthyroidism. It is decreased by hypothyroidism, genetic defects in synthesis, and protein deficiency states. Albumin has a large capacity but low affinity for cortisol, and for practical purposes albumin-bound cortisol should be considered free. Synthetic corticosteroids such as dexamethasone are largely bound to albumin rather than CBG.

The half-life of cortisol in the circulation is normally about 60–90 minutes; it may be increased when hydrocortisone (the pharmaceutical preparation of cortisol) is administered in large

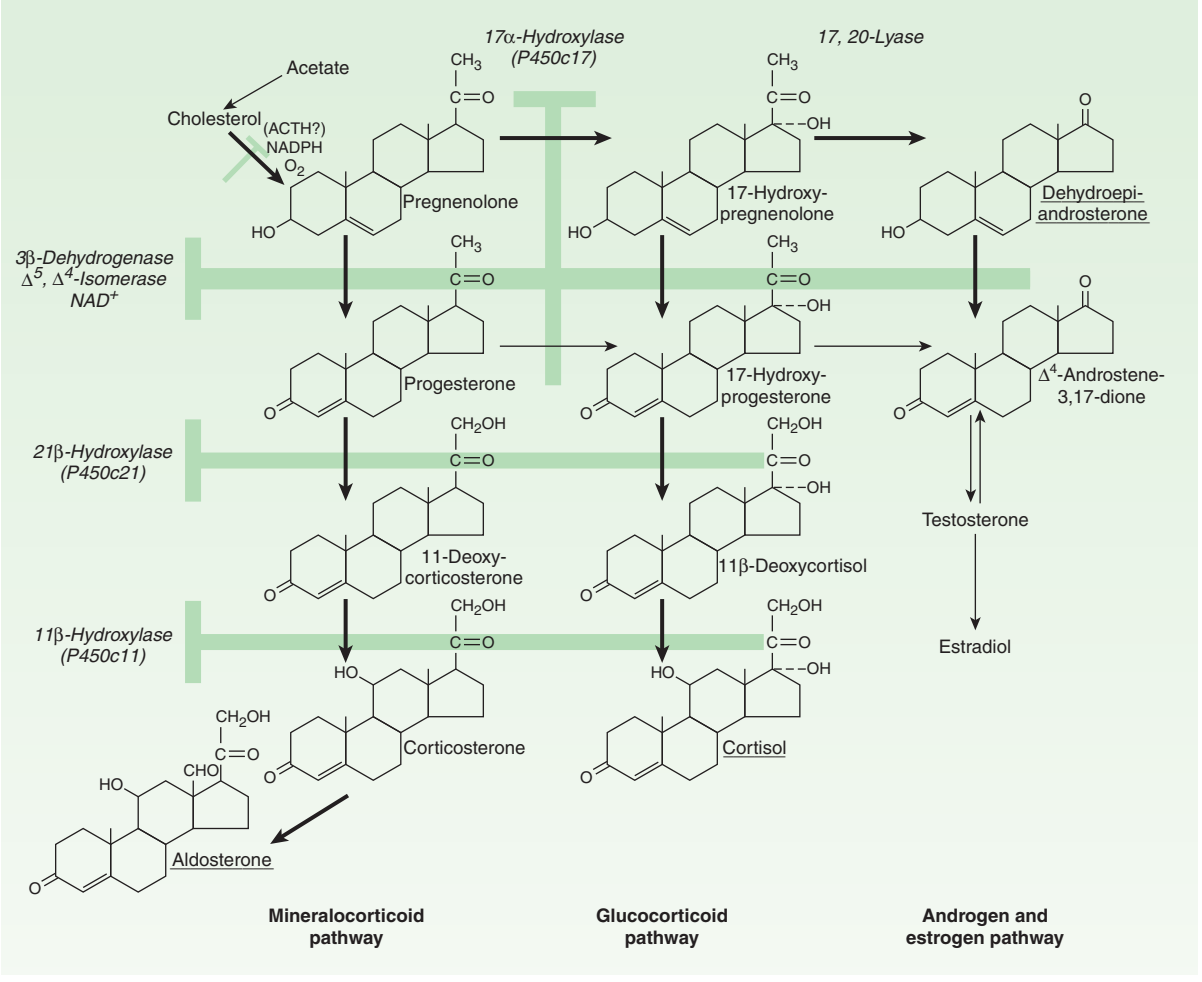


FIGURE 39–1 Outline of major pathways in adrenocortical hormone biosynthesis. The major secretory products are underlined. Pregnenolone is the major precursor of corticosterone and aldosterone, and 17-hydroxypregnenolone is the major precursor of cortisol. The enzymes and cofactors for the reactions progressing down each column are shown on the left and across columns at the top of the figure. When a particular enzyme is deficient, hormone production is blocked at the points indicated by the shaded bars. (Modified after Welikey et al; reproduced, with permission, from Ganong WF: *Review of Medical Physiology*, 17th ed. Originally published by Appleton & Lange. Copyright © 1995 by The McGraw-Hill Companies, Inc.)

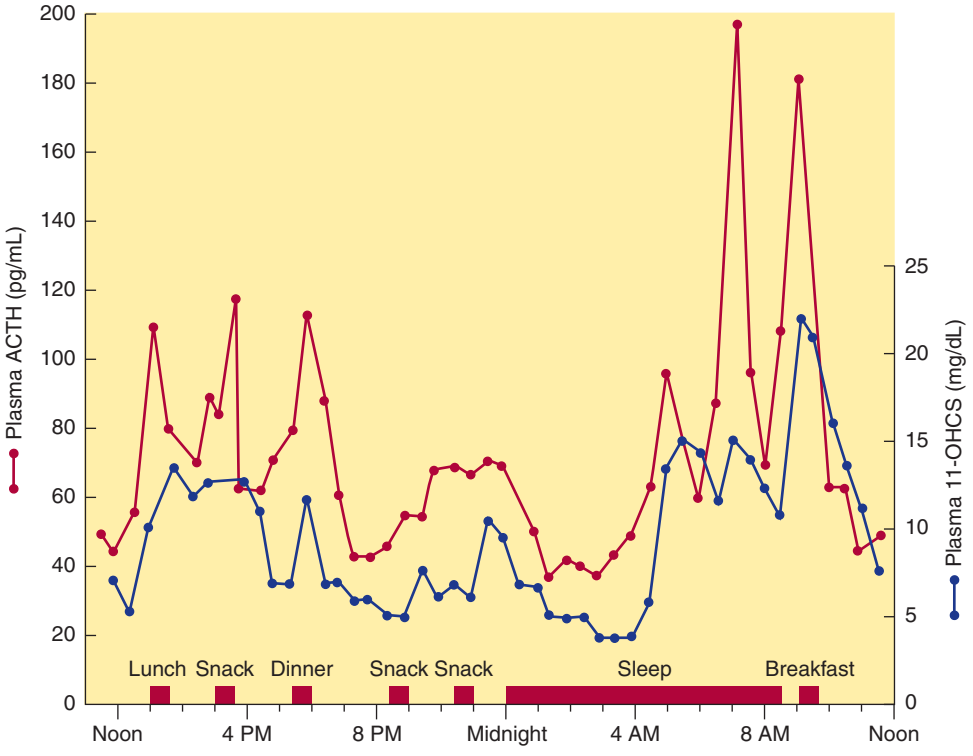


FIGURE 39–2 Fluctuations in plasma ACTH and glucocorticoids throughout the day in a normal girl (age 16). The ACTH was measured by immunoassay and the glucocorticoids as 11-oxysteroids (11-OHCS). Note the marked ACTH and glucocorticoid rises in the morning, before awakening from sleep. (Reproduced, with permission, from Krieger DT et al: Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 1971;32:266.)

amounts or when stress, hypothyroidism, or liver disease is present. Only 1% of cortisol is excreted unchanged in the urine as free cortisol; about 20% of cortisol is converted to cortisone by 11-hydroxysteroid dehydrogenase in the kidney and other tissues with mineralocorticoid receptors (see below) before reaching the liver. Most cortisol is metabolized in the liver. About one third of the cortisol produced daily is excreted in the urine as dihydroxy ketone metabolites and is measured as 17-hydroxysteroids (see Figure 39–3 for carbon numbering). Many cortisol metabolites are conjugated with glucuronic acid or sulfate at the C_3 and C_{21} hydroxyls, respectively, in the liver; they are then excreted in the urine.

In some species (eg, the rat), corticosterone is the major glucocorticoid. It is less firmly bound to protein and therefore metabolized more rapidly. The pathways of its degradation are similar to those of cortisol.

Pharmacodynamics

A. Mechanism of Action

Most of the known effects of the glucocorticoids are mediated by widely distributed glucocorticoid receptors. These proteins are members of the superfamily of nuclear receptors, which includes steroid, sterol (vitamin D), thyroid, retinoic acid, and many other receptors with unknown or nonexistent ligands (orphan receptors). All these receptors interact with the promoters of—and regulate the transcription of—target genes (Figure 39–4). In the absence of the hormonal ligand, glucocorticoid receptors are primarily cytoplasmic, in oligomeric complexes with heat-shock proteins (hsp). The most important of these are two molecules of hsp90, although other proteins are certainly involved. Free hormone from the plasma and interstitial fluid enters the cell and binds to the receptor, inducing conformational changes that allow it to dissociate from the heat shock proteins. The ligand-bound receptor complex then is actively transported into the nucleus, where it interacts with DNA and nuclear proteins. As a homodimer, it binds to **glucocorticoid receptor elements (GREs)** in the promoters of responsive genes. The GRE is composed of two palindromic sequences that bind to the hormone receptor dimer.

In addition to binding to GREs, the ligand-bound receptor also forms complexes with and influences the function of other transcription factors, such as AP1 and NF-κB, which act on non-GRE-containing promoters, to contribute to the regulation of transcription of their responsive genes. These transcription factors have broad actions on the regulation of growth factors, proinflammatory cytokines, etc, and to a great extent mediate the anti-growth, anti-inflammatory, and immunosuppressive effects of glucocorticoids.

Two genes for the corticoid receptor have been identified: one encoding the classic glucocorticoid receptor **(GR)** and the other encoding the mineralocorticoid receptor **(MR).** Alternative splicing of human glucocorticoid receptor pre-mRNA generates two highly homologous isoforms, termed hGR alpha and hGR beta. Human GR alpha is the classic ligand-activated glucocorticoid receptor

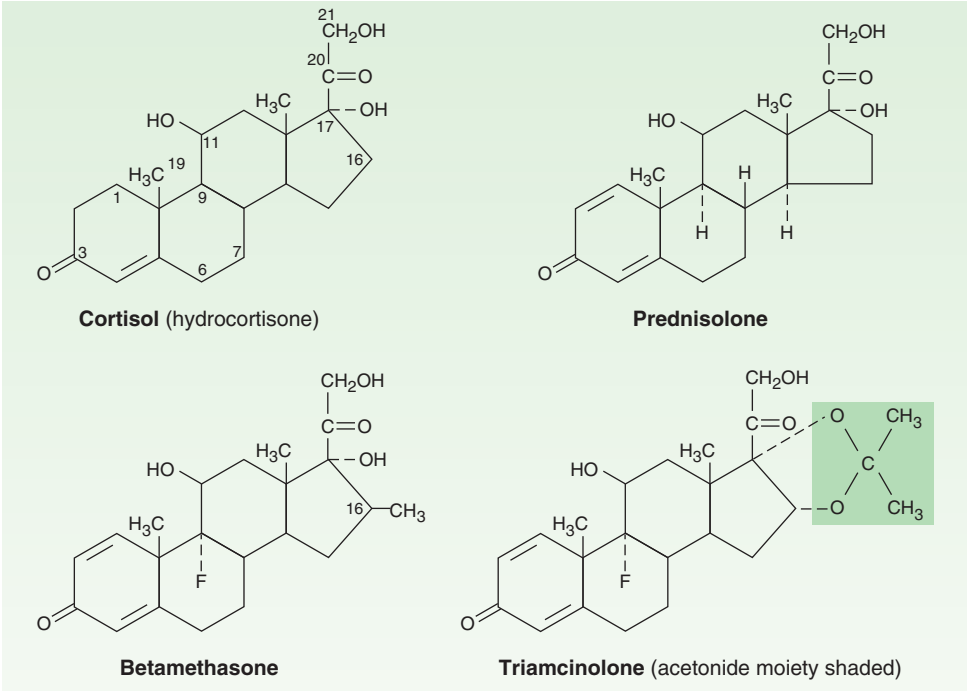


FIGURE 39–3 Chemical structures of several glucocorticoids. The acetonide-substituted derivatives (eg, triamcinolone acetonide) have increased surface activity and are useful in dermatology. Dexamethasone is identical to betamethasone except for the configuration of the methyl group at C_{16}: in betamethasone it is beta (projecting *up* from the plane of the rings); in dexamethasone it is alpha.

which, in the hormone-bound state, modulates the expression of glucocorticoid-responsive genes. In contrast, hGR beta does not bind glucocorticoids and is transcriptionally inactive. However, hGR beta is able to inhibit the effects of hormone-activated hGR alpha on glucocorticoid-responsive genes, playing the role of a physiologically relevant endogenous inhibitor of glucocorticoid action. It was recently shown that the two hGR alternative transcripts have eight distinct translation initiation sites; ie, in a human cell there may be up to 16 GRα and GRβ isoforms, which may form up to 256 homodimers and heterodimers with different transcriptional and possibly non-transcriptional activities. This variability suggests that this important class of steroid receptors has complex stochastic activities.

The prototype glucocorticoid receptor isoform is composed of about 800 amino acids and can be divided into three functional domains (see Figure 2–6). The glucocorticoid-binding domain is located at the carboxyl terminal of the molecule. The DNA-binding domain is located in the middle of the protein and contains nine cysteine residues. This region folds into a "two-finger" structure stabilized by zinc ions connected to cysteines to form two tetrahedrons. This part of the molecule binds to the GREs that regulate glucocorticoid action on glucocorticoid-regulated genes. The zinc fingers represent the basic structure by which the DNA-binding domain recognizes specific nucleic acid sequences. The amino-terminal domain is involved in the transactivation activity of the receptor and increases its specificity.

The interaction of glucocorticoid receptors with GREs or other transcription factors is facilitated or inhibited by several families of proteins called steroid receptor *coregulators*, divided into *coactivators* and *corepressors*. The coregulators do this by serving as bridges between the receptors and other nuclear proteins and by expressing enzymatic activities such as histone acetylase or deacetylase, which alter the conformation of nucleosomes and the transcribability of genes.

Between 10% and 20% of expressed genes in a cell are regulated by glucocorticoids. The number and affinity of receptors for the hormone, the complement of transcription factors and coregulators, and post-transcription events determine the relative specificity of these hormones' actions in various cells. The effects of glucocorticoids are mainly due to proteins synthesized from mRNA transcribed from their target genes.

Some of the effects of glucocorticoids can be attributed to their binding to mineralocorticoid receptors (MRs). Indeed, MRs bind aldosterone and cortisol with similar affinity. A mineralocorticoid effect of cortisol is avoided in some tissues by expression of 11β-hydroxysteroid dehydrogenase type 2, the enzyme responsible for biotransformation to its 11-keto derivative (cortisone), which has minimal affinity for aldosterone receptors.

Recently, the GR was found to interact with CLOCK/BMAL-1, a transcription factor dimer expressed in all tissues and generating the circadian rhythm of cortisol secretion at the suprachiasmatic nucleus of the hypothalamus. CLOCK is an acetyltransferase that acetylates the hinge region of the GR, neutralizing its transcriptional activity and thus rendering target tissues resistant to glucocorticoids. Interestingly, the glucocorticoid target tissue sensitivity rhythm generated is in reverse phase to that of circulating cortisol concentrations, explaining the increased sensitivity of the organism to evening administration of glucocorticoids.

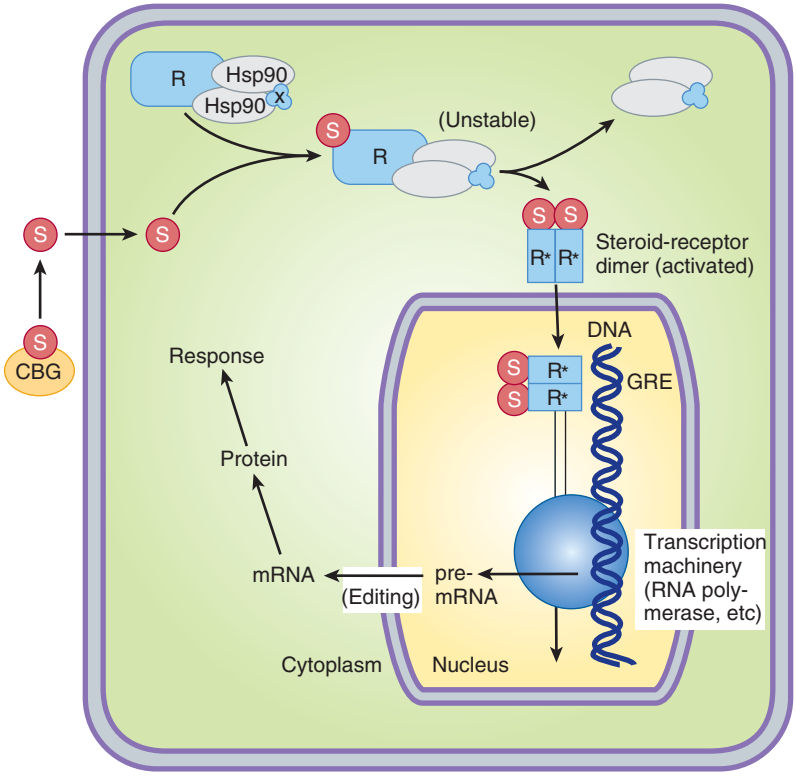


FIGURE 39–4 A model of the interaction of a steroid, S (eg, cortisol), and its receptor, R, and the subsequent events in a target cell. The steroid is present in the blood in bound form on the corticosteroid-binding globulin (CBG) but enters the cell as the free molecule. The intracellular receptor is bound to stabilizing proteins, including two molecules of heat-shock protein 90 (hsp90) and several others, denoted as "X" in the figure. This receptor complex is incapable of activating transcription. When the complex binds a molecule of cortisol, an unstable complex is created and the hsp90 and associated molecules are released. The steroid-receptor complex is now able to dimerize, enter the nucleus, bind to a glucocorticoid response element (GRE) on the regulatory region of the gene, and regulate transcription by RNA polymerase II and associated transcription factors. A variety of regulatory factors (not shown) may participate in facilitating (coactivators) or inhibiting (corepressors) the steroid response. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response. An alternative to the steroid-receptor complex interaction with a GRE is an interaction with and altering the function of other transcription factors, such as NF-κB in the nucleus of cells.

Prompt effects such as initial feedback suppression of pituitary ACTH occur in minutes and are too rapid to be explained on the basis of gene transcription and protein synthesis. It is not known how these effects are mediated. Among the proposed mechanisms are direct effects on cell membrane receptors for the hormone or nongenomic effects of the classic hormone-bound glucocorticoid receptor. The putative membrane receptors might be entirely different from the known intracellular receptors. Recently, all steroid receptors (except the MRs) were shown to have palmitoylation motifs that allow enzymatic addition of palmitate and increased localization of the receptors in the vicinity of plasma membranes. Such receptors are available for direct interactions with and effects on various membrane-associated or cytoplasmic proteins without the need for entry into the nucleus and induction of transcriptional actions.

B. Physiologic Effects

The glucocorticoids have widespread effects because they influence the function of most cells in the body. The major metabolic consequences of glucocorticoid secretion or administration are due to direct actions of these hormones in the cell. However, some important effects are the result of homeostatic responses by insulin and glucagon. Although many of the effects of glucocorticoids are dose-related and become magnified when large amounts are administered for therapeutic purposes, there are also other effects—called *permissive* effects—without which many normal functions become deficient. For example, the response of vascular and bronchial smooth muscle to catecholamines is diminished in the absence of cortisol and restored by physiologic amounts of this glucocorticoid. Similarly, the lipolytic responses of fat cells to catecholamines, ACTH, and growth hormone are attenuated in the absence of glucocorticoids.

C. Metabolic Effects

The glucocorticoids have important dose-related effects on carbohydrate, protein, and fat metabolism. The same effects are responsible for some of the serious adverse effects associated with their use in therapeutic doses. Glucocorticoids stimulate and are required for gluconeogenesis and glycogen synthesis in the fasting state.

They stimulate phosphoenolpyruvate carboxykinase, glucose-6-phosphatase, and glycogen synthase and the release of amino acids in the course of muscle catabolism.

Glucocorticoids increase serum glucose levels and thus stimulate insulin release and inhibit the uptake of glucose by muscle cells, while they stimulate hormone sensitive lipase and thus lipolysis. The increased insulin secretion stimulates lipogenesis and to a lesser degree inhibits lipolysis, leading to a net increase in fat deposition combined with increased release of fatty acids and glycerol into the circulation.

The net results of these actions are most apparent in the fasting state, when the supply of glucose from gluconeogenesis, the release of amino acids from muscle catabolism, the inhibition of peripheral glucose uptake, and the stimulation of lipolysis all contribute to maintenance of an adequate glucose supply to the brain.

D. Catabolic and Antianabolic Effects

Although glucocorticoids stimulate RNA and protein synthesis in the liver, they have catabolic and antianabolic effects in lymphoid and connective tissue, muscle, peripheral fat, and skin. Supraphysiologic amounts of glucocorticoids lead to decreased muscle mass and weakness and thinning of the skin. Catabolic and antianabolic effects on bone are the cause of osteoporosis in Cushing's syndrome and impose a major limitation in the long-term therapeutic use of glucocorticoids. In children, glucocorticoids reduce growth. This effect may be partially prevented by administration of growth hormone in high doses, but this use of growth hormone is not recommended.

E. Anti-Inflammatory and Immunosuppressive Effects

Glucocorticoids dramatically reduce the manifestations of inflammation. This is due to their profound effects on the concentration, distribution, and function of peripheral leukocytes and to their suppressive effects on the inflammatory cytokines and chemokines and on other mediators of inflammation. Inflammation, regardless of its cause, is characterized by the extravasation and infiltration of leukocytes into the affected tissue. These events are mediated by a complex series of interactions of white cell adhesion molecules with those on endothelial cells and are inhibited by glucocorticoids. After a single dose of a short-acting glucocorticoid, the concentration of neutrophils in the circulation increases while the lymphocytes (T and B cells), monocytes, eosinophils, and basophils decrease. The changes are maximal at 6 hours and are dissipated in 24 hours. The increase in neutrophils is due both to the increased influx into the blood from the bone marrow and to the decreased migration from the blood vessels, leading to a reduction in the number of cells at the site of inflammation. The reduction in circulating lymphocytes, monocytes, eosinophils, and basophils is primarily the result of their movement from the vascular bed to lymphoid tissue.

Glucocorticoids also inhibit the functions of tissue macrophages and other antigen-presenting cells. The ability of these cells to respond to antigens and mitogens is reduced. The effect on macrophages is particularly marked and limits their ability to phagocytose and kill microorganisms and to produce tumor necrosis factor-α, interleukin-1, metalloproteinases, and plasminogen activator. Both macrophages and lymphocytes produce less interleukin-12 and interferon-γ, important inducers of TH1 cell activity, and cellular immunity.

In addition to their effects on leukocyte function, glucocorticoids influence the inflammatory response by reducing the prostaglandin, leukotriene, and platelet-activating factor synthesis that results from activation of phospholipase A_2. Finally, glucocorticoids reduce expression of cyclooxygenase-2, the inducible form of this enzyme, in inflammatory cells, thus reducing the amount of enzyme available to produce prostaglandins (see Chapters 18 and 36).

Glucocorticoids cause vasoconstriction when applied directly to the skin, possibly by suppressing mast cell degranulation. They also decrease capillary permeability by reducing the amount of histamine released by basophils and mast cells.

The anti-inflammatory and immunosuppressive effects of glucocorticoids are largely due to the actions described above. In humans, complement activation is unaltered, but its effects are inhibited. Antibody production can be reduced by large doses of steroids, although it is unaffected by moderate doses (eg, 20 mg/d of prednisone).

The anti-inflammatory and immunosuppressive effects of these agents are widely useful therapeutically but are also responsible for some of their most serious adverse effects (see text that follows).

F. Other Effects

Glucocorticoids have important effects on the nervous system. Adrenal insufficiency causes marked slowing of the alpha rhythm of the electroencephalogram and is associated with depression. Increased amounts of glucocorticoids often produce behavioral disturbances in humans: initially insomnia and euphoria and subsequently depression. Large doses of glucocorticoids may increase intracranial pressure (pseudotumor cerebri).

Glucocorticoids given chronically suppress the pituitary release of ACTH, growth hormone, thyroid-stimulating hormone, and luteinizing hormone.

Large doses of glucocorticoids have been associated with the development of peptic ulcer, possibly by suppressing the local immune response against *Helicobacter pylori.* They also promote fat redistribution in the body, with increase of visceral, facial, nuchal, and supraclavicular fat, and they appear to antagonize the effect of vitamin D on calcium absorption. The glucocorticoids also have important effects on the hematopoietic system. In addition to their effects on leukocytes, they increase the number of platelets and red blood cells.

Cortisol deficiency results in impaired renal function (particularly glomerular filtration), augmented vasopressin secretion, and diminished ability to excrete a water load.

Glucocorticoids have important effects on the development of the fetal lungs. Indeed, the structural and functional changes in the lungs near term, including the production of pulmonary surface-active material required for air breathing (surfactant), are stimulated by glucocorticoids.

SYNTHETIC CORTICOSTEROIDS

Glucocorticoids have become important agents for use in the treatment of many inflammatory, immunologic, hematologic, and other disorders. This has stimulated the development of many synthetic steroids with anti-inflammatory and immunosuppressive activity.

Pharmacokinetics

A. Source

Pharmaceutical steroids are usually synthesized from cholic acid obtained from cattle or steroid sapogenins found in plants. Further modifications of these steroids have led to the marketing of a large group of synthetic steroids with special characteristics that are pharmacologically and therapeutically important (Table 39–1; Figure 39–3).

B. Disposition

The metabolism of the naturally occurring adrenal steroids has been discussed above. The synthetic corticosteroids (Table 39–1) are in most cases rapidly and completely absorbed when given by mouth. Although they are transported and metabolized in a fashion similar to that of the endogenous steroids, important differences exist.

Alterations in the glucocorticoid molecule influence its affinity for glucocorticoid and mineralocorticoid receptors as well as its protein-binding affinity, side chain stability, rate of elimination, and metabolic products. Halogenation at the 9 position, unsaturation of the Δ1–2 bond of the A ring, and methylation at the 2 or 16 position prolong the half-life by more than 50%. The Δ1 compounds are excreted in the free form. In some cases, the agent given is a prodrug; for example, prednisone is rapidly converted to the active product prednisolone in the body.

Pharmacodynamics

The actions of the synthetic steroids are similar to those of cortisol (see above). They bind to the specific intracellular receptor proteins and produce the same effects but have different ratios of glucocorticoid to mineralocorticoid potency (Table 39–1).

CLINICAL PHARMACOLOGY

A. Diagnosis and Treatment of Disturbed Adrenal Function

1. Adrenocortical insufficiency

a. Chronic (Addison's disease)—Chronic adrenocortical insufficiency is characterized by weakness, fatigue, weight loss, hypotension, hyperpigmentation, and inability to maintain the blood glucose level during fasting. In such individuals, minor noxious,

TABLE 39–1 Some commonly used natural and synthetic corticosteroids for general use.

Agent	Activity[1]			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	*Topical*	*Salt-Retaining*		
Short- to medium-acting glucocorticoids					
Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable, topical
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0.25	4	Oral, injectable
Meprednisone[2]	5		0	4	Oral, injectable
Intermediate-acting glucocorticoids					
Triamcinolone	5	5[3]	0	4	Oral, injectable, topical
Paramethasone[2]	10		0	2	Oral, injectable
Fluprednisolone[2]	15	7	0	1.5	Oral
Long-acting glucocorticoids					
Betamethasone	25–40	10	0	0.6	Oral, injectable, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate[2]	0	0	20		Injectable, pellets

[1]Potency relative to hydrocortisone.

[2]Outside USA.

[3]Triamcinolone acetonide: Up to 100.

traumatic, or infectious stimuli may produce acute adrenal insufficiency with circulatory shock and even death.

In primary adrenal insufficiency, about 20–30 mg of hydrocortisone must be given daily, with increased amounts during periods of stress. Although hydrocortisone has some mineralocorticoid activity, this must be supplemented by an appropriate amount of a salt-retaining hormone such as fludrocortisone. Synthetic glucocorticoids that are long-acting and devoid of salt-retaining activity should not be administered to these patients.

b. Acute—When acute adrenocortical insufficiency is suspected, treatment must be instituted immediately. Therapy consists of large amounts of parenteral hydrocortisone in addition to correction of fluid and electrolyte abnormalities and treatment of precipitating factors.

Hydrocortisone sodium succinate or phosphate in doses of 100 mg intravenously is given every 8 hours until the patient is stable. The dose is then gradually reduced, achieving maintenance dosage within 5 days.

The administration of salt-retaining hormone is resumed when the total hydrocortisone dosage has been reduced to 50 mg/d.

2. Adrenocortical hypo- and hyperfunction

a. Congenital adrenal hyperplasia—This group of disorders is characterized by specific defects in the synthesis of cortisol. In pregnancies at high risk for congenital adrenal hyperplasia, fetuses can be protected from genital abnormalities by administration of dexamethasone to the mother. The most common defect is a decrease in or lack of P450c21 (21β-hydroxylase) activity.*

As can be seen in Figure 39–1, this would lead to a reduction in cortisol synthesis and thus produce a compensatory increase in ACTH release. The gland becomes hyperplastic and produces abnormally large amounts of precursors such as 17-hydroxyprogesterone that can be diverted to the androgen pathway, leading to virilization. Metabolism of this compound in the liver leads to pregnanetriol, which is characteristically excreted into the urine in large amounts in this disorder and can be used to make the diagnosis and to monitor efficacy of glucocorticoid substitution. However, the most reliable method of detecting this disorder is the increased response of plasma 17-hydroxyprogesterone to ACTH stimulation.

If the defect is in 11-hydroxylation, large amounts of deoxycorticosterone are produced, and because this steroid has mineralocorticoid activity, hypertension with or without hypokalemic alkalosis ensues. When 17-hydroxylation is defective in the adrenals and gonads, hypogonadism is also present. However, increased amounts of 11-deoxycorticosterone are formed, and the signs and symptoms associated with mineralocorticoid excess—such as hypertension and hypokalemia—are also observed.

When first seen, the infant with congenital adrenal hyperplasia may be in acute adrenal crisis and should be treated as described above, using appropriate electrolyte solutions and an intravenous preparation of hydrocortisone in stress doses.

Once the patient is stabilized, oral hydrocortisone, 12–18 mg/m^2/d in two unequally divided doses (two thirds in the morning, one third in late afternoon) is begun. The dosage is adjusted to allow normal growth and bone maturation and to prevent androgen excess. Alternate-day therapy with prednisone has also been used to achieve greater ACTH suppression without increasing growth inhibition. Fludrocortisone, 0.05–0.2 mg/d, should also be administered by mouth, with added salt to maintain normal blood pressure, plasma renin activity, and electrolytes.

b. Cushing's syndrome—Cushing's syndrome is usually the result of bilateral adrenal hyperplasia secondary to an ACTH-secreting pituitary adenoma (Cushing's disease) but occasionally is due to tumors or nodular hyperplasia of the adrenal gland or ectopic production of ACTH by other tumors. The manifestations are those associated with the chronic presence of excessive glucocorticoids. When glucocorticoid hypersecretion is marked and prolonged, a rounded, plethoric face and trunk obesity are striking in appearance. The manifestations of protein loss are often found and include muscle wasting; thinning, purple striae, and easy bruising of the skin; poor wound healing; and osteoporosis. Other serious disturbances include mental disorders, hypertension, and diabetes. This disorder is treated by surgical removal of the tumor producing ACTH or cortisol, irradiation of the pituitary tumor, or resection of one or both adrenals. These patients must receive large doses of cortisol during and after the surgical procedure. Doses of up to 300 mg of soluble hydrocortisone may be given as a continuous intravenous infusion on the day of surgery. The dose must be reduced slowly to normal replacement levels, since rapid reduction in dose may produce withdrawal symptoms, including fever and joint pain. If adrenalectomy has been performed, long-term maintenance is similar to that outlined above for adrenal insufficiency.

c. Primary generalized glucocorticoid resistance (Chrousos) syndrome—This rare sporadic or familial genetic condition is usually due to inactivating mutations of the glucocorticoid receptor gene. In its attempt to compensate for the defect, the hypothalamic-pituitary-adrenal (HPA) axis is hyperfunctioning with the increased production of ACTH leading to high circulating levels of cortisol and cortisol precursors such as corticosterone and 11-deoxycorticosterone with mineralocorticoid activity, as well as of adrenal androgens. These may result in hypertension with or without hypokalemic alkalosis and hyperandrogenism expressed as virilization and precocious puberty in children and acne, hirsutism, male pattern baldness, and menstrual irregularities (mostly oligo-amenorrhea and hypofertility) in women. The therapy of this syndrome is high doses of synthetic glucocorticoids such as dexamethasone with no inherent mineralocorticoid activity. These doses are titrated to normalize the production of cortisol, cortisol precursors, and adrenal androgens.

d. Aldosteronism—Primary aldosteronism usually results from the excessive production of aldosterone by an adrenal adenoma. However, it may also result from abnormal secretion by hyperplastic

*Names for the adrenal steroid synthetic enzymes include the following:
P450c11 (11-hydroxylase)
P450c17 (17-hydroxylase)
P450c21 (21-hydroxylase)

glands or from a malignant tumor. The clinical findings of hypertension, weakness, and tetany are related to the continued renal loss of potassium, which leads to hypokalemia, alkalosis, and elevation of serum sodium concentrations. This syndrome can also be produced in disorders of adrenal steroid biosynthesis by excessive secretion of deoxycorticosterone, corticosterone, or 18-hydroxycorticosterone—all compounds with inherent mineralocorticoid activity.

In contrast to patients with secondary aldosteronism (see text that follows), these patients have low (suppressed) levels of plasma renin activity and angiotensin II. When treated with fludrocortisone (0.2 mg twice daily orally for 3 days) or deoxycorticosterone acetate (20 mg/d intramuscularly for 3 days—but not available in the USA), patients fail to retain sodium and the secretion of aldosterone is not significantly reduced. When the disorder is mild, it may escape detection if serum potassium levels are used for screening. However, it may be detected by an increased ratio of plasma aldosterone to renin. Patients generally improve when treated with spironolactone, an aldosterone receptor-blocking agent, and the response to this agent is of diagnostic and therapeutic value.

3. Use of glucocorticoids for diagnostic purposes—It is sometimes necessary to suppress the production of ACTH to identify the source of a particular hormone or to establish whether its production is influenced by the secretion of ACTH. In these circumstances, it is advantageous to use a very potent substance such as dexamethasone because the use of small quantities reduces the possibility of confusion in the interpretation of hormone assays in blood or urine. For example, if complete suppression is achieved by the use of 50 mg of cortisol, the urinary 17-hydroxycorticosteroids will be 15–18 mg/24 h, since one third of the dose given will be recovered in urine as 17-hydroxycorticosteroid. If an equivalent dose of 1.5 mg of dexamethasone is used, the urinary excretion will be only 0.5 mg/24 h and blood levels will be low.

The **dexamethasone suppression test** is used for the diagnosis of Cushing's syndrome and has also been used in the differential diagnosis of depressive psychiatric states. As a screening test, 1 mg dexamethasone is given orally at 11 PM, and a plasma sample is obtained the following morning. In normal individuals, the morning cortisol concentration is usually less than 3 mcg/dL, whereas in Cushing's syndrome the level is usually greater than 5 mcg/dL. The results are not reliable in the patient with depression, anxiety, concurrent illness, and other stressful conditions or in the patient who is receiving a medication that enhances the catabolism of dexamethasone in the liver. To distinguish between hypercortisolism due to anxiety, depression, and alcoholism (pseudo-Cushing syndrome) and bona fide Cushing's syndrome, a combined test is carried out, consisting of dexamethasone (0.5 mg orally every 6 hours for 2 days) followed by a standard corticotropin-releasing hormone (CRH) test (1 mg/kg given as a bolus intravenous infusion 2 hours after the last dose of dexamethasone).

In patients in whom the diagnosis of Cushing's syndrome has been established clinically and confirmed by a finding of elevated free cortisol in the urine, suppression with large doses of dexamethasone will help to distinguish patients with Cushing's disease from those with steroid-producing tumors of the adrenal cortex or with the ectopic ACTH syndrome. Dexamethasone is given in a dosage of 0.5 mg orally every 6 hours for 2 days, followed by 2 mg orally every 6 hours for 2 days, and the urine is then assayed for cortisol or its metabolites (Liddle's test); or dexamethasone is given as a single dose of 8 mg at 11 PM, and the plasma cortisol is measured at 8 AM the following day. In patients with Cushing's disease, the suppressant effect of dexamethasone usually produces a 50% reduction in hormone levels. In patients in whom suppression does not occur, the ACTH level will be low in the presence of a cortisol-producing adrenal tumor and elevated in patients with an ectopic ACTH-producing tumor.

B. Corticosteroids and Stimulation of Lung Maturation in the Fetus

Lung maturation in the fetus is regulated by the fetal secretion of cortisol. Treatment of the mother with large doses of glucocorticoid reduces the incidence of respiratory distress syndrome in infants delivered prematurely. When delivery is anticipated before 34 weeks of gestation, intramuscular betamethasone, 12 mg, followed by an additional dose of 12 mg 18–24 hours later, is commonly used. Betamethasone is chosen because maternal protein binding and placental metabolism of this corticosteroid is less than that of cortisol, allowing increased transfer across the placenta to the fetus.

C. Corticosteroids and Nonadrenal Disorders

The synthetic analogs of cortisol are useful in the treatment of a diverse group of diseases unrelated to any known disturbance of adrenal function (Table 39–2). The usefulness of corticosteroids in these disorders is a function of their ability to suppress inflammatory and immune responses and to alter leukocyte function, as previously described and as described in Chapter 55. These agents are useful in disorders in which host response is the cause of the major manifestations of the disease. In instances in which the inflammatory or immune response is important in controlling the pathologic process, therapy with corticosteroids may be dangerous but justified to prevent irreparable damage from an inflammatory response—if used in conjunction with specific therapy for the disease process.

Since corticosteroids are not usually curative, the pathologic process may progress while clinical manifestations are suppressed. Therefore, chronic therapy with these drugs should be undertaken with great care and only when the seriousness of the disorder warrants their use and when less hazardous measures have been exhausted.

In general, attempts should be made to bring the disease process under control using medium- to intermediate-acting glucocorticoids such as prednisone and prednisolone (Table 39–1), as well as all ancillary measures possible to keep the dose low. Where possible, alternate-day therapy should be used (see the following text). Therapy should not be decreased or stopped abruptly. When prolonged therapy is anticipated, it is helpful to obtain chest x-rays and a tuberculin test, since glucocorticoid therapy can reactivate dormant tuberculosis. The presence of diabetes, peptic ulcer, osteoporosis, and psychological disturbances should be taken into consideration, and cardiovascular function should be assessed.

TABLE 39–2 Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders.

Disorder	Examples
Allergic reactions	Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria
Collagen-vascular disorders	Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis
Eye diseases	Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis
Gastrointestinal diseases	Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis
Hematologic disorders	Acquired hemolytic anemia, acute allergic purpura, leukemia, lymphoma, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma
Systemic inflammation	Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality)
Infections	Acute respiratory distress syndrome, sepsis
Inflammatory conditions of bones and joints	Arthritis, bursitis, tenosynovitis
Neurologic disorders	Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis
Renal disorders	Nephrotic syndrome
Skin diseases	Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis
Thyroid diseases	Malignant exophthalmos, subacute thyroiditis
Miscellaneous	Hypercalcemia, mountain sickness

Treatment for transplant rejection is a very important application of glucocorticoids. The efficacy of these agents is based on their ability to reduce antigen expression from the grafted tissue, delay revascularization, and interfere with the sensitization of cytotoxic T lymphocytes and the generation of primary antibody-forming cells.

Toxicity

The benefits obtained from glucocorticoids vary considerably. Use of these drugs must be carefully weighed in each patient against their widespread effects on every part of the organism. The major undesirable effects of glucocorticoids are the result of their hormonal actions, which lead to the clinical picture of iatrogenic Cushing's syndrome (see later in text).

When glucocorticoids are used for short periods (< 2 weeks), it is unusual to see serious adverse effects even with moderately large doses. However, insomnia, behavioral changes (primarily hypomania), and acute peptic ulcers are occasionally observed even after only a few days of treatment. Acute pancreatitis is a rare but serious acute adverse effect of high-dose glucocorticoids.

A. Metabolic Effects

Most patients who are given daily doses of 100 mg of hydrocortisone or more (or the equivalent amount of synthetic steroid) for longer than 2 weeks undergo a series of changes that have been termed iatrogenic Cushing's syndrome. The rate of development is a function of the dosage and the genetic background of the patient. In the face, rounding, puffiness, fat deposition, and plethora usually appear (moon facies). Similarly, fat tends to be redistributed from the extremities to the trunk, the back of the neck, and the supraclavicular fossae. There is an increased growth of fine hair over the face, thighs and trunk. Steroid-induced punctate acne may appear, and insomnia and increased appetite are noted. In the treatment of dangerous or disabling disorders, these changes may not require cessation of therapy. However, the underlying metabolic changes accompanying them can be very serious by the time they become obvious. The continuing breakdown of protein and diversion of amino acids to glucose production increase the need for insulin and over time result in weight gain; visceral fat deposition; myopathy and muscle wasting; thinning of the skin, with striae and bruising; hyperglycemia; and eventually osteoporosis, diabetes, and aseptic necrosis of the hip. Wound healing is also impaired under these circumstances. When diabetes occurs, it is treated with diet and insulin. These patients are often resistant to insulin but rarely develop ketoacidosis. In general, patients treated with corticosteroids should be on high-protein and potassium-enriched diets.

B. Other Complications

Other serious adverse effects of glucocorticoids include peptic ulcers and their consequences. The clinical findings associated with certain disorders, particularly bacterial and mycotic infections, may be masked by the corticosteroids, and patients must be carefully monitored to avoid serious mishap when large doses are used. Severe myopathy is more frequent in patients treated with long-acting glucocorticoids. The administration of such compounds has been associated with nausea, dizziness, and weight loss in some patients. It is treated by changing drugs, reducing dosage, and increasing potassium and protein intake.

Hypomania or acute psychosis may occur, particularly in patients receiving very large doses of corticosteroids. Long-term therapy with intermediate- and long-acting steroids is associated with depression and the development of posterior subcapsular cataracts. Psychiatric follow-up and periodic slit-lamp examination is indicated in such patients. Increased intraocular pressure is common, and glaucoma may be induced. Benign intracranial

hypertension also occurs. In dosages of 45 mg/m^2/d or more of hydrocortisone or its equivalent, growth retardation occurs in children. Medium-, intermediate-, and long-acting glucocorticoids have greater growth-suppressing potency than the natural steroid at equivalent doses.

When given in larger than physiologic amounts, steroids such as cortisone and hydrocortisone, which have mineralocorticoid effects in addition to glucocorticoid effects, cause some sodium and fluid retention and loss of potassium. In patients with normal cardiovascular and renal function, this leads to a hypokalemic, hypochloremic alkalosis and eventually to a rise in blood pressure. In patients with hypoproteinemia, renal disease, or liver disease, edema may also occur. In patients with heart disease, even small degrees of sodium retention may lead to heart failure. These effects can be minimized by using synthetic non-salt-retaining steroids, sodium restriction, and judicious amounts of potassium supplements.

C. Adrenal Suppression

When corticosteroids are administered for more than 2 weeks, adrenal suppression may occur. If treatment extends over weeks to months, the patient should be given appropriate supplementary therapy at times of minor stress (two-fold dosage increases for 24–48 hours) or severe stress (up to ten-fold dosage increases for 48–72 hours) such as accidental trauma or major surgery. If corticosteroid dosage is to be reduced, it should be tapered slowly. If therapy is to be stopped, the reduction process should be quite slow when the dose reaches replacement levels. It may take 2–12 months for the hypothalamic-pituitary-adrenal axis to function acceptably, and cortisol levels may not return to normal for another 6–9 months. The glucocorticoid-induced suppression is not a pituitary problem, and treatment with ACTH does not reduce the time required for the return of normal function.

If the dosage is reduced too rapidly in patients receiving glucocorticoids for a certain disorder, the symptoms of the disorder may reappear or increase in intensity. However, patients without an underlying disorder (eg, patients cured surgically of Cushing's disease) also develop symptoms with rapid reductions in corticosteroid levels. These symptoms include anorexia, nausea or vomiting, weight loss, lethargy, headache, fever, joint or muscle pain, and postural hypotension. Although many of these symptoms may reflect true glucocorticoid deficiency, they may also occur in the presence of normal or even elevated plasma cortisol levels, suggesting glucocorticoid dependence.

Contraindications & Cautions

A. Special Precautions

Patients receiving glucocorticoids must be monitored carefully for the development of hyperglycemia, glycosuria, sodium retention with edema or hypertension, hypokalemia, peptic ulcer, osteoporosis, and hidden infections.

The dosage should be kept as low as possible, and intermittent administration (eg, alternate-day) should be used when satisfactory therapeutic results can be obtained on this schedule. Even patients maintained on relatively low doses of corticosteroids may require supplementary therapy at times of stress, such as when surgical procedures are performed or intercurrent illness or accidents occur.

B. Contraindications

Glucocorticoids must be used with great caution in patients with peptic ulcer, heart disease or hypertension with heart failure, certain infectious illnesses such as varicella and tuberculosis, psychoses, diabetes, osteoporosis, or glaucoma.

Selection of Drug & Dosage Schedule

Glucocorticoid preparations differ with respect to relative anti-inflammatory and mineralocorticoid effect, duration of action, cost, and dosage forms available (Table 39–1), and these factors should be taken into account in selecting the drug to be used.

A. ACTH versus Adrenocortical Steroids

In patients with normal adrenals, ACTH was used in the past to induce the endogenous production of cortisol to obtain similar effects. However, except when an increase in androgens is desirable, the use of ACTH as a therapeutic agent has been abandoned. Instances in which ACTH was claimed to be more effective than glucocorticoids were probably due to the administration of smaller amounts of corticosteroids than were produced by the dosage of ACTH.

B. Dosage

In determining the dosage regimen to be used, the physician must consider the seriousness of the disease, the amount of drug likely to be required to obtain the desired effect, and the duration of therapy. In some diseases, the amount required for maintenance of the desired therapeutic effect is less than the dose needed to obtain the initial effect, and the lowest possible dosage for the needed effect should be determined by gradually lowering the dose until a small increase in signs or symptoms is noted.

When it is necessary to maintain continuously elevated plasma corticosteroid levels to suppress ACTH, a slowly absorbed parenteral preparation or small oral doses at frequent intervals are required. The opposite situation exists with respect to the use of corticosteroids in the treatment of inflammatory and allergic disorders. The same total quantity given in a few doses may be more effective than that given in many smaller doses or in a slowly absorbed parenteral form.

Severe autoimmune conditions involving vital organs must be treated aggressively, and undertreatment is as dangerous as overtreatment. To minimize the deposition of immune complexes and the influx of leukocytes and macrophages, 1 mg/kg/d of prednisone in divided doses is required initially. This dosage is maintained until the serious manifestations respond. The dosage can then be gradually reduced.

When large doses are required for prolonged periods of time, alternate-day administration of the compound may be tried after control is achieved. When used in this manner, very large amounts (eg, 100 mg of prednisone) can sometimes be administered with less

marked adverse effects because there is a recovery period between each dose. The transition to an alternate-day schedule can be made after the disease process is under control. It should be done gradually and with additional supportive measures between doses.

When selecting a drug for use in large doses, a medium- or intermediate-acting synthetic steroid with little mineralocorticoid effect is advisable. If possible, it should be given as a single morning dose.

C. Special Dosage Forms

Local therapy, such as topical preparations for skin disease, ophthalmic forms for eye disease, intra-articular injections for joint disease, inhaled steroids for asthma, and hydrocortisone enemas for ulcerative colitis, provides a means of delivering large amounts of steroid to the diseased tissue with reduced systemic effects.

Beclomethasone dipropionate, and several other glucocorticoids—primarily budesonide, flunisolide, and mometasone furoate, administered as aerosols—have been found to be extremely useful in the treatment of asthma (see Chapter 20).

Beclomethasone dipropionate, triamcinolone acetonide, budesonide, flunisolide, and mometasone furoate are available as nasal sprays for the topical treatment of allergic rhinitis. They are effective at doses (one or two sprays one, two, or three times daily) that in most patients result in plasma levels that are too low to influence adrenal function or have any other systemic effects.

Corticosteroids incorporated in ointments, creams, lotions, and sprays are used extensively in dermatology. These preparations are discussed in more detail in Chapter 61.

MINERALOCORTICOIDS (ALDOSTERONE, DEOXYCORTICOSTERONE, FLUDROCORTISONE)

The most important mineralocorticoid in humans is aldosterone. However, small amounts of deoxycorticosterone (DOC) are also formed and released. Although the amount is normally insignificant, DOC was of some importance therapeutically in the past. Its actions, effects, and metabolism are qualitatively similar to those described below for aldosterone.

Fludrocortisone, a synthetic corticosteroid, is the most commonly prescribed salt-retaining hormone.

Aldosterone

Aldosterone is synthesized mainly in the zona glomerulosa of the adrenal cortex. Its structure and synthesis are illustrated in Figure 39–1.

The rate of aldosterone secretion is subject to several influences. ACTH produces a moderate stimulation of its release, but this effect is not sustained for more than a few days in the normal individual. Although aldosterone is no less than one third as effective as cortisol in suppressing ACTH, the quantities of aldosterone produced by the adrenal cortex and its plasma concentrations are insufficient to participate in any significant feedback control of ACTH secretion.

Without ACTH, aldosterone secretion falls to about half the normal rate, indicating that other factors, eg, angiotensin, are able to maintain and perhaps regulate its secretion (see Chapter 17). Independent variations between cortisol and aldosterone secretion can also be demonstrated by means of lesions in the nervous system such as decerebration, which decreases the secretion of cortisol while increasing the secretion of aldosterone.

A. Physiologic and Pharmacologic Effects

Aldosterone and other steroids with mineralocorticoid properties promote the reabsorption of sodium from the distal part of the distal convoluted renal tubule and from the cortical collecting tubules, loosely coupled to the excretion of potassium and hydrogen ion. Sodium reabsorption in the sweat and salivary glands, gastrointestinal mucosa, and across cell membranes in general is also increased. Excessive levels of aldosterone produced by tumors or overdosage with synthetic mineralocorticoids lead to hypokalemia, metabolic alkalosis, increased plasma volume, and hypertension.

Mineralocorticoids act by binding to the mineralocorticoid receptor in the cytoplasm of target cells, especially principal cells of the distal convoluted and collecting tubules of the kidney. The drug-receptor complex activates a series of events similar to those described above for the glucocorticoids and illustrated in Figure 39–4. It is of interest that this receptor has the same affinity for cortisol, which is present in much higher concentrations in the extracellular fluid. The specificity for mineralocorticoids in the kidney appears to be conferred, at least in part, by the presence of the enzyme 11β-hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone. The latter has low affinity for the receptor and is inactive as a mineralocorticoid or glucocorticoid in the kidney. The major effect of activation of the aldosterone receptor is increased expression of Na^+/K^+-ATPase and the epithelial sodium channel (ENaC).

B. Metabolism

Aldosterone is secreted at the rate of 100–200 mcg/d in normal individuals with a moderate dietary salt intake. The plasma level in men (resting supine) is about 0.007 mcg/dL. The half-life of aldosterone injected in tracer quantities is 15–20 minutes, and it does not appear to be firmly bound to serum proteins.

The metabolism of aldosterone is similar to that of cortisol, about 50 mcg/24 h appearing in the urine as conjugated tetrahydroaldosterone. Approximately 5–15 mcg/24 h is excreted free or as the 3-oxo glucuronide.

Deoxycorticosterone (DOC)

DOC, which also serves as a precursor of aldosterone (Figure 39–1), is normally secreted in amounts of about 200 mcg/d. Its half-life when injected into the human circulation is about 70 minutes. Preliminary estimates of its concentration in plasma are approximately 0.03 mcg/dL. The control of its secretion differs from that of aldosterone in that the secretion of DOC is primarily under the control of ACTH. Although the response to ACTH is enhanced by dietary sodium restriction, a low-salt diet does not

increase DOC secretion. The secretion of DOC may be markedly increased in abnormal conditions such as adrenocortical carcinoma and congenital adrenal hyperplasia with reduced P450c11 or P450c17 activity.

Fludrocortisone

This compound, a potent steroid with both glucocorticoid and mineralocorticoid activity, is the most widely used mineralocorticoid. Oral doses of 0.1 mg two to seven times weekly have potent salt-retaining activity and are used in the treatment of adrenocortical insufficiency associated with mineralocorticoid deficiency. These dosages are too small to have important anti-inflammatory or antigrowth effects.

ADRENAL ANDROGENS

The adrenal cortex secretes large amounts of DHEA and smaller amounts of androstenedione and testosterone. Although these androgens are thought to contribute to the normal maturation process, they do not stimulate or support major androgen-dependent pubertal changes in humans. Recent studies suggest that DHEA and its sulfate may have other important physiologic actions. If that is correct, these results are probably due to the peripheral conversion of DHEA to more potent androgens or to estrogens and interaction with androgen and estrogen receptors, respectively. Additional effects may be exerted through an interaction with the $GABA_A$ and glutamate receptors in the brain or with a nuclear receptor in several central and peripheral sites. The therapeutic use of DHEA in humans has been explored, but the substance has already been adopted with uncritical enthusiasm by members of the sports drug culture and the vitamin and food supplement culture.

The results of a placebo-controlled trial of DHEA in patients with systemic lupus erythematosus have been reported as well as those of a study of DHEA replacement in women with adrenal insufficiency. In both studies a small beneficial effect was seen, with significant improvement of the disease in the former and a clearly added sense of well-being in the latter. The androgenic or estrogenic actions of DHEA could explain the effects of the compound in both situations.

■ ANTAGONISTS OF ADRENOCORTICAL AGENTS

SYNTHESIS INHIBITORS & GLUCOCORTICOID ANTAGONISTS

Inhibitors of steroid synthesis act at several different steps and one glucocorticoid antagonist acts at the receptor level.

Aminoglutethimide

Aminoglutethimide (Figure 39–5) blocks the conversion of cholesterol to pregnenolone (see Figure 39–1) and causes a reduction

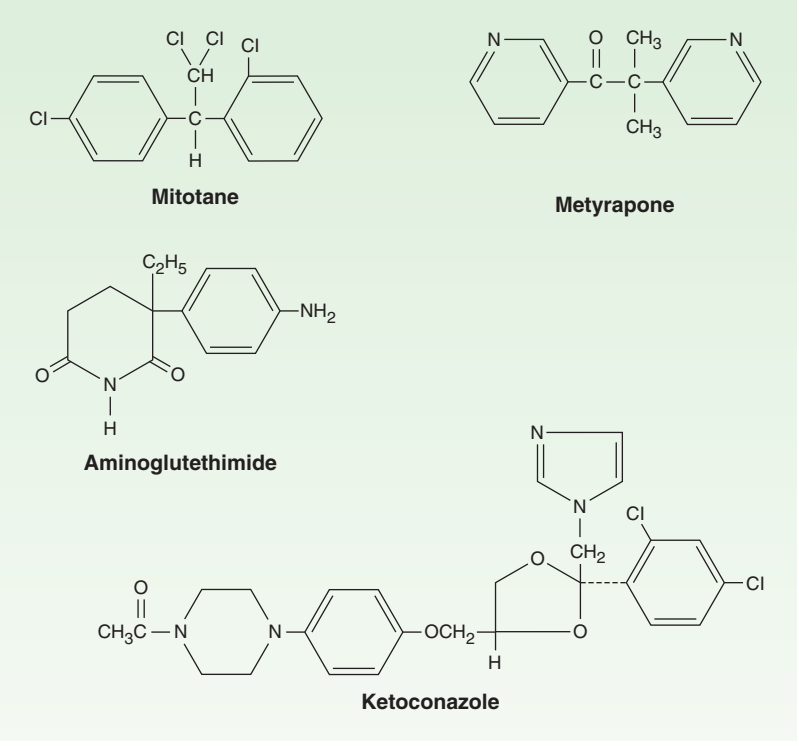


FIGURE 39–5 Some adrenocortical antagonists. Because of their toxicity, some of these compounds are no longer available in the USA.

in the synthesis of all hormonally active steroids. It has been used in conjunction with dexamethasone or hydrocortisone to reduce or eliminate estrogen production in patients with carcinoma of the breast. In a dosage of 1 g/d it was well tolerated; however, with higher dosages, lethargy and skin rash were common effects. The use of aminoglutethimide in breast cancer patients has now been supplanted by tamoxifen or by another class of drugs, the aromatase inhibitors (see Chapters 40 and 54). Aminoglutethimide can be used in conjunction with metyrapone or ketoconazole to reduce steroid secretion in patients with Cushing's syndrome due to adrenocortical cancer who do not respond to mitotane.

Aminoglutethimide also apparently increases the clearance of some steroids. It has been shown to enhance the metabolism of dexamethasone, reducing its half-life from 4–5 hours to 2 hours.

Ketoconazole

Ketoconazole, an antifungal imidazole derivative (see Chapter 48), is a potent and rather nonselective inhibitor of adrenal and gonadal steroid synthesis. This compound inhibits the cholesterol side-chain cleavage, P450c17, C17,20-lyase, 3β-hydroxysteroid dehydrogenase, and P450c11 enzymes required for steroid hormone synthesis. The sensitivity of the P450 enzymes to this compound in mammalian tissues is much lower than that needed to treat fungal infections, so that its inhibitory effects on steroid biosynthesis are seen only at high doses.

Ketoconazole has been used for the treatment of patients with Cushing's syndrome due to several causes. Dosages of 200–1200 mg/d have produced a reduction in hormone levels and clinical improvement in some patients. This drug has some hepatotoxicity and should be started at 200 mg/d and slowly increased by 200 mg/d every 2–3 days up to a total daily dose of 1000 mg.

Metyrapone

Metyrapone (Figure 39–5) is a relatively selective inhibitor of steroid 11-hydroxylation, interfering with cortisol and corticosterone synthesis. In the presence of a normal pituitary gland, there is a compensatory increase in pituitary ACTH release and adrenal 11-deoxycortisol secretion. This response is a measure of the capacity of the anterior pituitary to produce ACTH and has been adapted for clinical use as a diagnostic test. Although the toxicity of metyrapone is much lower than that of mitotane (see text that follows), the drug may produce transient dizziness and gastrointestinal disturbances. This agent has not been widely used for the treatment of Cushing's syndrome. However, in doses of 0.25 g twice daily to 1 g four times daily, metyrapone can reduce cortisol production to normal levels in some patients with endogenous Cushing's syndrome. Thus, it may be useful in the management of severe manifestations of cortisol excess while the cause of this condition is being determined or in conjunction with radiation or surgical treatment. Metyrapone is the only adrenal-inhibiting medication that can be administered to pregnant women with Cushing's syndrome. The major adverse effects observed are salt and water retention and hirsutism resulting from diversion of the 11-deoxycortisol precursor to DOC and androgen synthesis.

Metyrapone is commonly used in tests of adrenal function. The blood levels of 11-deoxycortisol and the urinary excretion of 17-hydroxycorticoids are measured before and after administration of the compound. Normally, there is a twofold or greater increase in the urinary 17-hydroxycorticoid excretion. A dose of 300–500 mg every 4 hours for six doses is often used, and urine collections are made on the day before and the day after treatment. In patients with Cushing's syndrome, a normal response to metyrapone indicates that the cortisol excess is not the result of a cortisol-secreting adrenal carcinoma or adenoma, since secretion by such tumors produces suppression of ACTH and atrophy of normal adrenal cortex.

Pituitary function may also be tested by administering metyrapone, 2–3 g orally at midnight and by measuring the level of ACTH or 11-deoxycortisol in blood drawn at 8 AM or by comparing the excretion of 17-hydroxycorticosteroids in the urine during the 24-hour periods preceding and following administration of the drug. In patients with suspected or known lesions of the pituitary, this procedure is a means of estimating the ability of the gland to produce ACTH. Metyrapone has been withdrawn from the market in the USA but is available on a compassionate basis.

Trilostane

Trilostane is a 3β-17 hydroxysteroid dehydrogenase inhibitor that interferes with the synthesis of adrenal and gonadal hormones and is comparable to aminoglutethimide. Trilostane's adverse effects are predominantly gastrointestinal; adverse effects occur in about 50% of patients with both trilostane and aminoglutethimide. There is no cross-resistance or crossover of side effects between these compounds. Trilostane is not available in the USA.

Abiraterone

Abiraterone is the newest of the steroid synthesis inhibitors to enter clinical trials. It blocks 17α-hydroxylase (P450c17) and 17,20-lyase (Figure 39–1), and predictably reduces synthesis of cortisol and gonadal steroids in the adrenal and gonadal steroids in the gonads. A compensatory increase occurs in ACTH and aldosterone synthesis, but this can be prevented by concomitant administration of dexamethasone. Abiraterone is an orally active steroid prodrug and has been studied in the treatment of refractory prostate cancer.

Mifepristone (RU-486)

The search for a glucocorticoid receptor antagonist finally succeeded in the early 1980s with the development of the 11β-aminophenyl-substituted 19-norsteroid called RU-486, later named mifepristone. Unlike the enzyme inhibitors previously discussed, mifepristone is a pharmacologic antagonist at the steroid receptor. This compound has strong antiprogestin activity and initially was proposed as a contraceptive-contragestive agent. High doses of mifepristone exert antiglucocorticoid activity by blocking the glucocorticoid receptor, since mifepristone binds to it with high affinity, causing (1) some stabilization of the

hsp-glucocorticoid receptor complex and inhibition of the dissociation of the RU-486–bound glucocorticoid receptor from the hsp chaperone proteins; and (2) alteration of the interaction of the glucocorticoid receptor with coregulators, favoring the formation of a transcriptionally inactive complex in the cell nucleus. The result is inhibition of glucocorticoid receptor activation.

The mean half-life of mifepristone is 20 hours. This is longer than that of many natural and synthetic glucocorticoid agonists (dexamethasone has a half-life of 4–5 hours). Less than 1% of the daily dose is excreted in the urine, suggesting a minor role of kidneys in the clearance of the compound. The long plasma half-life of mifepristone results from extensive and strong binding to plasma proteins. Less than 5% of the compound is found in the free form when plasma is analyzed by equilibrium dialysis. Mifepristone can bind to albumin and α_1-acid glycoprotein, but it has no affinity for corticosteroid-binding globulin.

In humans, mifepristone causes generalized glucocorticoid resistance. Given orally to several patients with Cushing's syndrome due to ectopic ACTH production or adrenal carcinoma, it was able to reverse the cushingoid phenotype, to eliminate carbohydrate intolerance, normalize blood pressure, to correct thyroid and gonadal hormone suppression, and to ameliorate the psychological sequelae of hypercortisolism in these patients. At present, this use of mifepristone can only be recommended for inoperable patients with ectopic ACTH secretion or adrenal carcinoma who have failed to respond to other therapeutic manipulations. Its pharmacology and use in women as a progesterone antagonist are discussed in Chapter 40.

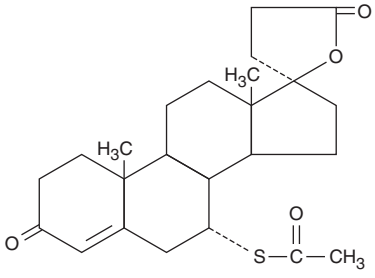
Mitotane

Mitotane (Figure 39–5), a drug related to the DDT class of insecticides, has a nonselective cytotoxic action on the adrenal cortex in dogs and to a lesser extent in humans. This drug is administered orally in divided doses up to 12 g daily. About one third of patients with adrenal carcinoma show a reduction in tumor mass. In 80% of patients, the toxic effects are sufficiently severe to require dose reduction. These include diarrhea, nausea, vomiting, depression, somnolence, and skin rashes. The drug has been withdrawn from the market in the USA but is available on a compassionate basis.

MINERALOCORTICOID ANTAGONISTS

In addition to agents that interfere with aldosterone synthesis (see above), there are steroids that compete with aldosterone for its receptor and decrease its effect peripherally. Progesterone is mildly active in this respect.

Spironolactone is a 7α-acetylthiospironolactone. Its onset of action is slow, and the effects last for 2–3 days after the drug is discontinued. It is used in the treatment of primary aldosteronism in dosages of 50–100 mg/d. This agent reverses many of the manifestations of aldosteronism. It has been useful in establishing the diagnosis in some patients and in ameliorating the signs and symptoms when surgical removal of an adenoma is delayed. When used diagnostically for the detection of aldosteronism in hypokalemic patients with hypertension, dosages of 400–500 mg/d for 4–8 days—with an adequate intake of sodium and potassium—restore potassium levels to or toward normal. Spironolactone is also useful in preparing these patients for surgery. Dosages of 300–400 mg/d for 2 weeks are used for this purpose and may reduce the incidence of cardiac arrhythmias.



Spironolactone

Spironolactone is also an androgen antagonist and as such is sometimes used in the treatment of hirsutism in women. Dosages of 50–200 mg/d cause a reduction in the density, diameter, and rate of growth of facial hair in patients with idiopathic hirsutism or hirsutism secondary to androgen excess. The effect can usually be seen in 2 months and becomes maximal in about 6 months.

Spironolactone as a diuretic is discussed in Chapter 15. The drug has benefits in heart failure greater than those predicted from its diuretic effects alone (see Chapter 13). Adverse effects reported for spironolactone include hyperkalemia, cardiac arrhythmia, menstrual abnormalities, gynecomastia, sedation, headache, gastrointestinal disturbances, and skin rashes.

Eplerenone, another aldosterone antagonist, is approved for the treatment of hypertension (see Chapters 11 and 15). Like spironolactone, eplerenone has also been found to reduce mortality in heart failure. This aldosterone receptor antagonist is somewhat more selective than spironolactone and has no reported effects on androgen receptors. The standard dosage in hypertension is 50–100 mg/d. The most common toxicity is hyperkalemia, but this is usually mild.

Drospirenone, a progestin in an oral contraceptive (see Chapter 40), also antagonizes the effects of aldosterone.

PREPARATIONS AVAILABLE[1]

GLUCOCORTICOIDS FOR ORAL & PARENTERAL USE

Betamethasone (Celestone)
Oral: 0.6 mg/5 mL syrup

Betamethasone sodium phosphate (Celestone Phosphate)
Parenteral: 4 mg/mL for IV, IM, intralesional, or intra-articular injection

Cortisone (generic, Cortone Acetate)
Oral: 25 mg tablets

Dexamethasone (generic, Decadron)
Oral: 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 mg tablets; 0.5 mg/5 mL elixir; 0.5 mg/5 mL, 1 mg/mL solution

Dexamethasone acetate (generic, Decadron-LA)
Parenteral: 8 mg/mL suspension for IM, intralesional, or intra-articular injection; 16 mg/mL suspension for intralesional injection

Dexamethasone sodium phosphate (generic, Decadron Phosphate)
Parenteral: 4, 10, 20 mg/mL for IV, IM, intralesional, or intra-articular injection; 24 mg/mL for IV use only

Hydrocortisone [cortisol] (generic, Cortef)
Oral: 5, 10, 20 mg tablets

Hydrocortisone acetate (generic)
Parenteral: 25, 50 mg/mL suspension for intralesional, soft tissue, or intra-articular injection

Hydrocortisone cypionate (Cortef)
Oral: 10 mg/5 mL suspension

Hydrocortisone sodium phosphate (Hydrocortone)
Parenteral: 50 mg/mL for IV, IM, or SC injection

Hydrocortisone sodium succinate (generic, SoluCortef)
Parenteral: 100, 250, 500, 1000 mg/vial for IV, IM injection

Methylprednisolone (generic, Medrol)
Oral: 2, 4, 8, 16, 24, 32 mg tablets

Methylprednisolone acetate (generic, DepoMedrol)
Parenteral: 20, 40, 80 mg/mL for IM, intralesional, or intra-articular injection

Methylprednisolone sodium succinate (generic, Solu-Medrol)
Parenteral: 40, 125, 500, 1000, 2000 mg/vial

Prednisolone (generic, Delta-Cortef, Prelone)
Oral: 5 mg tablets; 5, 15 mg/5 mL syrup

Prednisolone acetate (generic)
Parenteral: 25, 50 mg/mL for soft tissue or intra-articular injection

Prednisolone sodium phosphate (generic, Hydeltrasol)
Oral: 5 mg/5 mL solution

Parenteral: 20 mg/mL for IV, IM, intra-articular, or intralesional injection

Prednisone (generic, Meticorten)
Oral: 1, 2.5, 5, 10, 20, 50 mg tablets; 1, 5 mg/mL solution and syrup

Triamcinolone acetonide (generic, Kenalog)
Parenteral: 3, 10, 40 mg/mL for IM, intra-articular, or intralesional injection

Triamcinolone hexacetonide (Aristospan)
Parenteral: 5, 20 mg/mL for intra-articular, intralesional, or sublesional injection

MINERALOCORTICOIDS

Fludrocortisone acetate (generic, Florinef Acetate)
Oral: 0.1 mg tablets

ADRENAL STEROID INHIBITORS

Ketoconazole (generic, Nizoral)
Oral: 200 mg tablets (unlabeled use)

Mifepristone (Mifeprex)
Oral: 200 mg tablets

Mitotane (Lysodren)
Oral: 500 mg tablets

[1]Glucocorticoids for aerosol use: See Chapter 20. Glucocorticoids for dermatologic use: See Chapter 61. Glucocorticoids for gastrointestinal use: See Chapter 62.

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CASE STUDY ANSWER

The patient should be placed on replacement oral hydrocortisone at 10 mg/m^2/d and fludrocortisone at 75 mcg/d. He should be given a MedicAlert bracelet and instructions for minor and major stress glucocorticoid coverage at 2 times and 10 times replacement of hydrocortisone over 24 and 48 hours, respectively.

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CHAPTER

40

The Gonadal Hormones & Inhibitors

George P. Chrousos, MD

CASE STUDY

A 25-year-old woman with menarche at 13 years and menstrual periods until about 1 year ago complains of hot flushes, skin and vaginal dryness, weakness, poor sleep, and scanty and infrequent menstrual periods of a year's duration. She visits her gynecologist, who obtains plasma levels of follicle-stimulating hormone and luteinizing hormone, both of which are moderately elevated. She is diagnosed with premature ovarian failure and recommended estrogen and progesterone replacement therapy. A dual-energy absorptiometry scan (DEXA) reveals a bone density t-score of <2.5 SD, ie, frank osteoporosis. How should the ovarian hormones she lacks be replaced? What extra measures should she take for her osteoporosis while receiving treatment?

THE OVARY (ESTROGENS, PROGESTINS, OTHER OVARIAN HORMONES, ORAL CONTRACEPTIVES, INHIBITORS & ANTAGONISTS, & OVULATION-INDUCING AGENTS)

The ovary has important gametogenic functions that are integrated with its hormonal activity. In the human female, the gonad is relatively quiescent during childhood, the period of rapid growth and maturation. At puberty, the ovary begins a 30- to 40-year period of cyclic function called the **menstrual cycle** because of the regular episodes of bleeding that are its most obvious manifestation. It then fails to respond to gonadotropins secreted by the anterior pituitary gland, and the cessation of cyclic bleeding that occurs is called **menopause.**

The mechanism responsible for the onset of ovarian function at the time of puberty is thought to be neural in origin, because the immature gonad can be stimulated by gonadotropins already present in the pituitary and because the pituitary is responsive to exogenous hypothalamic gonadotropin-releasing hormone. The maturation of centers in the brain may withdraw a childhood-related inhibitory effect upon hypothalamic arcuate nucleus neurons, allowing them to produce **gonadotropin-releasing hormone (GnRH)** in pulses with the appropriate amplitude, which stimulates the release of **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** (see Chapter 37). At first, small amounts of the latter two hormones are released during the night, and the limited quantities of ovarian estrogen secreted in response start to cause breast development. Subsequently, FSH and LH are secreted throughout the day and night, causing secretion of higher amounts of estrogen and leading to further breast enlargement, alterations in fat distribution, and a growth spurt that culminates in epiphysial closure in the long bones. The change of ovarian function at puberty is called **gonadarche.**

A year or so after gonadarche, sufficient estrogen is produced to induce endometrial changes and periodic bleeding. After the first few irregular cycles, which may be anovulatory, normal cyclic function is established.

At the beginning of each cycle, a variable number of follicles (vesicular follicles), each containing an ovum, begin to enlarge in response to FSH. After 5 or 6 days, one follicle, called the dominant

ACRONYMS

CBG	Corticosteroid-binding globulin (transcortin)
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
ERE	Estrogen response element
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HDL	High-density lipoprotein
HRT	Hormone replacement therapy (also called HT)
LDL	Low-density lipoprotein
LH	Luteinizing hormone
PRE	Progesterone response element
SERM	Selective estrogen receptor modulator
SHBG	Sex hormone-binding globulin
TBG	Thyroxine-binding globulin

follicle, begins to develop more rapidly. The outer theca and inner granulosa cells of this follicle multiply and, under the influence of LH, synthesize and release estrogens at an increasing rate. The estrogens appear to inhibit FSH release and may lead to regression of the smaller, less mature follicles. The mature dominant ovarian follicle consists of an ovum surrounded by a fluid-filled antrum lined by granulosa and theca cells. The estrogen secretion reaches a peak just before midcycle, and the granulosa cells begin to secrete progesterone. These changes stimulate the brief surge in LH and FSH release that precedes and causes ovulation. When the follicle ruptures, the ovum is released into the abdominal cavity near the opening of the uterine tube.

Following the above events, the cavity of the ruptured follicle fills with blood (corpus hemorrhagicum), and the luteinized theca and granulosa cells proliferate and replace the blood to form the corpus luteum. The cells of this structure produce estrogens and progesterone for the remainder of the cycle, or longer if pregnancy occurs.

If pregnancy does not occur, the corpus luteum begins to degenerate and ceases hormone production, eventually becoming a corpus albicans. The endometrium, which proliferated during the follicular phase and developed its glandular function during the luteal phase, is shed in the process of menstruation. These events are summarized in Figure 40–1.

The ovary normally ceases its gametogenic and endocrine function with time. This change is accompanied by a cessation in uterine bleeding (menopause) and occurs at a mean age of 52 years in the USA. Although the ovary ceases to secrete estrogen, significant levels of estrogen persist in many women as a result of conversion of adrenal and ovarian steroids such as androstenedione to estrone and estradiol in adipose and possibly other nonendocrine tissues.

Disturbances in Ovarian Function

Disturbances of cyclic function are common even during the peak years of reproduction. A minority of these result from inflammatory or neoplastic processes that influence the functions of the uterus,

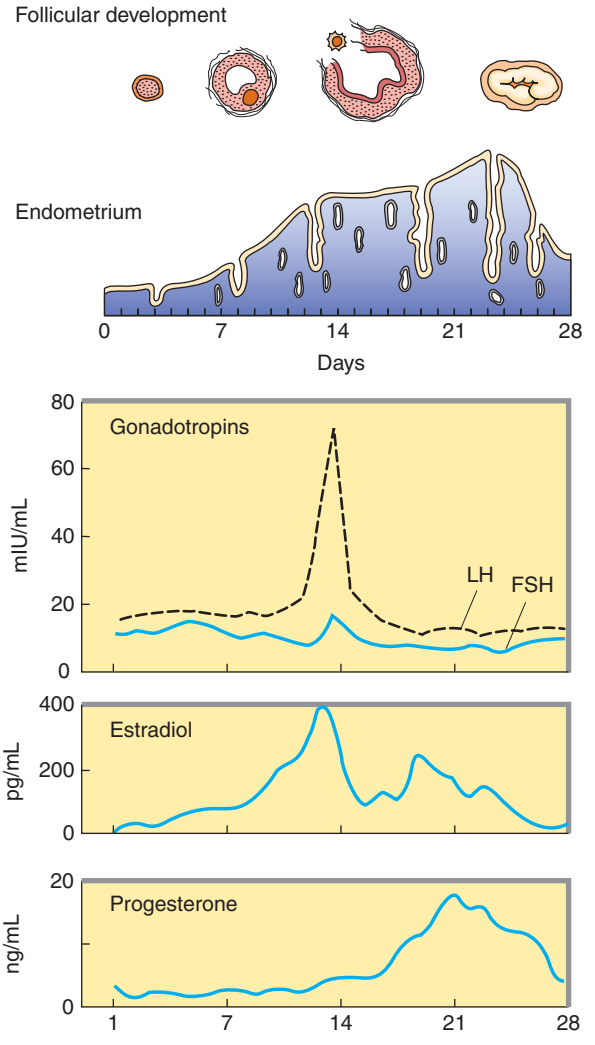


FIGURE 40–1 The menstrual cycle, showing plasma levels of pituitary and ovarian hormones and histologic changes.

ovaries, or pituitary. Many of the minor disturbances leading to periods of amenorrhea or anovulatory cycles are self-limited. They are often associated with emotional or physical stress and reflect temporary alterations in the stress centers in the brain that control the secretion of GnRH. Anovulatory cycles are also associated with eating disorders (bulimia, anorexia nervosa) and with severe exercise such as distance running and swimming. Among the more common organic causes of persistent ovulatory disturbances are pituitary prolactinomas and syndromes and tumors characterized by excessive ovarian or adrenal androgen production. Normal ovarian function can be modified by androgens produced by the adrenal cortex or tumors arising from it. The ovary also gives rise to androgen-producing neoplasms such as arrhenoblastomas, as well as to estrogen-producing granulosa cell tumors.

THE ESTROGENS

Estrogenic activity is shared by a large number of chemical substances. In addition to the variety of steroidal estrogens derived from animal sources, numerous nonsteroidal estrogens have been

synthesized. Many phenols are estrogenic, and estrogenic activity has been identified in such diverse forms of life as those found in ocean sediments. Estrogen-mimetic compounds (flavonoids) are found in many plants, including saw palmetto, and soybeans and other foods. Studies have shown that a diet rich in these plant products may cause slight estrogenic effects. Additionally, some compounds used in the manufacture of plastics (bisphenols, alkylphenols, phthalate phenols) have been found to be estrogenic. It has been proposed that these agents are associated with an increased breast cancer incidence in both women and men in the industrialized world.

Natural Estrogens

The major estrogens produced by women are **estradiol** (estradiol-17β, E_2), **estrone** (E_1), and **estriol** (E_3) (Figure 40–2). Estradiol is the major secretory product of the ovary. Although some estrone is produced in the ovary, most estrone and estriol are formed in the liver from estradiol or in peripheral tissues from androstenedione and other androgens (see Figure 39–1). As noted above, during the first part of the menstrual cycle estrogens are produced in the ovarian follicle by the theca and granulosa cells. After ovulation, the estrogens as well as progesterone are synthesized by the luteinized granulosa and theca cells of the corpus luteum, and the pathways of biosynthesis are slightly different.

During pregnancy, a large amount of estrogen is synthesized by the fetoplacental unit—consisting of the fetal adrenal zone, secreting androgen precursor, and the placenta, which aromatizes it into estrogen. The estriol synthesized by the fetoplacental unit is released into the maternal circulation and excreted into the urine. Repeated assay of maternal urinary estriol excretion has been used in the assessment of fetal well-being.

One of the most prolific natural sources of estrogenic substances is the stallion, which liberates more of these hormones than the pregnant mare or pregnant woman. The equine estrogens—equilenin and equilin—and their congeners are unsaturated in the B as well as the A ring and are excreted in large quantities in urine, from which they can be recovered and used for medicinal purposes.

In normal women, estradiol is produced at a rate that varies during the menstrual cycle, resulting in plasma levels as low as

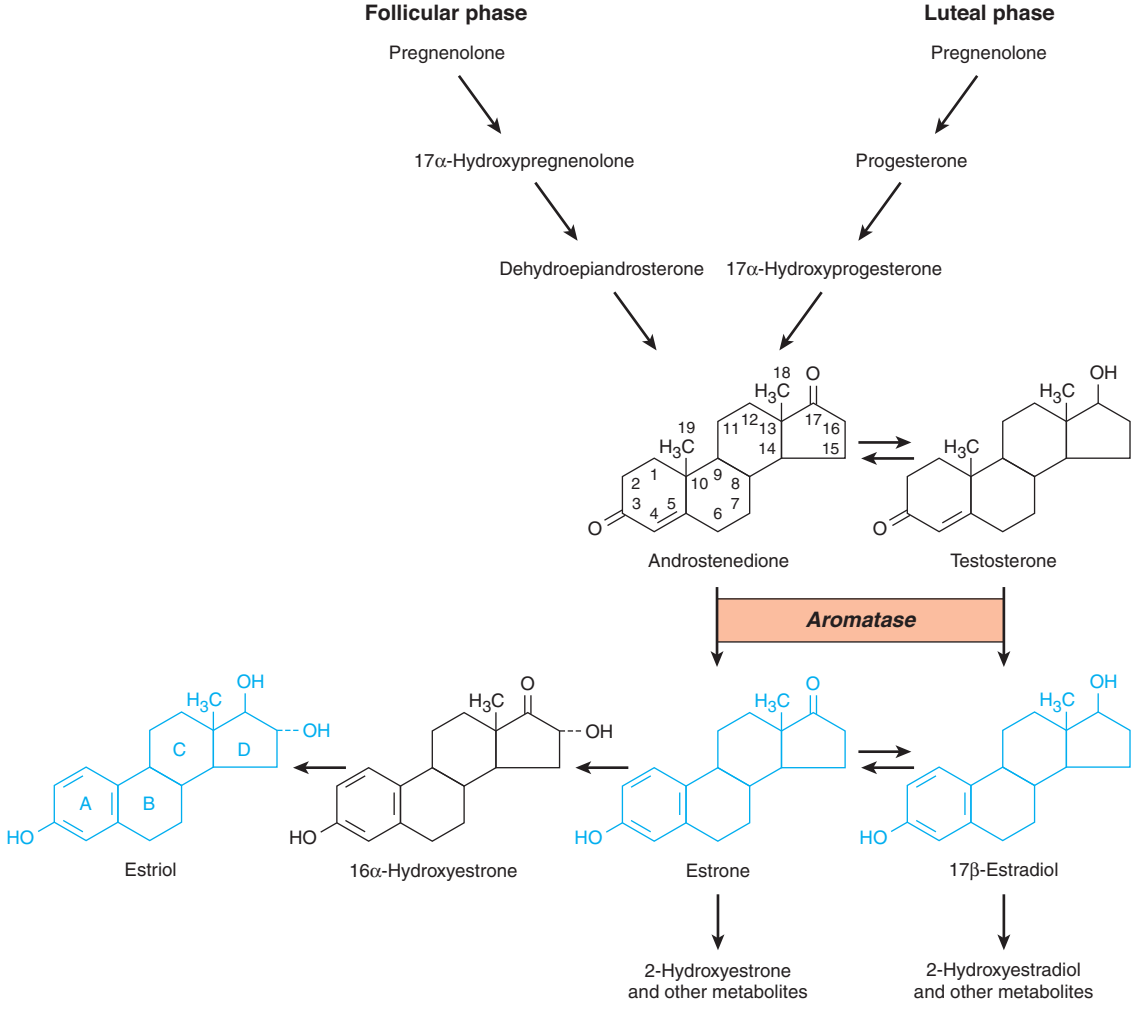


FIGURE 40–2 Biosynthesis and metabolism of estrogens and testosterone.

50 pg/mL in the early follicular phase to as high as 350–850 pg/mL at the time of the preovulatory peak (Figure 40–1).

Synthetic Estrogens

A variety of chemical alterations have been applied to the natural estrogens. The most important effect of these alterations has been to increase their oral effectiveness. Some structures are shown in Figure 40–3. Those with therapeutic use are listed in Table 40–1.

In addition to the steroidal estrogens, a variety of nonsteroidal compounds with estrogenic activity have been synthesized and used clinically. These include dienestrol, diethylstilbestrol, benzestrol, hexestrol, methestrol, methallenestril, and chlorotrianisene (Figure 40–3).

Pharmacokinetics

When released into the circulation, estradiol binds strongly to an α_2 globulin (sex hormone-binding globulin [SHBG]) and with lower affinity to albumin. Bound estrogen is relatively unavailable for diffusion into cells, and it is the free fraction that is physiologically active. Estradiol is converted by the liver and other tissues to estrone and estriol (Figure 40–2) and their 2-hydroxylated derivatives and conjugated metabolites (which are too insoluble in lipid to cross the cell membrane readily) and excreted in the bile. Estrone and estriol have low affinity for the estrogen receptor. However, the conjugates may be hydrolyzed in the intestine to active, reabsorbable compounds. Estrogens are also excreted in small amounts in the breast milk of nursing mothers.

Because significant amounts of estrogens and their active metabolites are excreted in the bile and reabsorbed from the intestine, the resulting enterohepatic circulation ensures that orally administered estrogens will have a high ratio of hepatic to peripheral effects. As noted below, the hepatic effects are thought to be responsible for some undesirable actions such as synthesis of increased clotting factors and plasma renin substrate. The hepatic effects of estrogen can be minimized by routes that avoid first-pass liver exposure, ie, vaginal, transdermal, or by injection.

Physiologic Effects

A. Mechanism

Plasma estrogens in the blood and interstitial fluid are bound to SHBG, from which they dissociate to enter the cell and bind to their receptor. Two genes code for two estrogen receptor isoforms,

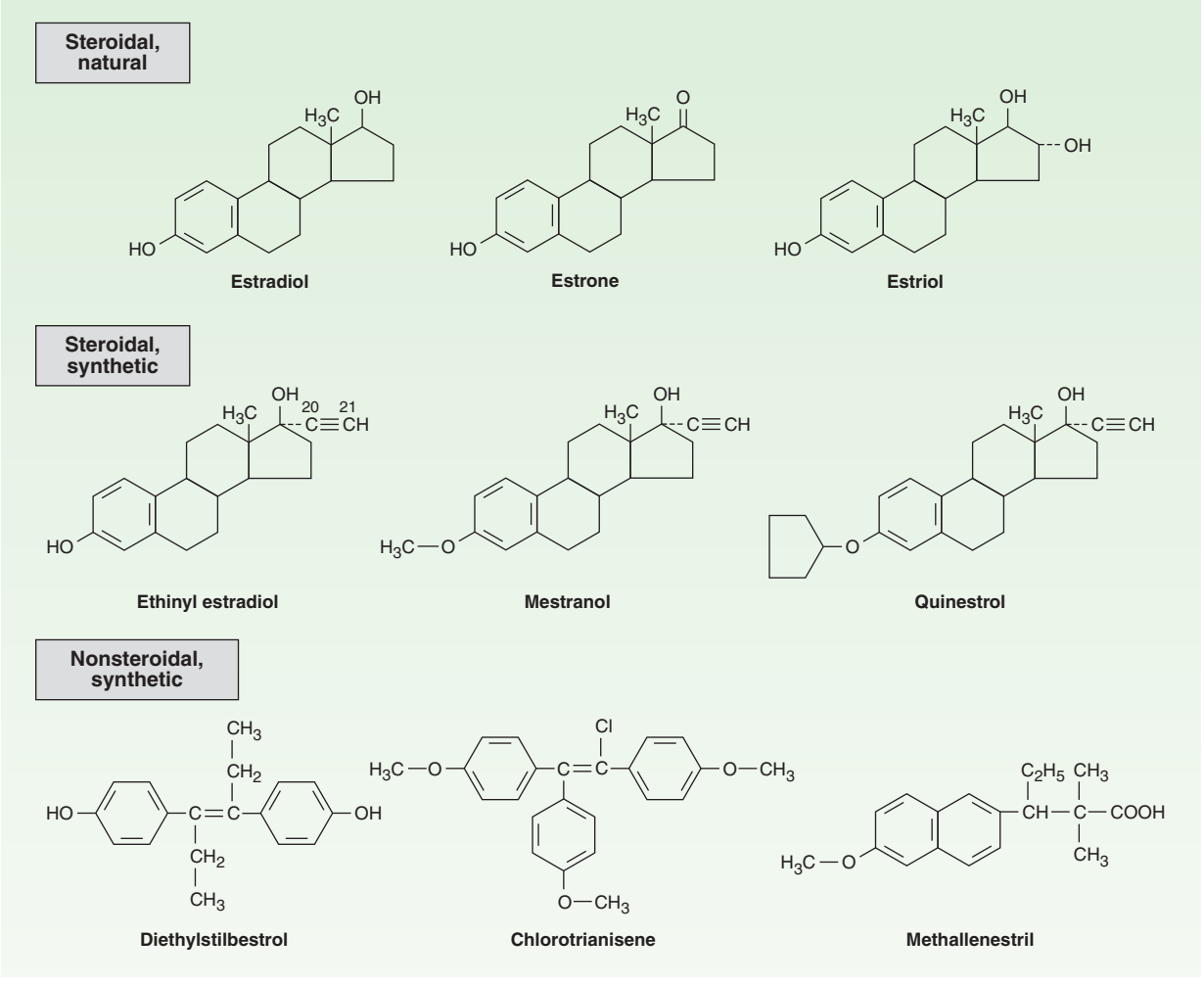


FIGURE 40–3 Compounds with estrogenic activity.

TABLE 40–1 Commonly used estrogens.

Preparation	Average Replacement Dosage
Ethinyl estradiol	0.005–0.02 mg/d
Micronized estradiol	1–2 mg/d
Estradiol cypionate	2–5 mg every 3–4 weeks
Estradiol valerate	2–20 mg every other week
Estropipate	1.25–2.5 mg/d
Conjugated, esterified, or mixed estrogenic substances:	
Oral	0.3–1.25 mg/d
Injectable	0.2–2 mg/d
Transdermal	Patch
Quinestrol	0.1–0.2 mg/week
Chlorotrianisene	12–25 mg/d
Methallenestril	3–9 mg/d

α and β, which are members of the superfamily of steroid, sterol, retinoic acid, and thyroid receptors. The estrogen receptors are found predominantly in the nucleus bound to heat shock proteins that stabilize them (see Figure 39–4).

Binding of the hormone to its receptor alters its conformation and releases it from the stabilizing proteins (predominantly Hsp90). The receptor-hormone complex forms homodimers that bind to a specific sequence of nucleotides called **estrogen response elements (EREs)** in the promoters of various genes and regulate their transcription. The ERE is composed of two half-sites arranged as a palindrome separated by a small group of nucleotides called the spacer. The interaction of a receptor dimer with the ERE also involves a number of nuclear proteins, the coregulators, as well as components of the transcription machinery. The receptor may also bind to other transcription factors to influence the effects of these factors on their responsive genes.

The relative concentrations and types of receptors, receptor coregulators, and transcription factors confer the cell specificity of the hormone's actions. The genomic effects of estrogens are mainly due to proteins synthesized by translation of RNA transcribed from a responsive gene. Some of the effects of estrogens are indirect, mediated by the autocrine and paracrine actions of autacoids such as growth factors, lipids, glycolipids, and cytokines produced by the target cells in response to estrogen.

Rapid estrogen-induced effects such as granulosa cell Ca^{2+} uptake and increased uterine blood flow do not require gene activation. These appear to be mediated by nongenomic effects of the classic estrogen receptor-estrogen complex, influencing several intracellular signaling pathways.

Recently, all steroid receptors except the mineralocorticoid receptors were shown to have palmitoylation motifs that allow enzymatic addition of palmitate and increased localization of the receptors in the vicinity of plasma membranes. Such receptors are available for direct interactions with, and effects on, various membrane-associated or cytoplasmic proteins without the need for entry into the nucleus and induction of transcriptional actions.

B. Female Maturation

Estrogens are required for the normal sexual maturation and growth of the female. They stimulate the development of the vagina, uterus, and uterine tubes as well as the secondary sex characteristics. They stimulate stromal development and ductal growth in the breast and are responsible for the accelerated growth phase and the closing of the epiphyses of the long bones that occur at puberty. They contribute to the growth of axillary and pubic hair and alter the distribution of body fat to produce typical female body contours. Larger quantities also stimulate development of pigmentation in the skin, most prominent in the region of the nipples and areolae and in the genital region.

C. Endometrial Effects

In addition to its growth effects on uterine muscle, estrogen plays an important role in the development of the endometrial lining. When estrogen production is properly coordinated with the production of progesterone during the normal human menstrual cycle, regular periodic bleeding and shedding of the endometrial lining occur. Continuous exposure to estrogens for prolonged periods leads to hyperplasia of the endometrium that is usually associated with abnormal bleeding patterns.

D. Metabolic and Cardiovascular Effects

Estrogens have a number of important metabolic and cardiovascular effects. They seem to be partially responsible for maintenance of the normal structure and function of the skin and blood vessels in women. Estrogens also decrease the rate of resorption of bone by promoting the apoptosis of osteoclasts and by antagonizing the osteoclastogenic and pro-osteoclastic effects of parathyroid hormone and interleukin-6. Estrogens also stimulate adipose tissue production of leptin and are in part responsible for the higher levels of this hormone in women than in men.

In addition to stimulating the synthesis of enzymes and growth factors leading to uterine and breast growth and differentiation, estrogens alter the production and activity of many other proteins in the body. Metabolic alterations in the liver are especially important, so that there is a higher circulating level of proteins such as transcortin (corticosteroid-binding globulin, CBG), thyroxine-binding globulin (TBG), SHBG, transferrin, renin substrate, and fibrinogen. This leads to increased circulating levels of thyroxine, estrogen, testosterone, iron, copper, and other substances.

Alterations in the composition of the plasma lipids caused by estrogens are characterized by an increase in the high-density lipoproteins (HDL), a slight reduction in the low-density lipoproteins (LDL), and a reduction in total plasma cholesterol levels. Plasma triglyceride levels are increased. Estrogens decrease hepatic oxidation of adipose tissue lipid to ketones and increase synthesis of triglycerides.

E. Effects on Blood Coagulation

Estrogens enhance the coagulability of blood. Many changes in factors influencing coagulation have been reported, including increased circulating levels of factors II, VII, IX, and X and

decreased antithrombin III, partially as a result of the hepatic effects mentioned above. Increased plasminogen levels and decreased platelet adhesiveness have also been found (see Hormonal Contraception, below).

F. Other Effects

Estrogens induce the synthesis of progesterone receptors. They are responsible for estrous behavior in animals and may influence behavior and libido in humans. Administration of estrogens stimulates central components of the stress system, including the production of corticotropin-releasing hormone and the activity of the sympathetic system, and promotes a sense of well-being when given to women who are estrogen-deficient. They also facilitate the loss of intravascular fluid into the extracellular space, producing edema. The resulting decrease in plasma volume causes a compensatory retention of sodium and water by the kidney. Estrogens also modulate sympathetic nervous system control of smooth muscle function.

Clinical Uses*

A. Primary Hypogonadism

Estrogens have been used extensively for replacement therapy in estrogen-deficient patients. The estrogen deficiency may be due to primary failure of development of the ovaries, premature menopause, castration, or menopause.

Treatment of primary hypogonadism is usually begun at 11–13 years of age in order to stimulate the development of secondary sex characteristics and menses, to stimulate optimal growth, to prevent osteoporosis and to avoid the psychological consequences of delayed puberty and estrogen deficiency. Treatment attempts to mimic the physiology of puberty. It is initiated with small doses of estrogen (0.3 mg conjugated estrogens or 5–10 mcg ethinyl estradiol) on days 1–21 each month and is slowly increased to adult doses and then maintained until the age of menopause (approximately 51 years of age). A progestin is added after the first uterine bleeding. When growth is completed, chronic therapy consists mainly of the administration of adult doses of both estrogens and progestins, as described below.

B. Postmenopausal Hormonal Therapy

In addition to the signs and symptoms that follow closely upon the cessation of normal ovarian function—such as loss of menstrual periods, vasomotor symptoms, sleep disturbances, and genital atrophy—there are longer-lasting changes that influence the health and well-being of postmenopausal women. These include an acceleration of bone loss, which in susceptible women may lead to vertebral, hip, and wrist fractures; and lipid changes, which may contribute to the acceleration of atherosclerotic cardiovascular disease noted in postmenopausal women. The effects of estrogens on bone have been extensively studied, and the effects of hormone withdrawal have been well-characterized. However, the role of estrogens and progestins in the cause and prevention of cardiovascular disease, which is responsible for 350,000 deaths per year, and breast cancer, which causes 35,000 deaths per year, is less well understood.

When normal ovulatory function ceases and the estrogen levels fall after menopause, oophorectomy, or premature ovarian failure, there is an accelerated rise in plasma cholesterol and LDL concentrations, while LDL receptors decline. HDL is not much affected, and levels remain higher than in men. Very-low-density lipoprotein and triglyceride levels are also relatively unaffected. Since cardiovascular disorders account for most deaths in this age group, the risk for these disorders constitutes a major consideration in deciding whether or not hormonal "replacement" therapy (HRT, also correctly called HT) is indicated and influences the selection of hormones to be administered. Estrogen replacement therapy has a beneficial effect on circulating lipids and lipoproteins, and this was earlier thought to be accompanied by a reduction in myocardial infarction by about 50% and of fatal strokes by as much as 40%. These findings, however, have been disputed by the results of a large study from the Women's Health Initiative (WHI) project showing no cardiovascular benefit from estrogen plus progestin replacement therapy in perimenopausal or older postmenopausal patients. In fact, there may be a small increase in cardiovascular problems as well as breast cancer in women who received the replacement therapy. Interestingly, a small protective effect against colon cancer was observed. Although current clinical guidelines do not recommend routine hormone therapy in postmenopausal women, the validity of the WHI report has been questioned. In any case, there is no increased risk for breast cancer if therapy is given immediately after menopause and for the first 7 years, while the cardiovascular risk depends on the degree of atherosclerosis at the onset of therapy. Transdermal or vaginal administration of estrogen may be associated with decreased cardiovascular risk because it bypasses the liver circulation. Women with premature menopause should definitely receive hormone therapy.

In some studies, a protective effect of estrogen replacement therapy against Alzheimer's disease was observed. However, several other studies have not supported these results.

Progestins antagonize estrogen's effects on LDL and HDL to a variable extent. However, one large study has shown that the addition of a progestin to estrogen replacement therapy does not influence the cardiovascular risk.

Optimal management of the postmenopausal patient requires careful assessment of her symptoms as well as consideration of her age and the presence of (or risks for) cardiovascular disease, osteoporosis, breast cancer, and endometrial cancer. Bearing in mind the effects of the gonadal hormones on each of these disorders, the goals of therapy can then be defined and the risks of therapy assessed and discussed with the patient.

If the main indication for therapy is hot flushes and sleep disturbances, therapy with the lowest dose of estrogen required for symptomatic relief is recommended. Treatment may be required for only a limited period of time and the possible increased risk for breast cancer avoided. In women who have undergone hysterectomy, estrogens alone can be given 5 days per week or continuously, since progestins are not required to reduce the risk for endometrial hyperplasia and cancer. Hot flushes, sweating, insomnia, and atrophic

*The use of estrogens in contraception is discussed later in this chapter.

vaginitis are generally relieved by estrogens; many patients experience some increased sense of well-being; and climacteric depression and other psychopathologic states are improved.

The role of estrogens in the prevention and treatment of osteoporosis has been carefully studied (see Chapter 42). The amount of bone present in the body is maximal in the young active adult in the third decade of life and begins to decline more rapidly in middle age in both men and women. The development of osteoporosis also depends on the amount of bone present at the start of this process, on vitamin D and calcium intake, and on the degree of physical activity. The risk of osteoporosis is highest in smokers who are thin, Caucasian, and inactive and have a low calcium intake and a strong family history of osteoporosis. Depression also is a major risk factor for development of osteoporosis in women.

Estrogens should be used in the smallest dosage consistent with relief of symptoms. In women who have not undergone hysterectomy, it is most convenient to prescribe estrogen on the first 21–25 days of each month. The recommended dosages of estrogen are 0.3–1.25 mg/d of conjugated estrogen or 0.01–0.02 mg/d of ethinyl estradiol. Dosages in the middle of these ranges have been shown to be maximally effective in preventing the decrease in bone density occurring at menopause. From this point of view, it is important to begin therapy as soon as possible after the menopause for maximum effect. In these patients and others not taking estrogen, calcium supplements that bring the total daily calcium intake up to 1500 mg are useful.

Patients at low risk of developing osteoporosis who manifest only mild atrophic vaginitis can be treated with topical preparations. The vaginal route of application is also useful in the treatment of urinary tract symptoms in these patients. It is important to realize, however, that although locally administered estrogens escape the first-pass effect (so that some undesirable hepatic effects are reduced), they are almost completely absorbed into the circulation, and these preparations should be given cyclically.

As noted below, the administration of estrogen is associated with an increased risk of endometrial carcinoma. The administration of a progestational agent with the estrogen prevents endometrial hyperplasia and markedly reduces the risk of this cancer. When estrogen is given for the first 25 days of the month and the progestin medroxyprogesterone (10 mg/d) is added during the last 10–14 days, the risk is only half of that in women not receiving hormone replacement therapy. On this regimen, some women will experience a return of symptoms during the period off estrogen administration. In these patients, the estrogen can be given continuously. If the progestin produces sedation or other undesirable effects, its dose can be reduced to 2.5–5 mg for the last 10 days of the cycle with a slight increase in the risk for endometrial hyperplasia. These regimens are usually accompanied by bleeding at the end of each cycle. Some women experience migraine headaches during the last few days of the cycle. The use of a continuous estrogen regimen will often prevent their occurrence. Women who object to the cyclic bleeding associated with sequential therapy can also consider continuous therapy. Daily therapy with 0.625 mg of conjugated equine estrogens and 2.5–5 mg of medroxyprogesterone will eliminate cyclic bleeding, control vasomotor symptoms, prevent genital atrophy, maintain bone density, and show a favorable lipid profile with a small decrease in LDL and an increase in HDL concentrations. These women have endometrial atrophy on biopsy. About half of these patients experience breakthrough bleeding during the first few months of therapy. Seventy to 80 percent become amenorrheic after the first 4 months, and most remain so. The main disadvantage of continuous therapy is the need for uterine biopsy if bleeding occurs after the first few months.

As noted above, estrogens may also be administered vaginally or transdermally. When estrogens are given by these routes, the liver is bypassed on the first circulation, and the ratio of the liver effects to peripheral effects is reduced.

In patients in whom estrogen replacement therapy is contraindicated, such as those with estrogen-sensitive tumors, relief of vasomotor symptoms may be obtained by the use of clonidine.

C. Other Uses

Estrogens combined with progestins can be used to suppress ovulation in patients with intractable dysmenorrhea or when suppression of ovarian function is used in the treatment of hirsutism and amenorrhea due to excessive secretion of androgens by the ovary. Under these circumstances, greater suppression may be needed, and oral contraceptives containing 50 mcg of estrogen or a combination of a low estrogen pill with GnRH suppression may be required.

Adverse Effects

Adverse effects of variable severity have been reported with the therapeutic use of estrogens. Many other effects reported in conjunction with hormonal contraceptives may be related to their estrogen content. These are discussed below.

A. Uterine Bleeding

Estrogen therapy is a major cause of postmenopausal uterine bleeding. Unfortunately, vaginal bleeding at this time of life may also be due to carcinoma of the endometrium. To avoid confusion, patients should be treated with the smallest amount of estrogen possible. It should be given cyclically so that bleeding, if it occurs, will be more likely to occur during the withdrawal period. As noted above, endometrial hyperplasia can be prevented by administration of a progestational agent with estrogen in each cycle.

B. Cancer

The relation of estrogen therapy to cancer continues to be the subject of active investigation. Although no adverse effect of short-term estrogen therapy on the incidence of breast cancer has been demonstrated, a small increase in the incidence of this tumor may occur with prolonged therapy. Although the risk factor is small (1.25), the impact may be great since this tumor occurs in 10% of women, and addition of progesterone does not confer a protective effect. Studies indicate that following unilateral excision of breast cancer, women receiving tamoxifen (an estrogen partial agonist, see below) show a 35% decrease in contralateral breast cancer compared with controls. These studies also demonstrate that tamoxifen is well tolerated by most patients, produces estrogen-like alterations in plasma

lipid levels, and stabilizes bone mineral loss. Studies bearing on the possible efficacy of tamoxifen in postmenopausal women at high risk for breast cancer are under way. A recent study shows that postmenopausal hormone replacement therapy with estrogens plus progestins was associated with greater breast epithelial cell proliferation and breast epithelial cell density than estrogens alone or no replacement therapy. Furthermore, with estrogens plus progestins, breast proliferation was localized to the terminal duct-lobular unit of the breast, which is the main site of development of breast cancer. Thus, further studies are needed to conclusively assess the possible association between progestins and breast cancer risk.

Many studies show an increased risk of endometrial carcinoma in patients taking estrogens alone. The risk seems to vary with the dose and duration of treatment: 15 times greater in patients taking large doses of estrogen for 5 or more years, in contrast with two to four times greater in patients receiving lower doses for short periods. However, as noted above, the concomitant use of a progestin prevents this increased risk and may in fact reduce the incidence of endometrial cancer to less than that in the general population.

There have been a number of reports of adenocarcinoma of the vagina in young women whose mothers were treated with large doses of diethylstilbestrol early in pregnancy. These cancers are most common in young women (ages 14–44). The incidence is less than 1 per 1000 women exposed—too low to establish a cause-and-effect relationship with certainty. However, the risks for infertility, ectopic pregnancy, and premature delivery are also increased. It is now recognized that there is no indication for the use of diethylstilbestrol during pregnancy, and it should be avoided. It is not known whether other estrogens have a similar effect or whether the observed phenomena are peculiar to diethylstilbestrol. This agent should be used only in the treatment of cancer (eg, of the prostate) or as a "morning after" contraceptive (see below).

C. Other Effects

Nausea and breast tenderness are common and can be minimized by using the smallest effective dose of estrogen. Hyperpigmentation also occurs. Estrogen therapy is associated with an increase in frequency of migraine headaches as well as cholestasis, gallbladder disease, and hypertension.

Contraindications

Estrogens should not be used in patients with estrogen-dependent neoplasms such as carcinoma of the endometrium or in those with—or at high risk for—carcinoma of the breast. They should be avoided in patients with undiagnosed genital bleeding, liver disease, or a history of thromboembolic disorder. In addition, the use of estrogens should be avoided by heavy smokers.

Preparations & Dosages

The dosages of commonly used natural and synthetic preparations are listed in Table 40–1. Although all of the estrogens produce almost the same hormonal effects, their potencies vary both between agents and depending on the route of administration. As noted above, estradiol is the most active endogenous estrogen, and it has the highest affinity for the estrogen receptor. However, its metabolites estrone and estriol have weak uterine effects.

For a given level of gonadotropin suppression, oral estrogen preparations have more effect on the circulating levels of CBG, SHBG, and a host of other liver proteins, including angiotensinogen, than do transdermal preparations. The oral route of administration allows greater concentrations of hormone to reach the liver, thus increasing the synthesis of these proteins. Transdermal preparations were developed to avoid this effect. When administered transdermally, 50–100 mcg of estradiol has effects similar to those of 0.625–1.25 mg of conjugated oral estrogens on gonadotropin concentrations, endometrium, and vaginal epithelium. Furthermore, the transdermal estrogen preparations do not significantly increase the concentrations of renin substrate, CBG, and TBG and do not produce the characteristic changes in serum lipids. Combined oral preparations containing 0.625 mg of conjugated estrogens and 2.5 mg of medroxyprogesterone acetate are available for menopausal replacement therapy. Tablets containing 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate are available to be used in conjunction with conjugated estrogens in a sequential fashion. Estrogens alone are taken on days 1–14 and the combination on days 15–28.

THE PROGESTINS

Natural Progestins: Progesterone

Progesterone is the most important progestin in humans. In addition to having important hormonal effects, it serves as a precursor to the estrogens, androgens, and adrenocortical steroids. It is synthesized in the ovary, testis, and adrenal cortex from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy.

In the ovary, progesterone is produced primarily by the corpus luteum. Normal males appear to secrete 1–5 mg of progesterone daily, resulting in plasma levels of about 0.03 mcg/dL. The level is only slightly higher in the female during the follicular phase of the cycle, when only a few milligrams per day of progesterone are secreted. During the luteal phase, plasma levels range from 0.5 mcg/dL to more than 2 mcg/dL (Figure 40–1). Plasma levels of progesterone are further elevated and reach their peak levels in the third trimester of pregnancy.

Synthetic Progestins

A variety of progestational compounds have been synthesized. Some are active when given by mouth. They are not a uniform group of compounds, and all of them differ from progesterone in one or more respects. Table 40–2 lists some of these compounds and their effects. In general, the 21-carbon compounds (hydroxyprogesterone, medroxyprogesterone, megestrol, and dimethisterone) are the most closely related, pharmacologically as well as chemically, to progesterone. A new group of third-generation synthetic progestins has been introduced, principally as components of oral contraceptives. These "19-nor, 13-ethyl" steroid compounds

TABLE 40–2 Properties of some progestational agents.

	Route	Duration of Action	Activities[1]				
			Estrogenic	*Androgenic*	*Antiestrogenic*	*Antiandrogenic*	*Anabolic*
Progesterone and derivatives							
Progesterone	IM	1 day	–	–	+	–	–
Hydroxyprogesterone caproate	IM	8–14 days	sl	sl	–	–	–
Medroxyprogesterone acetate	IM, PO	Tabs: 1–3 days; injection: 4–12 weeks	–	+	+	–	–
Megestrol acetate	PO	1–3 days	–	+	–	+	–
17-Ethinyl testosterone derivatives							
Dimethisterone	PO	1–3 days	–	–	sl	–	–
19-Nortestosterone derivatives							
Desogestrel	PO	1–3 days	–	–	–	–	–
Norethynodrel[2]	PO	1–3 days	+	–	–	–	–
Lynestrenol[3]	PO	1–3 days	+	+	–	–	+
Norethindrone[2]	PO	1–3 days	sl	+	+	–	+
Norethindrone acetate[2]	PO	1–3 days	sl	+	+	–	+
Ethynodiol diacetate[2]	PO	1–3 days	sl	+	+	–	–
L-Norgestrel[2]	PO	1–3 days	–	+	+	–	+

[1] **Interpretation:** + = active; – = inactive; sl = slightly active. Activities have been reported in various species using various end points and may not apply to humans.

[2] See Table 40–3.

[3] Not available in USA.

include desogestrel (Figure 40–4), gestodene, and norgestimate. They are claimed to have lower androgenic activity than older synthetic progestins.

Pharmacokinetics

Progesterone is rapidly absorbed following administration by any route. Its half-life in the plasma is approximately 5 minutes, and small amounts are stored temporarily in body fat. It is almost completely metabolized in one passage through the liver, and for that reason it is quite ineffective when the usual formulation is administered orally. However, high-dose oral micronized progesterone preparations have been developed that provide adequate progestational effect.

In the liver, progesterone is metabolized to pregnanediol and conjugated with glucuronic acid. It is excreted into the urine as pregnanediol glucuronide. The amount of pregnanediol in the urine has been used as an index of progesterone secretion. This measure has been very useful despite the fact that the proportion of secreted progesterone converted to this compound varies from day to day and from individual to individual. In addition to progesterone, 20α- and 20β-hydroxyprogesterone (20α- and 20β-hydroxy-4-pregnene-3-one) are also found. These compounds have about one fifth the progestational activity of progesterone in humans and other species. Little is known of their physiologic role, but 20α-hydroxyprogesterone is produced in large amounts in some species and may be of some importance biologically.

The usual routes of administration and durations of action of the synthetic progestins are listed in Table 40–2. Most of these agents are extensively metabolized to inactive products that are excreted mainly in the urine.

Physiologic Effects

A. Mechanism

The mechanism of action of progesterone—described in more detail above—is similar to that of other steroid hormones. Progestins enter the cell and bind to progesterone receptors that are distributed between the nucleus and the cytoplasm. The ligand-receptor complex binds to a progesterone response element (PRE) to activate gene transcription. The response element for progesterone appears to be similar to the corticosteroid response element, and the specificity of the response depends upon which receptor is present in the cell as well as upon other cell-specific receptor coregulators and interacting transcription factors. The progesterone-receptor complex forms a dimer before binding to DNA. Like the estrogen receptor, it can form heterodimers as well as homodimers between two isoforms, A and B. These isoforms are produced by alternative splicing of the same gene.

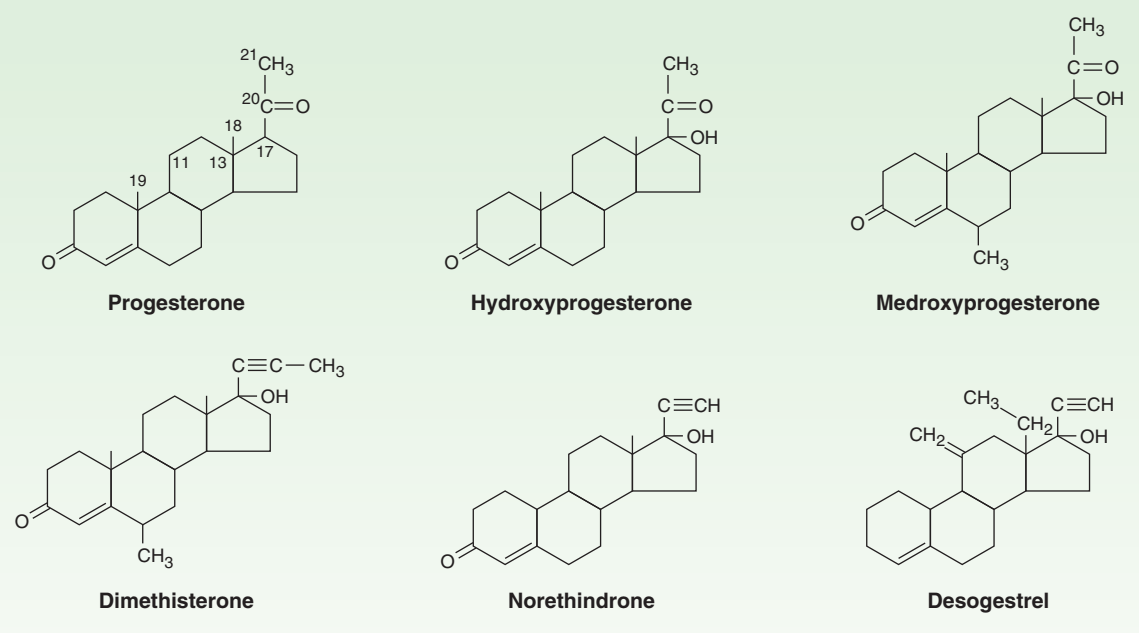


FIGURE 40–4 Progesterone and some progestational agents in clinical use.

B. Effects of Progesterone

Progesterone has little effect on protein metabolism. It stimulates lipoprotein lipase activity and seems to favor fat deposition. The effects on carbohydrate metabolism are more marked. Progesterone increases basal insulin levels and the insulin response to glucose. There is usually no manifest change in carbohydrate tolerance. In the liver, progesterone promotes glycogen storage, possibly by facilitating the effect of insulin. Progesterone also promotes ketogenesis.

Progesterone can compete with aldosterone for the mineralocorticoid receptor of the renal tubule, causing a decrease in Na^+ reabsorption. This leads to an increased secretion of aldosterone by the adrenal cortex (eg, in pregnancy). Progesterone increases body temperature in humans. The mechanism of this effect is not known, but an alteration of the temperature-regulating centers in the hypothalamus has been suggested. Progesterone also alters the function of the respiratory centers. The ventilatory response to CO_2 is increased by progesterone but synthetic progestins with an ethinyl group do not have respiratory effects. This leads to a measurable reduction in arterial and alveolar P_{CO_2} during pregnancy and in the luteal phase of the menstrual cycle. Progesterone and related steroids also have depressant and hypnotic effects on the brain.

Progesterone is responsible for the alveolobular development of the secretory apparatus in the breast. It also participates in the preovulatory LH surge and causes the maturation and secretory changes in the endometrium that are seen following ovulation (Figure 40–1).

Progesterone decreases the plasma levels of many amino acids and leads to increased urinary nitrogen excretion. It induces changes in the structure and function of smooth endoplasmic reticulum in experimental animals.

Other effects of progesterone and its analogs are noted below in the section, Hormonal Contraception.

C. Synthetic Progestins

The 21-carbon progesterone analogs antagonize aldosterone-induced sodium retention (see above). The remaining compounds ("19-nortestosterone" third-generation agents) produce a decidual change in the endometrial stroma, do not support pregnancy in test animals, are more effective gonadotropin inhibitors, and may have minimal estrogenic and androgenic or anabolic activity (Table 40–2; Figure 40–4). They are sometimes referred to as "impeded androgens." Progestins without androgenic activity include desogestrel, norgestimate, and gestodene. The first two of these compounds are dispensed in combination with ethinyl estradiol for oral contraception (Table 40–3) in the USA. Oral contraceptives containing the progestins cyproterone acetate (also an antiandrogen) in combination with ethinyl estradiol are investigational in the USA.

Clinical Uses

A. Therapeutic Applications

The major uses of progestational hormones are for hormone replacement therapy (see above) and hormonal contraception (see below). In addition, they are useful in producing long-term ovarian suppression for other purposes. When used alone in large doses parenterally (eg, medroxyprogesterone acetate, 150 mg intramuscularly every 90 days), prolonged anovulation and amenorrhea result. This therapy has been employed in the treatment of dysmenorrhea, endometriosis, and bleeding disorders when estrogens are contraindicated, and for contraception. The major problem

TABLE 40–3 Some oral and implantable contraceptive agents in use.[1]

	Estrogen (mg)		Progestin (mg)	
Monophasic combination tablets				
Alesse, Aviane, Lessinea, Levlite	Ethinyl estradiol	0.02	L-Norgestrel	0.1
Levlen, Levora, Nordette, Portia	Ethinyl estradiol	0.03	L-Norgestrel	0.15
Crysella, Lo-Ovral, Low-Ogestrel	Ethinyl estradiol	0.03	Norgestrel	0.30
Yasmin	Ethinyl estradiol	0.03	Drospirenone	3.0
Brevicon, Modicon, Necon 0.5/35, Nortrel 0.5/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-Cyclen, Sprintec	Ethinyl estradiol	0.035	Norgestimate	0.25
Necon 1/35, Norinyl 1+, Nortrel 1/35, Ortho-Novum 1/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ovcon-35	Ethinyl estradiol	0.035	Norethindrone	0.4
Demulen 1/50, Zovia 1/50E	Ethinyl estradiol	0.05	Ethynodiol diacetate	1.0
Ovcon 50	Ethinyl estradiol	0.05	Norethindrone	1.0
Ovral-28	Ethinyl estradiol	0.05	D,L-Norgestrel	0.5
Norinyl 1/50, Ortho-Novum 1/50	Mestranol	0.05	Norethindrone	1.0
Biphasic combination tablets				
Ortho-Novum 10/11, Necon 10/11				
Days 1–10	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 11–21	Ethinyl estradiol	0.035	Norethindrone	1.0
Triphasic combination tablets				
Enpresse, Triphasil, Tri-Levlen, Trivora				
Days 1–6	Ethinyl estradiol	0.03	L-Norgestrel	0.05
Days 7–11	Ethinyl estradiol	0.04	L-Norgestrel	0.075
Days 12–21	Ethinyl estradiol	0.03	L-Norgestrel	0.125
Ortho-Novum 7/7/7, Necon 7/7/7				
Days 1–7	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 8–14	Ethinyl estradiol	0.035	Norethindrone	0.75
Days 15–21	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-Tri-Cyclen				
Days 1–7	Ethinyl estradiol	0.035	Norgestimate	0.18
Days 8–14	Ethinyl estradiol	0.035	Norgestimate	0.215
Days 15–21	Ethinyl estradiol	0.035	Norgestimate	0.25
Daily progestin tablets				
Nora-BE, Nor-QD, Ortho Micronor, Jolivette, Camila, Errin	…		Norethindrone	0.35
Ovrette	…		D,L-Norgestrel	0.075
Implantable progestin preparation				
Implanon	…		Etonogestrel (one tube of 68 mg)	

[1]The estrogen-containing compounds are arranged in order of increasing content of estrogen. Other preparations are available. (Ethinyl estradiol and mestranol have similar potencies.)

with this regimen is the prolonged time required in some patients for ovulatory function to return after cessation of therapy. It should not be used for patients planning a pregnancy in the near future. Similar regimens will relieve hot flushes in some menopausal women and can be used if estrogen therapy is contraindicated.

Medroxyprogesterone acetate, 10–20 mg orally twice weekly—or intramuscularly in doses of 100 mg/m^2 every 1–2 weeks—will prevent menstruation, but it will not arrest accelerated bone maturation in children with precocious puberty.

Progestins do not appear to have any place in the therapy of threatened or habitual abortion. Early reports of the usefulness of these agents resulted from the unwarranted assumption that after several abortions the likelihood of repeated abortions was over 90%. When progestational agents were administered to patients with previous abortions, a salvage rate of 80% was achieved. It is now recognized that similar patients abort only 20% of the time even when untreated. On the other hand, progesterone was given experimentally to delay premature labor with encouraging results.

Progesterone and medroxyprogesterone have been used in the treatment of women who have difficulty in conceiving and who demonstrate a slow rise in basal body temperature. There is no convincing evidence that this treatment is effective.

Preparations of progesterone and medroxyprogesterone have been used to treat premenstrual syndrome. Controlled studies have not confirmed the effectiveness of such therapy except when doses sufficient to suppress ovulation have been used.

B. Diagnostic Uses

Progesterone can be used as a test of estrogen secretion. The administration of progesterone, 150 mg/d, or medroxyprogesterone, 10 mg/d, for 5–7 days, is followed by withdrawal bleeding in amenorrheic patients only when the endometrium has been stimulated by estrogens. A combination of estrogen and progestin can be given to test the responsiveness of the endometrium in patients with amenorrhea.

Contraindications, Cautions, & Adverse Effects

Studies of progestational compounds alone and with combination oral contraceptives indicate that the progestin in these agents may increase blood pressure in some patients. The more androgenic progestins also reduce plasma HDL levels in women. (See Hormonal Contraception, below.) Two recent studies suggest that combined progestin plus estrogen replacement therapy in postmenopausal women may increase breast cancer risk significantly compared with the risk in women taking estrogen alone. These findings require careful examination and if confirmed will lead to important changes in postmenopausal hormone replacement practice.

OTHER OVARIAN HORMONES

The normal ovary produces small amounts of **androgens,** including testosterone, androstenedione, and dehydroepiandrosterone. Of these, only testosterone has a significant amount of biologic activity, although androstenedione can be converted to testosterone or estrone in peripheral tissues. The normal woman produces less than 200 mcg of testosterone in 24 hours, and about one third of this is probably formed in the ovary directly. The physiologic significance of these small amounts of androgens is not established, but they may be partly responsible for normal hair growth at puberty, for stimulation of female libido, and, possibly, for metabolic effects. Androgen production by the ovary may be markedly increased in some abnormal states, usually in association with hirsutism and amenorrhea as noted above.

The ovary also produces **inhibin** and **activin.** These peptides consist of several combinations of α and β subunits and are described in greater detail later. The αβ dimer (inhibin) inhibits FSH secretion while the ββ dimer (activin) increases FSH secretion. Studies in primates indicate that inhibin has no direct effect on ovarian steroidogenesis but that activin modulates the response to LH and FSH. For example, simultaneous treatment with activin and human FSH enhances FSH stimulation of progesterone synthesis and aromatase activity in granulosa cells. When combined with LH, activin suppressed the LH-induced progesterone response by 50% but markedly enhanced basal and LH-stimulated aromatase activity. Activin may also act as a growth factor in other tissues. The physiologic roles of these modulators are not fully understood.

Relaxin is another peptide that can be extracted from the ovary. The three-dimensional structure of relaxin is related to that of growth-promoting peptides and is similar to that of insulin. Although the amino acid sequence differs from that of insulin, this hormone, like insulin, consists of two chains linked by disulfide bonds, cleaved from a prohormone. It is found in the ovary, placenta, uterus, and blood. Relaxin synthesis has been demonstrated in luteinized granulosa cells of the corpus luteum. It has been shown to increase glycogen synthesis and water uptake by the myometrium and decreases uterine contractility. In some species, it changes the mechanical properties of the cervix and pubic ligaments, facilitating delivery.

In women, relaxin has been measured by immunoassay. Levels were highest immediately after the LH surge and during menstruation. A physiologic role for this peptide has not been established.

Clinical trials with relaxin have been conducted in patients with dysmenorrhea. Relaxin has also been administered to patients in premature labor and during prolonged labor. When applied to the cervix of a woman at term, it facilitates dilation and shortens labor.

Several other nonsteroidal substances such as corticotropin-releasing hormone, follistatin, and prostaglandins are produced by the ovary. These probably have paracrine effects within the ovary.

HORMONAL CONTRACEPTION (ORAL, PARENTERAL, & IMPLANTED CONTRACEPTIVES)

A large number of oral contraceptives containing estrogens or progestins (or both) are now available for clinical use (Table 40–3). These preparations vary chemically and pharmacologically and have many properties in common as well as definite differences important for the correct selection of the optimum agent.

Two types of preparations are used for oral contraception: (1) combinations of estrogens and progestins and (2) continuous progestin therapy without concomitant administration of estrogens. The combination agents are further divided into **monophasic** forms (constant dosage of both components during the cycle) and **biphasic** or **triphasic** forms (dosage of one or both components is changed once or twice during the cycle). The preparations for oral use are all adequately absorbed, and in combination preparations the pharmacokinetics of neither drug is significantly altered by the other.

Only one implantable contraceptive preparation is available at present in the USA. Etonogestrel, also used in some oral contraceptives, is available in the subcutaneous implant form listed in Table 40–3. Several hormonal contraceptives are available as

vaginal rings or intrauterine devices. Intramuscular injection of large doses of medroxyprogesterone also provides contraception of long duration.

Pharmacologic Effects

A. Mechanism of Action

The combinations of estrogens and progestins exert their contraceptive effect largely through selective inhibition of pituitary function that results in inhibition of ovulation. The combination agents also produce a change in the cervical mucus, in the uterine endometrium, and in motility and secretion in the uterine tubes, all of which decrease the likelihood of conception and implantation. The continuous use of progestins alone does not always inhibit ovulation. The other factors mentioned, therefore, play a major role in the prevention of pregnancy when these agents are used.

B. Effects on the Ovary

Chronic use of combination agents depresses ovarian function. Follicular development is minimal, and corpora lutea, larger follicles, stromal edema, and other morphologic features normally seen in ovulating women are absent. The ovaries usually become smaller even when enlarged before therapy.

The great majority of patients return to normal menstrual patterns when these drugs are discontinued. About 75% will ovulate in the first posttreatment cycle and 97% by the third posttreatment cycle. About 2% of patients remain amenorrheic for periods of up to several years after administration is stopped.

The cytologic findings on vaginal smears vary depending on the preparation used. However, with almost all of the combined drugs, a low maturation index is found because of the presence of progestational agents.

C. Effects on the Uterus

After prolonged use, the cervix may show some hypertrophy and polyp formation. There are also important effects on the cervical mucus, making it more like postovulation mucus, ie, thicker and less copious.

Agents containing both estrogens and progestins produce further morphologic and biochemical changes of the endometrial stroma under the influence of the progestin, which also stimulates glandular secretion throughout the luteal phase. The agents containing "19-nor" progestins—particularly those with the smaller amounts of estrogen—tend to produce more glandular atrophy and usually less bleeding.

D. Effects on the Breast

Stimulation of the breasts occurs in most patients receiving estrogen-containing agents. Some enlargement is generally noted. The administration of estrogens and combinations of estrogens and progestins tends to suppress lactation. When the doses are small, the effects on breast-feeding are not appreciable. Studies of the transport of the oral contraceptives into breast milk suggest that only small amounts of these compounds cross into the milk, and they have not been considered to be of importance.

E. Other Effects of Oral Contraceptives

1. Effects on the central nervous system—The central nervous system effects of the oral contraceptives have not been well studied in humans. A variety of effects of estrogen and progesterone have been noted in animals. Estrogens tend to increase excitability in the brain, whereas progesterone tends to decrease it. The thermogenic action of progesterone and some of the synthetic progestins is also thought to occur in the central nervous system.

It is very difficult to evaluate any behavioral or emotional effects of these compounds in humans. Although the incidence of pronounced changes in mood, affect, and behavior appears to be low, milder changes are commonly reported, and estrogens are being successfully employed in the therapy of premenstrual tension syndrome, postpartum depression, and climacteric depression.

2. Effects on endocrine function—The inhibition of pituitary gonadotropin secretion has been mentioned. Estrogens also alter adrenal structure and function. Estrogens given orally or at high doses increase the plasma concentration of the α_2 globulin that binds cortisol (corticosteroid-binding globulin). Plasma concentrations may be more than double the levels found in untreated individuals, and urinary excretion of free cortisol is elevated.

These preparations cause alterations in the renin-angiotensin-aldosterone system. Plasma renin activity has been found to increase, and there is an increase in aldosterone secretion.

Thyroxine-binding globulin is increased. As a result, total plasma thyroxine (T_4) levels are increased to those commonly seen during pregnancy. Since more of the thyroxine is bound, the free thyroxine level in these patients is normal. Estrogens also increase the plasma level of SHBG and decrease plasma levels of free androgens by increasing their binding; large amounts of estrogen may decrease androgens by gonadotropin suppression.

3. Effects on blood—Serious thromboembolic phenomena occurring in women taking oral contraceptives gave rise to a great many studies of the effects of these compounds on blood coagulation. A clear picture of such effects has not yet emerged. The oral contraceptives do not consistently alter bleeding or clotting times. The changes that have been observed are similar to those reported in pregnancy. There is an increase in factors VII, VIII, IX, and X and a decrease in antithrombin III. Increased amounts of coumarin anticoagulants may be required to prolong prothrombin time in patients taking oral contraceptives.

There is an increase in serum iron and total iron-binding capacity similar to that reported in patients with hepatitis.

Significant alterations in the cellular components of blood have not been reported with any consistency. A number of patients have been reported to develop folic acid deficiency anemias.

4. Effects on the liver—These hormones also have profound effects on the function of the liver. Some of these effects are deleterious and will be considered below in the section on adverse effects. The effects on serum proteins result from the effects of the estrogens on the synthesis of the various α_2 globulins and fibrinogen. Serum haptoglobins produced in the liver are depressed

rather than increased by estrogen. Some of the effects on carbohydrate and lipid metabolism are probably influenced by changes in liver metabolism (see below).

Important alterations in hepatic drug excretion and metabolism also occur. Estrogens in the amounts seen during pregnancy or used in oral contraceptive agents delay the clearance of sulfobromophthalein and reduce the flow of bile. The proportion of cholic acid in bile acids is increased while the proportion of chenodeoxycholic acid is decreased. These changes may be responsible for the observed increase in cholelithiasis associated with the use of these agents.

5. Effects on lipid metabolism—As noted above, estrogens increase serum triglycerides and free and esterified cholesterol. Phospholipids are also increased, as are HDL; levels of LDL usually decrease. Although the effects are marked with doses of 100 mcg of mestranol or ethinyl estradiol, doses of 50 mcg or less have minimal effects. The progestins (particularly the "19-nortestosterone" derivatives) tend to antagonize these effects of estrogen. Preparations containing small amounts of estrogen and a progestin may slightly decrease triglycerides and HDL.

6. Effects on carbohydrate metabolism—The administration of oral contraceptives produces alterations in carbohydrate metabolism similar to those observed in pregnancy. There is a reduction in the rate of absorption of carbohydrates from the gastrointestinal tract. Progesterone increases the basal insulin level and the rise in insulin induced by carbohydrate ingestion. Preparations with more potent progestins such as norgestrel may cause progressive decreases in carbohydrate tolerance over several years. However, the changes in glucose tolerance are reversible on discontinuing medication.

7. Effects on the cardiovascular system—These agents cause small increases in cardiac output associated with higher systolic and diastolic blood pressure and heart rate. The pressure returns to normal when treatment is terminated. Although the magnitude of the pressure change is small in most patients, it is marked in a few. It is important that blood pressure be followed in each patient. An increase in blood pressure has been reported to occur in a few postmenopausal women treated with estrogens alone.

8. Effects on the skin—The oral contraceptives have been noted to increase pigmentation of the skin (chloasma). This effect seems to be enhanced in women with dark complexions and by exposure to ultraviolet light. Some of the androgen-like progestins might increase the production of sebum, causing acne in some patients. However, since ovarian androgen is suppressed, many patients note decreased sebum production, acne, and terminal hair growth. The sequential oral contraceptive preparations as well as estrogens alone often decrease sebum production.

Clinical Uses

The most important use of combined estrogens and progestins is for oral contraception. A large number of preparations are available for this specific purpose, some of which are listed in Table 40–3. They are specially packaged for ease of administration. In general, they are very effective; when these agents are taken according to directions, the risk of conception is extremely small. The pregnancy rate with combination agents is estimated to be about 0.5–1 per 100 woman years at risk. Contraceptive failure has been observed in some patients when one or more doses are missed, if phenytoin is also being used (which may increase catabolism of the compounds), or if antibiotics are taken that alter enterohepatic cycling of metabolites.

Progestins and estrogens are also useful in the treatment of endometriosis. When severe dysmenorrhea is the major symptom, the suppression of ovulation with estrogen alone may be followed by painless periods. However, in most patients this approach to therapy is inadequate. The long-term administration of large doses of progestins or combinations of progestins and estrogens prevents the periodic breakdown of the endometrial tissue and in some cases will lead to endometrial fibrosis and prevent the reactivation of implants for prolonged periods.

As is true with most hormonal preparations, many of the undesired effects are physiologic or pharmacologic actions that are objectionable only because they are not pertinent to the situation for which they are being used. Therefore, the product containing the smallest effective amounts of hormones should be selected for use.

Adverse Effects

The incidence of serious known toxicities associated with the use of these drugs is low—far lower than the risks associated with pregnancy. There are a number of reversible changes in intermediary metabolism. Minor adverse effects are frequent, but most are mild and many are transient. Continuing problems may respond to simple changes in pill formulation. Although it is not often necessary to discontinue medication for these reasons, as many as one third of all patients started on oral contraception discontinue use for reasons other than a desire to become pregnant.

A. Mild Adverse Effects

1. Nausea, mastalgia, breakthrough bleeding, and edema are related to the amount of estrogen in the preparation. These effects can often be alleviated by a shift to a preparation containing smaller amounts of estrogen or to agents containing progestins with more androgenic effects.
2. Changes in serum proteins and other effects on endocrine function (see above) must be taken into account when thyroid, adrenal, or pituitary function is being evaluated. Increases in sedimentation rate are thought to be due to increased levels of fibrinogen.
3. Headache is mild and often transient. However, migraine is often made worse and has been reported to be associated with an increased frequency of cerebrovascular accidents. When this occurs or when migraine has its onset during therapy with these agents, treatment should be discontinued.
4. Withdrawal bleeding sometimes fails to occur—most often with combination preparations—and may cause confusion with regard to pregnancy. If this is disturbing to the patient, a different preparation may be tried or other methods of contraception used.

B. Moderate Adverse Effects

Any of the following may require discontinuance of oral contraceptives:

1. Breakthrough bleeding is the most common problem in using progestational agents alone for contraception. It occurs in as many as 25% of patients. It is more frequently encountered in patients taking low-dose preparations than in those taking combination pills with higher levels of progestin and estrogen. The biphasic and triphasic oral contraceptives (Table 40–3) decrease breakthrough bleeding without increasing the total hormone content.
2. Weight gain is more common with the combination agents containing androgen-like progestins. It can usually be controlled by shifting to preparations with less progestin effect or by dieting.
3. Increased skin pigmentation may occur, especially in dark-skinned women. It tends to increase with time, the incidence being about 5% at the end of the first year and about 40% after 8 years. It is thought to be exacerbated by vitamin B deficiency. It is often reversible upon discontinuance of medication but may disappear very slowly.
4. Acne may be exacerbated by agents containing androgen-like progestins (Table 40–2), whereas agents containing large amounts of estrogen usually cause marked improvement in acne.
5. Hirsutism may also be aggravated by the "19-nortestosterone" derivatives, and combinations containing nonandrogenic progestins are preferred in these patients.
6. Ureteral dilation similar to that observed in pregnancy has been reported, and bacteriuria is more frequent.
7. Vaginal infections are more common and more difficult to treat in patients who are using oral contraceptives.
8. Amenorrhea occurs in some patients. Following cessation of administration of oral contraceptives, 95% of patients with normal menstrual histories resume normal periods and all but a few resume normal cycles during the next few months. However, some patients remain amenorrheic for several years. Many of these patients also have galactorrhea. Patients who have had menstrual irregularities before taking oral contraceptives are particularly susceptible to prolonged amenorrhea when the agents are discontinued. Prolactin levels should be measured in these patients, since many have prolactinomas.

C. Severe Adverse Effects

1. Vascular disorders—Thromboembolism was one of the earliest of the serious unanticipated effects to be reported and has been the most thoroughly studied.

a. Venous thromboembolic disease—Superficial or deep thromboembolic disease in women not taking oral contraceptives occurs in about 1 patient per 1000 woman years. The overall incidence of these disorders in patients taking low-dose oral contraceptives is about threefold higher. The risk for this disorder is increased during the first month of contraceptive use and remains constant for several years or more. The risk returns to normal within a month when use is discontinued. The risk of venous thrombosis or pulmonary embolism is increased among women with predisposing conditions such as stasis, altered clotting factors such as antithrombin III, increased levels of homocysteine, or injury. Genetic disorders, including mutations in the genes governing the production of protein C (factor V Leiden), protein S, hepatic cofactor II, and others, markedly increase the risk of venous thromboembolism. The incidence of these disorders is too low for cost-effective screening by current methods, but prior episodes or a family history may be helpful in identifying patients with increased risk.

The incidence of venous thromboembolism appears to be related to the estrogen but not the progestin content of oral contraceptives and is not related to age, parity, mild obesity, or cigarette smoking. Decreased venous blood flow, endothelial proliferation in veins and arteries, and increased coagulability of blood resulting from changes in platelet functions and fibrinolytic systems contribute to the increased incidence of thrombosis. The major plasma inhibitor of thrombin, antithrombin III, is substantially decreased during oral contraceptive use. This change occurs in the first month of treatment and lasts as long as treatment persists, reversing within a month thereafter.

b. Myocardial infarction—The use of oral contraceptives is associated with a slightly higher risk of myocardial infarction in women who are obese, have a history of preeclampsia or hypertension, or have hyperlipoproteinemia or diabetes. There is a much higher risk in women who smoke. The risk attributable to oral contraceptives in women 30–40 years of age who do not smoke is about 4 cases per 100,000 users per year, as compared with 185 cases per 100,000 among women 40–44 who smoke heavily. The association with myocardial infarction is thought to involve acceleration of atherogenesis because of decreased glucose tolerance, decreased levels of HDL, increased levels of LDL, and increased platelet aggregation. In addition, facilitation of coronary arterial spasm may play a role in some of these patients. The progestational component of oral contraceptives decreases HDL cholesterol levels, in proportion to the androgenic activity of the progestin. The net effect, therefore, will depend on the specific composition of the pill used and the patient's susceptibility to the particular effects. Recent studies suggest that risk of infarction is not increased in past users who have discontinued oral contraceptives.

c. Cerebrovascular disease—The risk of stroke is concentrated in women over age 35. It is increased in current users of oral contraceptives but not in past users. However, subarachnoid hemorrhages have been found to be increased among both current and past users and may increase with time. The risk of thrombotic or hemorrhagic stroke attributable to oral contraceptives (based on older, higher-dose preparations) has been estimated to about 37 cases per 100,000 users per year.

In summary, available data indicate that oral contraceptives increase the risk of various cardiovascular disorders at all ages and among both smokers and nonsmokers. However, this risk appears to be concentrated in women 35 years of age or older who are heavy smokers. It is clear that these risk factors must be considered in each individual patient for whom oral contraceptives are being considered. Some experts have suggested that screening for coagulopathy should be performed before starting oral contraception.

2. Gastrointestinal disorders—Many cases of cholestatic jaundice have been reported in patients taking progestin-containing drugs. The differences in incidence of these disorders from one population to another suggest that genetic factors may be involved. The jaundice caused by these agents is similar to that produced by other 17-alkyl-substituted steroids. It is most often observed in the first three cycles and is particularly common in women with a history of cholestatic jaundice during pregnancy. Jaundice and pruritus disappear 1–8 weeks after the drug is discontinued.

These agents have also been found to increase the incidence of symptomatic gallbladder disease, including cholecystitis and cholangitis. This is probably the result of the alterations responsible for jaundice and bile acid changes described above.

It also appears that the incidence of hepatic adenomas is increased in women taking oral contraceptives. Ischemic bowel disease secondary to thrombosis of the celiac and superior and inferior mesenteric arteries and veins has also been reported in women using these drugs.

3. Depression—Depression of sufficient degree to require cessation of therapy occurs in about 6% of patients treated with some preparations.

4. Cancer—The occurrence of malignant tumors in patients taking oral contraceptives has been studied extensively. It is now clear that these compounds *reduce* the risk of endometrial and ovarian cancer. The lifetime risk of breast cancer in the population as a whole does not seem to be affected by oral contraceptive use. Some studies have shown an increased risk in younger women, and it is possible that tumors that develop in younger women become clinically apparent sooner. The relation of risk of cervical cancer to oral contraceptive use is still controversial. It should be noted that a number of recent studies associate the use of oral contraceptives by women who are infected with human papillomavirus with an increased risk of cervical cancer.

5. Other—In addition to the above effects, a number of other adverse reactions have been reported for which a causal relation has not been established. These include alopecia, erythema multiforme, erythema nodosum, and other skin disorders.

Contraindications & Cautions

These drugs are contraindicated in patients with thrombophlebitis, thromboembolic phenomena, and cardiovascular and cerebrovascular disorders or a past history of these conditions. They should not be used to treat vaginal bleeding when the cause is unknown. They should be avoided in patients with known or suspected tumors of the breast or other estrogen-dependent neoplasms. Since these preparations have caused aggravation of preexisting disorders, they should be avoided or used with caution in patients with liver disease, asthma, eczema, migraine, diabetes, hypertension, optic neuritis, retrobulbar neuritis, or convulsive disorders.

The oral contraceptives may produce edema, and for that reason they should be used with great caution in patients in heart failure or in whom edema is otherwise undesirable or dangerous.

Estrogens may increase the rate of growth of fibroids. Therefore, for women with these tumors, agents with the smallest amounts of estrogen and the most androgenic progestins should be selected. The use of progestational agents alone for contraception might be especially useful in such patients (see below).

These agents are contraindicated in adolescents in whom epiphysial closure has not yet been completed.

Women using oral contraceptives must be made aware of an important interaction that occurs with antimicrobial drugs. Because the normal gastrointestinal flora increase the enterohepatic cycling (and bioavailability) of estrogens, antimicrobial drugs that interfere with these organisms may reduce the efficacy of oral contraceptives. Additionally, coadministration with potent inducers of the hepatic microsomal metabolizing enzymes, such as rifampin, may increase liver catabolism of estrogens or progestins and diminish the efficacy of oral contraceptives.

Contraception with Progestins Alone

Small doses of progestins administered orally or by implantation under the skin can be used for contraception. They are particularly suited for use in patients for whom estrogen administration is undesirable. They are about as effective as intrauterine devices or combination pills containing 20–30 mcg of ethinyl estradiol. There is a high incidence of abnormal bleeding.

Effective contraception can also be achieved by injecting 150 mg of depot medroxyprogesterone acetate (DMPA) every 3 months. After a 150 mg dose, ovulation is inhibited for at least 14 weeks. Almost all users experience episodes of unpredictable spotting and bleeding, particularly during the first year of use. Spotting and bleeding decrease with time, and amenorrhea is common. This preparation is not desirable for women planning a pregnancy soon after cessation of therapy because ovulation suppression can sometimes persist for as long as 18 months after the last injection. Long-term DMPA use reduces menstrual blood loss and is associated with a decreased risk of endometrial cancer. Suppression of endogenous estrogen secretion may be associated with a reversible reduction in bone density, and changes in plasma lipids are associated with an increased risk of atherosclerosis.

The progestin implant method utilizes the subcutaneous implantation of capsules containing etonogestrel. These capsules release one fifth to one third as much steroid as oral agents, are extremely effective, and last for 2–4 years. The low levels of hormone have little effect on lipoprotein and carbohydrate metabolism or blood pressure. The disadvantages include the need for surgical insertion and removal of capsules and some irregular bleeding rather than predictable menses. An association of intracranial hypertension with an earlier type of implant utilizing norgestrel was observed in a small number of women. Patients experiencing headache or visual disturbances should be checked for papilledema.

Contraception with progestins is useful in patients with hepatic disease, hypertension, psychosis or mental retardation, or prior thromboembolism. The side effects include headache, dizziness, bloating and weight gain of 1–2 kg, and a reversible reduction of glucose tolerance.

TABLE 40–4 Schedules for use of postcoital contraceptives.

Conjugated estrogens: 10 mg three times daily for 5 days
Ethinyl estradiol: 2.5 mg twice daily for 5 days
Diethylstilbestrol: 50 mg daily for 5 days
Mifepristone: 600 mg once with misoprostol, 400 mcg once[1]
L-Norgestrel: 0.75 mg twice daily for 1 day (eg, Plan B[2])
Norgestrel, 0.5 mg, with ethinyl estradiol, 0.05 mg (eg, Ovral, Preven[2]): Two tablets and then two in 12 hours

[1]Mifepristone given on day 1, misoprostol on day 3.

[2]Sold as emergency contraceptive kits.

Postcoital Contraceptives

Pregnancy can be prevented following coitus by the administration of estrogens alone, progestin alone, or in combination (**"morning after"** contraception). When treatment is begun within 72 hours, it is effective 99% of the time. Some effective schedules are shown in Table 40–4. The hormones are often administered with antiemetics, since 40% of patients have nausea or vomiting. Other adverse effects include headache, dizziness, breast tenderness, and abdominal and leg cramps.

Mifepristone, an antagonist at progesterone and glucocorticoid receptors, has a luteolytic effect and is effective as a postcoital contraceptive. When combined with a prostaglandin it is also an effective abortifacient.

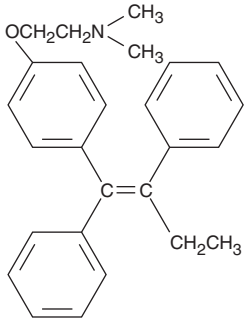
Beneficial Effects of Oral Contraceptives

It has become apparent that reduction in the dose of the constituents of oral contraceptives has markedly reduced mild and severe adverse effects, providing a relatively safe and convenient method of contraception for many young women. Treatment with oral contraceptives has also been shown to be associated with many benefits unrelated to contraception. These include a reduced risk of ovarian cysts, ovarian and endometrial cancer, and benign breast disease. There is a lower incidence of ectopic pregnancy. Iron deficiency and rheumatoid arthritis are less common, and premenstrual symptoms, dysmenorrhea, endometriosis, acne, and hirsutism may be ameliorated with their use.

■ ESTROGEN & PROGESTERONE INHIBITORS & ANTAGONISTS

TAMOXIFEN & RELATED PARTIAL AGONIST ESTROGENS

Tamoxifen, a competitive partial agonist inhibitor of estradiol at the estrogen receptor (Figure 40–5), was the first **selective estrogen receptor modulator (SERM)** to be introduced. It is extensively used in the palliative treatment of breast cancer in postmenopausal women and is approved for chemoprevention of breast cancer in high-risk women (see Chapter 54). It is a nonsteroidal agent (see structure below) that is given orally. Peak plasma levels are reached in a few hours. Tamoxifen has an initial half-life of 7–14 hours in the circulation and is predominantly excreted by the liver. It is used in doses of 10–20 mg twice daily. Hot flushes and nausea and vomiting occur in 25% of patients, and many other minor adverse effects are observed. Studies of patients treated with tamoxifen as adjuvant therapy for early breast cancer have shown a 35% decrease in contralateral breast cancer. However, adjuvant therapy extended beyond 5 years in patients with breast cancer has shown no further improvement in outcome. **Toremifene** is a structurally similar compound with very similar properties, indications, and toxicities.



Tamoxifen

Prevention of the expected loss of lumbar spine bone density and plasma lipid changes consistent with a reduction in the risk for atherosclerosis have also been reported in tamoxifen-treated patients following spontaneous or surgical menopause. However, this agonist activity also affects the uterus and may increase the risk of endometrial cancer.

Raloxifene is another partial estrogen agonist-antagonist (SERM) at some but not all target tissues. It has similar effects on lipids and bone but appears not to stimulate the endometrium or breast. Although subject to a high first-pass effect, raloxifene has a very large volume of distribution and a long half-life (>24 hours), so it can be taken once a day. Raloxifene has been approved in the USA for the prevention of postmenopausal osteoporosis and prophylaxis of breast cancer in women with risk factors.

Clomiphene is an older partial agonist, a weak estrogen that also acts as a competitive inhibitor of endogenous estrogens (Figure 40–5). It has found use as an ovulation-inducing agent (see below).

MIFEPRISTONE

Mifepristone is a "19-norsteroid" that binds strongly to the progesterone receptor and inhibits the activity of progesterone. The drug has luteolytic properties in 80% of women when given in the midluteal period. The mechanism of this effect is unknown, but it may provide the basis for using mifepristone as a contraceptive (as opposed to an abortifacient). However, because the compound has a long half-life, large doses may prolong the follicular phase of

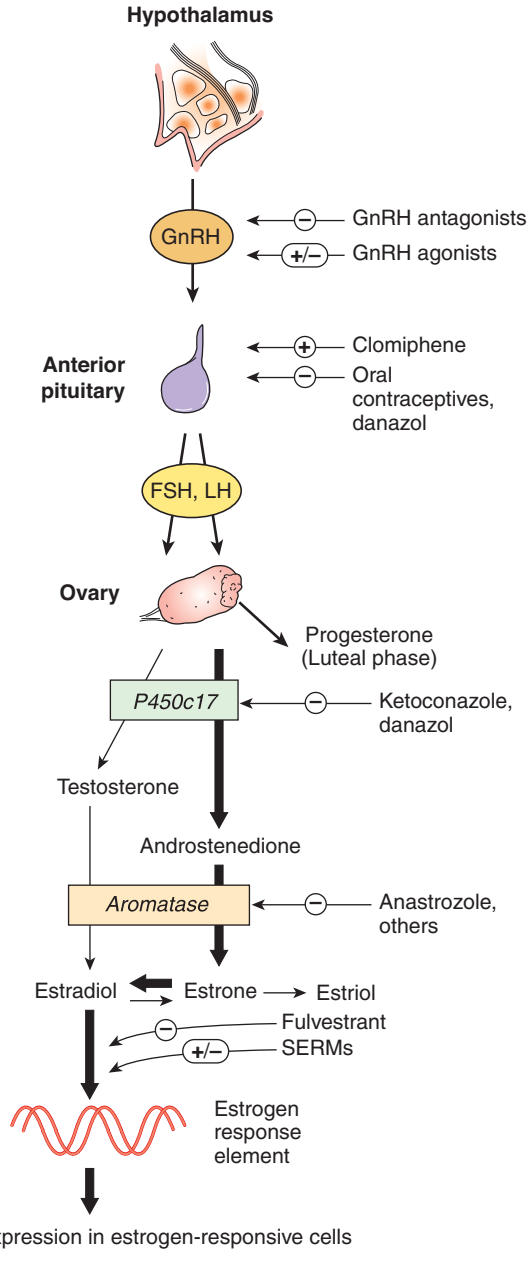
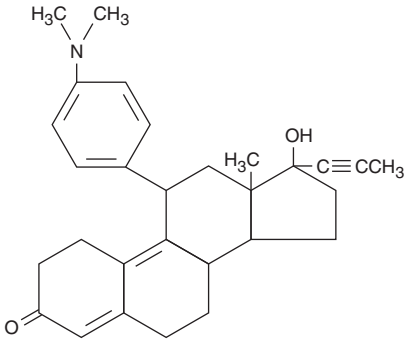


FIGURE 40–5 Control of ovarian secretion and the actions of its hormones. In the follicular phase the ovary produces mainly estrogens; in the luteal phase it produces estrogens and progesterone. SERMs, selective estrogen receptor modulators. See text.

the subsequent cycle and so make it difficult to use continuously for this purpose. A single dose of 600 mg is an effective emergency postcoital contraceptive, though it may result in delayed ovulation in the following cycle. As noted in Chapter 39, the drug also binds to and acts as an antagonist at the glucocorticoid receptor. Limited clinical studies suggest that mifepristone or other analogs with similar properties may be useful in the treatment of endometriosis, Cushing's syndrome, breast cancer, and possibly other neoplasms such as meningiomas that contain glucocorticoid or progesterone receptors.



Mifepristone

Mifepristone's major use thus far has been to terminate early pregnancies. Doses of 400–600 mg/d for 4 days or 800 mg/d for 2 days successfully terminated pregnancy in over 85% of the women studied. The major adverse effect was prolonged bleeding that on most occasions did not require treatment. The combination of a single oral dose of 600 mg of mifepristone and a vaginal pessary containing 1 mg of prostaglandin E_1 or oral misoprostol has been found to effectively terminate pregnancy in over 95% of patients treated during the first 7 weeks after conception. The adverse effects of the medications included vomiting, diarrhea, and abdominal or pelvic pain. As many as 5% of patients have vaginal bleeding requiring intervention. Because of these adverse effects, mifepristone is administered only by physicians at family planning centers. **Note:** In a very small number of cases, use of a vaginal tablet for the prostaglandin dose has been associated with sepsis, so it is recommended that *both* drugs be given by mouth in all patients.

ZK 98734 (lilopristone) is a potent experimental progesterone inhibitor and abortifacient in doses of 25 mg twice daily. Like mifepristone, it also appears to have antiglucocorticoid activity.

DANAZOL

Danazol, an isoxazole derivative of ethisterone (17α-ethinyltestosterone) with weak progestational, androgenic, and glucocorticoid activities, is used to suppress ovarian function. Danazol inhibits the midcycle surge of LH and FSH and can prevent the compensatory increase in LH and FSH following castration in animals, but it does not significantly lower or suppress basal LH or FSH levels in normal women (Figure 40–5). Danazol binds to androgen, progesterone, and glucocorticoid receptors and can translocate the androgen receptor into the nucleus to initiate androgen-specific RNA synthesis. It does not bind to intracellular estrogen receptors, but it does bind to sex hormone-binding and corticosteroid-binding globulins. It inhibits P450scc (the cholesterol side chain-cleaving enzyme), 3β-hydroxysteroid dehydrogenase, 17α-hydroxysteroid dehydrogenase, P450c17 (17α-hydroxylase), P450c11 (11β-hydroxylase), and P450c21 (21β-hydroxylase). However, it does not inhibit aromatase, the enzyme required for estrogen synthesis. It increases the mean clearance of progesterone, probably by competing with the hormone for binding proteins, and may have similar effects on

other active steroid hormones. Ethisterone, a major metabolite of danazol, has both progestational and mild androgenic effects.

Danazol is slowly metabolized in humans, having a half-life of over 15 hours. This results in stable circulating levels when the drug is administered twice daily. It is highly concentrated in the liver, adrenals, and kidneys and is excreted in both feces and urine.

Danazol has been employed as an inhibitor of gonadal function and has found its major use in the treatment of endometriosis. For this purpose, it can be given in a dosage of 600 mg/d. The dosage is reduced to 400 mg/d after 1 month and to 200 mg/d in 2 months. About 85% of patients show marked improvement in 3–12 months.

Danazol has also been used in the treatment of fibrocystic disease of the breast and hematologic or allergic disorders, including hemophilia, Christmas disease, idiopathic thrombocytopenic purpura, and angioneurotic edema.

The major adverse effects are weight gain, edema, decreased breast size, acne and oily skin, increased hair growth, deepening of the voice, headache, hot flushes, changes in libido, and muscle cramps. Although mild adverse effects are very common, it is seldom necessary to discontinue the drug because of them. Occasionally, because of its inherent glucocorticoid activity, danazol may cause adrenal suppression.

Danazol should be used with great caution in patients with hepatic dysfunction, since it has been reported to produce mild to moderate hepatocellular damage in some patients, as evidenced by enzyme changes. It is also contraindicated during pregnancy and breast-feeding, as it may produce urogenital abnormalities in the offspring.

OTHER INHIBITORS

Anastrozole, a selective nonsteroidal inhibitor of aromatase (the enzyme required for estrogen synthesis, Figures 40–2 and 40–5), is effective in some women whose breast tumors have become resistant to tamoxifen (see Chapter 54). **Letrozole** is similar. **Exemestane,** a steroid molecule, is an irreversible inhibitor of aromatase. Like anastrozole and letrozole, it is approved for use in women with advanced breast cancer (see Chapter 54).

Several other aromatase inhibitors are undergoing clinical trials in patients with breast cancer. **Fadrozole** is an oral nonsteroidal (triazole) inhibitor of aromatase activity. These compounds appear to be as effective as tamoxifen. In addition to their use in breast cancer, aromatase inhibitors have been successfully employed as adjuncts to androgen antagonists in the treatment of precocious puberty and as primary treatment in the excessive aromatase syndrome.

Fulvestrant is a pure estrogen receptor antagonist that has been somewhat more effective than those with partial agonist effects in some patients who have become resistant to tamoxifen. ICI 164,384 is a newer antagonist; it inhibits dimerization of the occupied estrogen receptor and interferes with its binding to DNA. It has also been used experimentally in breast cancer patients who have become resistant to tamoxifen.

GnRH and its analogs (**nafarelin, buserelin,** etc) have become important in both stimulating and inhibiting ovarian function. They are discussed in Chapter 37.

OVULATION-INDUCING AGENTS

CLOMIPHENE

Clomiphene citrate, a partial estrogen agonist, is closely related to the estrogen chlorotrianisene (Figure 40–3). This compound is well absorbed when taken orally. It has a half-life of 5–7 days and is excreted primarily in the urine. It exhibits significant protein binding and enterohepatic circulation and is distributed to adipose tissues.

Pharmacologic Effects

A. Mechanisms of Action

Clomiphene is a partial agonist at estrogen receptors. The estrogenic agonist effects are best demonstrated in animals with marked gonadal deficiency. Clomiphene has also been shown to effectively inhibit the action of stronger estrogens. In humans it leads to an increase in the secretion of gonadotropins and estrogens by inhibiting estradiol's negative feedback effect on the gonadotropins (Figure 40–5).

B. Effects

The pharmacologic importance of this compound rests on its ability to stimulate ovulation in women with oligomenorrhea or amenorrhea and ovulatory dysfunction. The majority of patients suffer from polycystic ovary syndrome, a common disorder affecting about 7% of women of reproductive age. The syndrome is characterized by gonadotropin-dependent ovarian hyperandrogenism associated with anovulation and infertility. The disorder is frequently accompanied by adrenal hyperandrogenism. Clomiphene probably blocks the feedback inhibitory influence of estrogens on the hypothalamus, causing a surge of gonadotropins, which leads to ovulation.

Clinical Use

Clomiphene is used in the treatment of disorders of ovulation in patients who wish to become pregnant. Usually, a single ovulation is induced by a single course of therapy, and the patient must be treated repeatedly until pregnancy is achieved, since normal ovulatory function does not usually resume. The compound is of no value in patients with ovarian or pituitary failure.

When clomiphene is administered in a dosage of 100 mg/d for 5 days, a rise in plasma LH and FSH is observed after several days. In patients who ovulate, the initial rise is followed by a second rise of gonadotropin levels just prior to ovulation.

Adverse Effects

The most common adverse effects in patients treated with this drug are hot flushes, which resemble those experienced by

menopausal patients. They tend to be mild, and disappear when the drug is discontinued. There have been occasional reports of eye symptoms due to intensification and prolongation of afterimages. These are generally of short duration. Headache, constipation, allergic skin reactions, and reversible hair loss have been reported occasionally.

The effective use of clomiphene is associated with some stimulation of the ovaries and usually with ovarian enlargement. The degree of enlargement tends to be greater and its incidence higher in patients who have enlarged ovaries at the beginning of therapy.

A variety of other symptoms such as nausea and vomiting, increased nervous tension, depression, fatigue, breast soreness, weight gain, urinary frequency, and heavy menses have also been reported. However, these appear to result from the hormonal changes associated with an ovulatory menstrual cycle rather than from the medication. The incidence of multiple pregnancy is approximately 10%. Clomiphene has not been shown to have an adverse effect when inadvertently given to women who are already pregnant.

Contraindications & Cautions

Special precautions should be observed in patients with enlarged ovaries. These women are thought to be more sensitive to this drug and should receive small doses. Any patient who complains of abdominal symptoms should be examined carefully. Maximum ovarian enlargement occurs after the 5-day course has been completed, and many patients can be shown to have a palpable increase in ovarian size by the seventh to tenth days. Treatment with clomiphene for more than a year may be associated with an increased risk of low-grade ovarian cancer; however, the evidence for this effect is not conclusive.

Special precautions must also be taken in patients who have visual symptoms associated with clomiphene therapy, since these symptoms may make activities such as driving more hazardous.

OTHER DRUGS USED IN OVULATORY DISORDERS

In addition to clomiphene, a variety of other hormonal and nonhormonal agents are used in treating anovulatory disorders. They are discussed in Chapter 37.

■ THE TESTIS (ANDROGENS & ANABOLIC STEROIDS, ANTIANDROGENS, & MALE CONTRACEPTION)

The testis, like the ovary, has both gametogenic and endocrine functions. The onset of gametogenic function of the testes is controlled largely by the secretion of FSH by the pituitary. High concentrations of testosterone locally are also required for continuing sperm production in the seminiferous tubules. The Sertoli cells in the seminiferous tubules may be the source of the estradiol produced in the testes via aromatization of locally produced testosterone. With LH stimulation, testosterone is produced by the interstitial or Leydig cells found in the spaces between the seminiferous tubules.

The Sertoli cells in the testis synthesize and secrete a variety of active proteins, including müllerian duct inhibitory factor, inhibin, and activin. As in the ovary, inhibin and activin appear to be the product of three genes that produce a common α subunit and two β subunits, A and B. Activin is composed of the two β subunits ($\beta_A\beta_B$). There are two inhibins (A and B), which contain the α subunit and one of the β subunits. Activin stimulates pituitary FSH release and is structurally similar to transforming growth factor-β, which also increases FSH. The inhibins in conjunction with testosterone and dihydrotestosterone are responsible for the feedback inhibition of pituitary FSH secretion.

ANDROGENS & ANABOLIC STEROIDS

In humans, the most important androgen secreted by the testis is testosterone. The pathways of synthesis of testosterone in the testes are similar to those previously described for the adrenal gland and ovary (Figures 39–1 and 40–2).

In men, approximately 8 mg of testosterone is produced daily. About 95% is produced by the Leydig cells and only 5% by the adrenals. The testis also secretes small amounts of another potent androgen, dihydrotestosterone, as well as androstenedione and dehydroepiandrosterone, which are weak androgens. Pregnenolone and progesterone and their 17-hydroxylated derivatives are also released in small amounts. Plasma levels of testosterone in males are about 0.6 mcg/dL after puberty and appear to decline after age 50. Testosterone is also present in the plasma of women in concentrations of approximately 0.03 mcg/dL and is derived in approximately equal parts from the ovaries and adrenals and by the peripheral conversion of other hormones.

About 65% of circulating testosterone is bound to sex hormone-binding globulin. SHBG is increased in plasma by estrogen, by thyroid hormone, and in patients with cirrhosis of the liver. It is decreased by androgen and growth hormone and is lower in obese individuals. Most of the remaining testosterone is bound to albumin. Approximately 2% remains free and available to enter cells and bind to intracellular receptors.

METABOLISM

In many target tissues, testosterone is converted to dihydrotestosterone by 5α-reductase. In these tissues, dihydrotestosterone is the major active androgen. The conversion of testosterone to estradiol by P450 aromatase also occurs in some tissues, including adipose tissue, liver, and the hypothalamus, where it may be of importance in regulating gonadal function.

The major pathway for the degradation of testosterone in humans occurs in the liver, with the reduction of the double bond and ketone in the A ring, as is seen in other steroids with a Δ^4-ketone configuration in the A ring. This leads to the production of inactive substances such as androsterone and etiocholanolone that are then conjugated and excreted in the urine.

Androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) are also produced in significant amounts in humans, although largely in the adrenal gland rather than in the testes. They contribute slightly to the normal maturation process supporting other androgen-dependent pubertal changes in the human, primarily development of pubic and axillary hair and bone maturation. As noted in Chapter 39, some studies suggest that DHEA and DHEAS may have other central nervous system and metabolic effects and may prolong life in rabbits. In men they may improve the sense of well-being and inhibit atherosclerosis. In a placebo-controlled clinical trial in patients with systemic lupus erythematosus, DHEA demonstrated some beneficial effects (see Adrenal Androgens, Chapter 39). Adrenal androgens are to a large extent metabolized in the same fashion as testosterone. Both steroids—but particularly androstenedione—can be converted by peripheral tissues to estrone in very small amounts (1–5%). The P450 aromatase enzyme responsible for this conversion is also found in the brain and is thought to play an important role in development.

Physiologic Effects

In the normal male, testosterone or its active metabolite 5α-dihydrotestosterone is responsible for the many changes that occur in puberty. In addition to the general growth-promoting properties of androgens on body tissues, these hormones are responsible for penile and scrotal growth. Changes in the skin include the appearance of pubic, axillary, and beard hair. The sebaceous glands become more active, and the skin tends to become thicker and oilier. The larynx grows and the vocal cords become thicker, leading to a lower-pitched voice. Skeletal growth is stimulated and epiphysial closure accelerated. Other effects include growth of the prostate and seminal vesicles, darkening of the skin, and increased skin circulation. Androgens play an important role in stimulating and maintaining sexual function in men. Androgens increase lean body mass and stimulate body hair growth and sebum secretion. Metabolic effects include the reduction of hormone binding and other carrier proteins and increased liver synthesis of clotting factors, triglyceride lipase, α_1-antitrypsin, haptoglobin, and sialic acid. They also stimulate renal erythropoietin secretion and decrease HDL levels.

Synthetic Steroids with Androgenic & Anabolic Action

Testosterone, when administered by mouth, is rapidly absorbed. However, it is largely converted to inactive metabolites, and only about one sixth of the dose administered is available in active form. Testosterone can be administered parenterally, but it has a more prolonged absorption time and greater activity in the propionate, enanthate, undecanoate, or cypionate ester forms. These derivatives are hydrolyzed to release free testosterone at the site of injection. Testosterone derivatives alkylated at the 17 position, eg, methyltestosterone and fluoxymesterone, are active when given by mouth.

Testosterone and its derivatives have been used for their anabolic effects as well as in the treatment of testosterone deficiency.

TABLE 40–5 Androgens: Preparations available and relative androgenic:anabolic activity in animals.

Drug	Androgenic Anabolic Activity
Testosterone	1:1
Testosterone cypionate	1:1
Testosterone enanthate	1:1
Methyltestosterone	1:1
Fluoxymesterone	1:2
Oxymetholone	1:3
Oxandrolone	1:3–1:13
Nandrolone decanoate	1:2.5–1:4

Although testosterone and other known active steroids can be isolated in pure form and measured by weight, biologic assays are still used in the investigation of new compounds. In some of these studies in animals, the anabolic effects of the compound as measured by trophic effects on muscles or the reduction of nitrogen excretion may be dissociated from the other androgenic effects. This has led to the marketing of compounds claimed to have anabolic activity associated with only weak androgenic effects. Unfortunately, this dissociation is less marked in humans than in the animals used for testing (Table 40–5), and all are potent androgens.

Pharmacologic Effects

A. Mechanism of Action

Like other steroids, testosterone acts intracellularly in target cells. In skin, prostate, seminal vesicles, and epididymis, it is converted to 5α-dihydrotestosterone by 5α-reductase. In these tissues, dihydrotestosterone is the dominant androgen. The distribution of this enzyme in the fetus is different and has important developmental implications.

Testosterone and dihydrotestosterone bind to the intracellular androgen receptor, initiating a series of events similar to those described above for estradiol and progesterone, leading to growth, differentiation, and synthesis of a variety of enzymes and other functional proteins.

B. Effects

In the male at puberty, androgens cause development of the secondary sex characteristics (see above). In the adult male, large doses of testosterone—when given alone—or its derivatives suppress the secretion of gonadotropins and result in some atrophy of the interstitial tissue and the tubules of the testes. Since fairly large doses of androgens are required to suppress gonadotropin secretion, it has been postulated that inhibin, in combination with androgens, is responsible for the feedback control of secretion. In women, androgens are capable of producing changes similar to those observed in the prepubertal male. These include growth of

TABLE 40–6 Androgen preparations for replacement therapy.

Drug	Route of Administration	Dosage
Methyltestosterone	Oral	25–50 mg/d
	Sublingual (buccal)	5–10 mg/d
Fluoxymesterone	Oral	2–10 mg/d
Testosterone enanthate	Intramuscular	See text
Testosterone cypionate	Intramuscular	See text
Testosterone	Transdermal	2.5–10 mg/d
	Topical gel (1%)	5–10 g/d

facial and body hair, deepening of the voice, enlargement of the clitoris, frontal baldness, and prominent musculature. The natural androgens stimulate erythrocyte production.

The administration of androgens reduces the excretion of nitrogen into the urine, indicating an increase in protein synthesis or a decrease in protein breakdown within the body. This effect is much more pronounced in women and children than in normal men.

Clinical Uses

A. Androgen Replacement Therapy in Men

Androgens are used to replace or augment endogenous androgen secretion in hypogonadal men (Table 40–6). Even in the presence of pituitary deficiency, androgens are used rather than gonadotropin except when normal spermatogenesis is to be achieved. In patients with hypopituitarism, androgens are not added to the treatment regimen until puberty, at which time they are instituted in gradually increasing doses to achieve the growth spurt and the development of secondary sex characteristics. In these patients, therapy should be started with long-acting agents such as testosterone enanthate or cypionate in doses of 50 mg intramuscularly, initially every 4, then every 3, and finally every 2 weeks, with each change taking place at 3-month intervals. The dose is then doubled to 100 mg every 2 weeks until maturation is complete. Finally, it is changed to the adult replacement dose of 200 mg at 2-week intervals.

Testosterone propionate, though potent, has a short duration of action and is not practical for long-term use. Testosterone undecanoate can be given orally, administering large amounts of the steroid twice daily (eg, 40 mg/d); however, this is not recommended because oral testosterone administration has been associated with liver tumors. Testosterone can also be administered transdermally; skin patches or gels are available for scrotal or other skin area application. Two applications daily are usually required for replacement therapy. Implanted pellets and other longer-acting preparations are under study. The development of polycythemia or hypertension may require some reduction in dose.

B. Gynecologic Disorders

Androgens are used occasionally in the treatment of certain gynecologic disorders, but the undesirable effects in women are such that they must be used with great caution. Androgens have been used to reduce breast engorgement during the postpartum period, usually in conjunction with estrogens. The weak androgen danazol is used in the treatment of endometriosis (see above).

Androgens are sometimes given in combination with estrogens for replacement therapy in the postmenopausal period in an attempt to eliminate the endometrial bleeding that may occur when only estrogens are used and to enhance libido. They have been used for chemotherapy of breast tumors in premenopausal women.

C. Use as Protein Anabolic Agents

Androgens and anabolic steroids have been used in conjunction with dietary measures and exercises in an attempt to reverse protein loss after trauma, surgery, or prolonged immobilization and in patients with debilitating diseases.

D. Anemia

In the past, large doses of androgens were employed in the treatment of refractory anemias such as aplastic anemia, Fanconi's anemia, sickle cell anemia, myelofibrosis, and hemolytic anemias. Recombinant erythropoietin has largely replaced androgens for this purpose.

E. Osteoporosis

Androgens and anabolic agents have been used in the treatment of osteoporosis, either alone or in conjunction with estrogens. With the exception of substitution therapy in hypogonadism, bisphosphonates have largely replaced androgen use for this purpose.

F. Use as Growth Stimulators

These agents have been used to stimulate growth in boys with delayed puberty. If the drugs are used carefully, these children will probably achieve their expected adult height. If treatment is too vigorous, the patient may grow rapidly at first but will not achieve full predicted final stature because of the accelerated epiphysial closure that occurs. It is difficult to control this type of therapy adequately even with frequent X-ray examination of the epiphyses, since the action of the hormones on epiphysial centers may continue for many months after therapy is discontinued.

G. Anabolic Steroid and Androgen Abuse in Sports

The use of anabolic steroids by athletes has received worldwide attention. Many athletes and their coaches believe that anabolic steroids—in doses 10–200 times larger than the daily normal physiologic production—increase strength and aggressiveness, thereby improving competitive performance. Such effects have been unequivocally demonstrated only in women. Furthermore, the adverse effects of these drugs clearly make their use inadvisable.

H. Aging

Androgen production falls with age in men and may contribute to the decline in muscle mass, strength, and libido. Preliminary studies of androgen replacement in aging males with low androgen levels show an increase in lean body mass and hematocrit and a decrease in bone turnover. Longer studies will be required to assess the usefulness of this therapy.

Adverse Effects

The adverse effects of these compounds are due largely to their masculinizing actions and are most noticeable in women and prepubertal children. In women, the administration of more than 200–300 mg of testosterone per month is usually associated with hirsutism, acne, amenorrhea, clitoral enlargement, and deepening of the voice. These effects may occur with even smaller doses in some women. Some of the androgenic steroids exert progestational activity, leading to endometrial bleeding upon discontinuation. These hormones also alter serum lipids and could conceivably increase susceptibility to atherosclerotic disease in women.

Except under the most unusual circumstances, androgens should not be used in infants. Recent studies in animals suggest that administration of androgens in early life may have profound effects on maturation of central nervous system centers governing sexual development, particularly in the female. Administration of these drugs to pregnant women may lead to masculinization or undermasculinization of the external genitalia in the female and male fetus, respectively. Although the above-mentioned effects may be less marked with the anabolic agents, they do occur.

Sodium retention and edema are not common but must be carefully watched for in patients with heart and kidney disease.

Most of the synthetic androgens and anabolic agents are 17-alkyl-substituted steroids. Administration of drugs with this structure is often associated with evidence of hepatic dysfunction. Hepatic dysfunction usually occurs early in the course of treatment, and the degree is proportionate to the dose. Bilirubin levels may increase until clinical jaundice is apparent. The cholestatic jaundice is reversible upon cessation of therapy, and permanent changes do not occur. In older males, prostatic hyperplasia may develop, causing urinary retention.

Replacement therapy in men may cause acne, sleep apnea, erythrocytosis, gynecomastia, and azoospermia. Supraphysiologic doses of androgens produce azoospermia and decrease in testicular size, both of which may take months to recover after cessation of therapy. The alkylated androgens in high doses can produce peliosis hepatica, cholestasis, and hepatic failure. They lower plasma HDL and may increase LDL. Hepatic adenomas and carcinomas have also been reported. Behavioral effects include psychological dependence, increased aggressiveness, and psychotic symptoms.

Contraindications & Cautions

The use of androgenic steroids is contraindicated in pregnant women or women who may become pregnant during the course of therapy.

Androgens should not be administered to male patients with carcinoma of the prostate or breast. Until more is known about the effects of these hormones on the central nervous system in developing children, they should be avoided in infants and young children.

Special caution is required in giving these drugs to children to produce a growth spurt. In most patients, the use of somatotropin is more appropriate (see Chapter 37).

Care should be exercised in the administration of these drugs to patients with renal or cardiac disease predisposed to edema. If sodium and water retention occurs, it will respond to diuretic therapy.

Methyltestosterone therapy is associated with creatinuria, but the significance of this finding is not known.

Caution: Several cases of hepatocellular carcinoma have been reported in patients with aplastic anemia treated with androgen anabolic therapy. Erythropoietin and colony-stimulating factors (see Chapter 33) should be used instead.

ANDROGEN SUPPRESSION & ANTIANDROGENS

ANDROGEN SUPPRESSION

The treatment of advanced prostatic carcinoma often requires orchiectomy or large doses of estrogens to reduce available endogenous androgen. The psychological effects of the former and gynecomastia produced by the latter make these approaches undesirable. As noted in Chapter 37, the GnRH analogs such as goserelin, nafarelin, buserelin, and leuprolide acetate produce effective gonadal suppression when blood levels are continuous rather than pulsatile (see Chapter 37 and Figure 40–6).

ANTIANDROGENS

The potential usefulness of antiandrogens in the treatment of patients producing excessive amounts of testosterone has led to the search for effective drugs that can be used for this purpose. Several approaches to the problem, especially inhibition of synthesis and receptor antagonism, have met with some success.

Steroid Synthesis Inhibitors

Ketoconazole, used primarily in the treatment of fungal disease, is an inhibitor of adrenal and gonadal steroid synthesis, as described in Chapter 39. It does not affect ovarian aromatase, but it reduces human placental aromatase activity. It displaces estradiol and dihydrotestosterone from sex hormone-binding protein in vitro and increases the estradiol:testosterone ratio in plasma in vivo by a different mechanism. However, it does not appear to be clinically useful in women with increased androgen levels because of the toxicity associated with prolonged use of the 400–800 mg/d required. The drug has also been used experimentally to treat prostatic carcinoma, but the results have not been encouraging. Men treated with ketoconazole often develop reversible gynecomastia during therapy; this may be due to the demonstrated increase in the estradiol:testosterone ratio.

Conversion of Steroid Precursors to Androgens

Several compounds have been developed that inhibit the 17-hydroxylation of progesterone or pregnenolone, thereby preventing the action of the side chain-splitting enzyme and the further transformation of these steroid precursors to active androgens. A few of these compounds have been tested clinically but have been

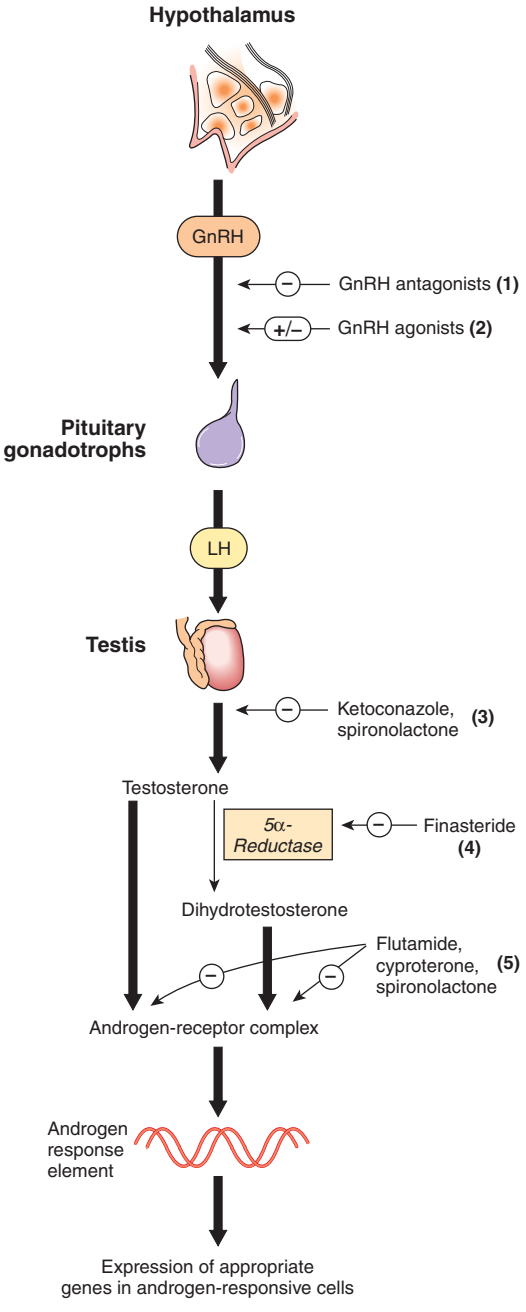
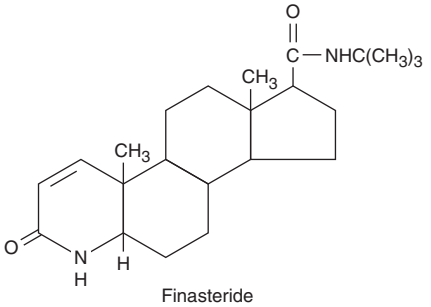


FIGURE 40–6 Control of androgen secretion and activity and some sites of action of antiandrogens: **(1)** competitive inhibition of GnRH receptors; **(2)** stimulation (+, pulsatile administration) or inhibition via desensitization of GnRH receptors (–, continuous administration); **(3)** decreased synthesis of testosterone in the testis; **(4)** decreased synthesis of dihydrotestosterone by inhibition of 5α-reductase; **(5)** competition for binding to cytosol androgen receptors.

too toxic for prolonged use. As noted in Chapter 39, **abiraterone,** a newer 17-hydroxylase inhibitor, may prove to be clinically successful.

Since dihydrotestosterone—not testosterone—appears to be the essential androgen in the prostate, androgen effects in this and similar dihydrotestosterone-dependent tissues can be reduced by an inhibitor of 5α-reductase (Figure 40–6). **Finasteride,** a steroid-like inhibitor of this enzyme, is orally active and causes a reduction in dihydrotestosterone levels that begins within 8 hours after administration and lasts for about 24 hours. The half-life is about 8 hours (longer in elderly individuals). Forty to 50 percent of the dose is metabolized; more than half is excreted in the feces. Finasteride has been reported to be moderately effective in reducing prostate size in men with benign prostatic hyperplasia and is approved for this use in the USA. The dosage is 5 mg/d. **Dutasteride** is a similar orally active steroid derivative with a slow onset of action and a much longer half-life than finasteride. The dosage is 0.5 mg daily. These drugs are not approved for use in women or children, although finasteride has been used successfully in the treatment of hirsutism in women and early male pattern baldness in men (1 mg/d).

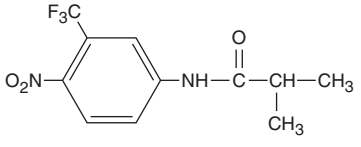


Finasteride

Receptor Inhibitors

Cyproterone and **cyproterone acetate** are effective antiandrogens that inhibit the action of androgens at the target organ. The acetate form has a marked progestational effect that suppresses the feedback enhancement of LH and FSH, leading to a more effective antiandrogen effect. These compounds have been used in women to treat hirsutism and in men to decrease excessive sexual drive and are being studied in other conditions in which the reduction of androgenic effects would be useful. Cyproterone acetate in a dosage of 2 mg/d administered concurrently with an estrogen is used in the treatment of hirsutism in women, doubling as a contraceptive pill; it has orphan drug status in the USA.

Flutamide, a substituted anilide, is a potent antiandrogen that has been used in the treatment of prostatic carcinoma. Although not a steroid, it behaves like a competitive antagonist at the androgen receptor. It is rapidly metabolized in humans. It frequently causes mild gynecomastia (probably by increasing testicular estrogen production) and occasionally causes mild reversible hepatic toxicity. Administration of this compound causes some improvement in most patients with prostatic carcinoma who have not had prior endocrine therapy. Preliminary studies indicate that flutamide is also useful in the management of excess androgen effect in women.



Flutamide

Bicalutamide and **nilutamide** are potent orally active antiandrogens that can be administered as a single daily dose and are used in patients with metastatic carcinoma of the prostate. Studies in patients with carcinoma of the prostate indicate that these agents are well tolerated. Bicalutamide is recommended for use in combination with a GnRH analog (to reduce tumor flare) and may have fewer gastrointestinal side effects than flutamide. A dosage of 150–200 mg/d (when used alone) is required to reduce prostate-specific antigen levels to those achieved by castration, but, in combination with a GnRH analog, 50 mg/d may be adequate. Nilutamide is approved for use following surgical castration in a dosage of 300 mg/d for 30 days followed by 150 mg/d.

Spironolactone, a competitive inhibitor of aldosterone (see Chapter 15), also competes with dihydrotestosterone for the androgen receptors in target tissues. It also reduces 17α-hydroxylase activity, lowering plasma levels of testosterone and androstenedione. It is used in dosages of 50–200 mg/d in the treatment of hirsutism in women and appears to be as effective as finasteride, flutamide, or cyproterone in this condition.

CHEMICAL CONTRACEPTION IN MEN

Although many studies have been conducted, an effective oral contraceptive for men has not yet been found. For example, various androgens, including testosterone and testosterone enanthate, in a dosage of 400 mg per month, produced azoospermia in less than half the men treated. Minor adverse reactions, including gynecomastia and acne, were encountered. Testosterone in combination with danazol was well tolerated but no more effective than testosterone alone. Androgens in combination with a progestin such as medroxyprogesterone acetate were no more effective. However, preliminary studies indicate that the intramuscular administration of 100 mg of testosterone enanthate weekly together with 500 mg of levonorgestrel daily orally can produce azoospermia in 94% of men.

Cyproterone acetate, a very potent progestin and antiandrogen, also produces oligospermia; however, it does not cause reliable contraception.

At present, pituitary hormones—and potent antagonist analogs of GnRH—are receiving increased attention. A GnRH antagonist in combination with testosterone has been shown to produce reversible azoospermia in nonhuman primates.

GOSSYPOL

Extensive trials of this cottonseed derivative have been conducted in China. This compound destroys elements of the seminiferous epithelium but does not significantly alter the endocrine function of the testis.

In Chinese studies, large numbers of men were treated with 20 mg/d of gossypol or gossypol acetic acid for 2 months, followed by a maintenance dosage of 60 mg/wk. On this regimen, 99% of men developed sperm counts below 4 million/mL. Preliminary data indicate that recovery (return of normal sperm count) following discontinuance of gossypol administration is more apt to occur in men whose counts do not fall to extremely low levels and when administration is not continued for more than 2 years. Hypokalemia is the major adverse effect and may lead to transient paralysis. Because of low efficacy and significant toxicity, gossypol has been abandoned as a candidate male contraceptive.

PREPARATIONS AVAILABLE[1]

ESTROGENS

Conjugated estrogens (Premarin)
Oral: 0.3, 0.45, 0.625, 0.9, 1.25 mg tablets
Parenteral: 25 mg/5 mL for IM, IV injection
Vaginal: 0.625 mg/g cream base

Diethylstilbestrol (Stilphostrol)
Oral: 50 mg tablets
Parenteral: 0.25 g

Esterified estrogens (Cenestin, Enjuvia, Menest)
Oral: 0.3, 0.45, 0.625, 0.9, 1.25, 2.5 mg tablets

Estradiol cypionate in oil (Depo-Estradiol)
Parenteral: 5 mg/mL for IM injection

Estradiol (generic, Estrace, others)
Oral: 0.45, 0.5, 0.9, 1, 1.5, 1.8, 2 mg tablets
Vaginal: 0.1 mg/g cream, 2 mg ring, 25 mcg tablets

Estradiol transdermal (generic, Estraderm, many others)
Transdermal patch: 0.014, 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/d release rates
Topical: 2.5 mg/g emulsion (Estrasorb); 0.75 mg/1.25 g unit dose (Estrogel)

Estradiol valerate in oil (generic)
Parenteral: 10, 20, 40 mg/mL for IM injection

Estrone (Menest)
Oral: 0.3, 0.625, 1.25, 2.5 mg tablets

Estropipate (generic, Ogen)
Oral: 0.625, 1.25, 2.5, 5 mg tablets
Vaginal: 1.5 mg/g cream base

PROGESTINS

Levonorgestrel (Norplant)
Kit for subcutaneous implant: 6 capsules of 36 mg each
Intrauterine system: 52 mg

Medroxyprogesterone acetate (generic, Provera)
Oral: 2.5, 5, 10 mg tablets
Parenteral (Depo-Provera): 150, 400 mg/mL for IM injection

Megestrol acetate (generic, Megace)
Oral: 20, 40 mg tablets; 40, 125 mg/mL suspension

Norethindrone acetate (generic, Aygestin)
Oral: 5 mg tablets

Progesterone (generic)
Oral: 100, 200 mg capsules
Topical: 4, 8% vaginal gel, 100 mg insert
Parenteral: 50 mg/mL in oil for IM injection
Intrauterine contraceptive system: 38 mg in silicone

ANDROGENS & ANABOLIC STEROIDS

Fluoxymesterone (generic)
Oral: 10 mg tablets

Methyltestosterone (generic)
Oral: 10, 25 mg tablets; 10 mg capsules; 10 mg buccal tablets

Nandrolone decanoate (generic)
Parenteral: 100, 200 mg/mL in oil for injection

Oxandrolone (Oxandrin)
Oral: 2.5, 10 mg tablets

Oxymetholone (Androl-50)
Oral: 50 mg tablets

Testosterone
Buccal system: 30 mg

Testosterone cypionate in oil (generic, Depo-testosterone)
Parenteral: 100, 200 mg/mL for IM injection

Testosterone enanthate in oil (generic, Delatestryl)
Parenteral: 200 mg/mL for IM injection

Testosterone transdermal system
Patch (Androderm): 2.5, 5 mg/24 h release rate
Gel (AndroGel): 1%

Testosterone pellets (Testopel)
Parenteral: 75 mg/pellet for parenteral injection (not IV)

ANTAGONISTS & INHIBITORS

See also Chapter 37

Anastrozole (Arimidex)
Oral: 1 mg tablets

Bicalutamide (Casodex)
Oral: 50 mg tablets

Clomiphene (generic, Clomid, Serophene, Milophene)
Oral: 50 mg tablets

Danazol (generic, Danocrine)
Oral: 50, 100, 200 mg capsules

Dutasteride (Avodart)
Oral: 0.5 mg tablets

Exemestane (Aromasin)
Oral: 25 mg tablets

Finasteride
Oral: 1 mg tablets (Propecia); 5 mg tablets (Proscar)

Flutamide (Eulexin)
Oral: 125 mg capsules

Fulvestrant (Faslodex)
Parenteral: 50 mg/mL for IM injection

Letrozole (Femara)
Oral: 2.5 mg tablets

Mifepristone (Mifeprex)
Oral: 200 mg tablets

Nilutamide (Nilandron)
Oral: 50, 150 mg tablets

Raloxifene (Evista)
Oral: 60 mg tablets

Tamoxifen (generic, Nolvadex)
Oral: 10, 20 mg tablets; 10 mg/5 mL oral solution

Toremifene (Fareston)
Oral: 60 mg tablets

[1]Oral contraceptives are listed in Table 40–3.

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CASE STUDY ANSWER

The patient should be advised to start daily transdermal estradiol therapy (100 mcg/d) along with oral natural progesterone (200 mg/d) for the last 12 days of each 28-day cycle. On this regimen, her symptoms should disappear and normal monthly uterine bleeding resume. She should also be advised to get adequate exercise and increase her calcium and vitamin D intake as treatment for her osteoporosis.