can be identified within 48 to 96 h after inoculation. Spin-amplified culture with subsequent staining for HSV antigen has shortened the time needed to identify HSV to <24 h. The sensitivity of viral isolation depends on the stage of lesions (with higher sensitivity in vesicular than in ulcerative lesions), on whether the patient has a first or a recurrent episode of the disease (with higher sensitivity in first than in recurrent episodes), and on whether the sample is from an immunosuppressed or an immunocompetent patient (with more antigen in immunosuppressed patients). Antigen detection procedures have approached viral isolation in terms of sensitivity in detecting HSV in genital or oral-labial lesions; however, antigen detection appears to be only ~50% as sensitive as viral isolation for the identification of HSV in cervical or salivary secretions of asymptomatic patients.PCRtechniques appear to be more sensitive for HSV than viral isolation, especially for the diagnosis ofCNSinfections and for the detection of HSV as a cause of late-stage ulcerative lesions. Laboratory confirmation permits subtyping of the virus; information on subtype may be useful epidemiologically and may help to predict the frequency of reactivation after first-episode oral-labial or genital HSV infection.

Acute- and convalescent-phase serum can be useful in demonstrating seroconversion during primaryHSV-1 or HSV-2 infection. However, only 5% of patients with recurrent mucocutaneous HSV infections have a fourfold or greater rise in titer of antibody to HSV in the interval between the collection of the first and second samples. Serologic assays, especially type-specific assays, should be used to identify asymptomatic carriers of HSV-1 or HSV-2 infection.

Several studies have shown that persons seropositive forHSV-2 to whom the clinical manifestations of HSV have been explained are able to identify symptomatic reactivations. Individuals seropositive for HSV-2 should be told about the high frequency of subclinical reactivation in mucosal surfaces not visible to the eye (e.g., cervix, urethra, perianal skin) or in microscopic ulcerations that may not be clinically symptomatic. Transmission of infection during such episodes is well established. HSV-2-seropositive persons should be educated about the high likelihood of subclinical shedding and the role condoms (male or female) may play in reducing transmission. Chronic antiviral therapy is being studied as a means of reducing the transmission of infection.

TREATMENT

Many aspects of mucocutaneous and visceralHSVinfections are amenable to antiviral chemotherapy. For mucocutaneous infections, acyclovir and its congeners famciclovir and valacyclovir have been the mainstay of therapy. Several antiviral agents are available for topical use in HSV eye infections: idoxuridine, trifluorothymidine, topical vidarabine, and cidofovir. For HSV encephalitis and neonatal herpes, intravenous acyclovir is the treatment of choice.

All licensed antivirals forHSVinhibit the viral DNA polymerase. One class of drugs, typified by the drug acyclovir, is made up of substrates for the HSV enzyme thymidine kinase. Acyclovir, ganciclovir, famciclovir, and valacyclovir are all selectively phosphorylated to the monophosphate form in virus-infected cells. Cellular enzymes convert the monophosphate form of the drug to the triphosphate, which is then

incorporated into the viral DNA chain.

Acyclovir is the most frequently used agent for the treatment ofHSVinfections and is available in intravenous, oral, and topical formulations. Famciclovir, the oral formulation of penciclovir, is clinically effective in the treatment of a variety of HSV-1 and HSV-2 infections. Intravenous penciclovir is also available. Valacyclovir is the valyl ester of acyclovir and has greater bioavailability than acyclovir. Ganciclovir has activity against both HSV-1 and HSV-2; however, it is more toxic than acyclovir, valacyclovir, and famciclovir and is generally not recommended for the treatment of HSV infections.

All three compounds -- acyclovir, valacyclovir, and famciclovir -- have proven effective in shortening the duration of symptoms and lesions of mucocutaneousHSVinfections in both immunocompromised and immunocompetent patients (Table 182-1). Intravenous and oral formulations prevent reactivation of HSV in seropositive immunocompromised patients during induction chemotherapy or in the period immediately after bone marrow or solid organ transplantation. Chronic daily suppressive therapy reduces the frequency of reactivation disease among patients with frequent genital or oral-labial herpes.

Intravenous acyclovir (30 mg/kg per day, given as a 10-mg/kg infusion over 1 h at 8-h intervals) is effective in reducing rates of death and morbidity fromHSVencephalitis. Early initiation of therapy is a critical factor in outcome. The major side effect associated with intravenous acyclovir is transient renal insufficiency, usually due to crystallization of the compound in the renal parenchyma. This adverse reaction can be avoided if the medication is given slowly over 1 h and the patient is well hydrated. BecauseCSFlevels of acyclovir average only 30 to 50% of plasma levels, the dosage of acyclovir used for treatment ofCNSinfection (30 mg/kg per day) is double that used for treatment of mucocutaneous or visceral disease (15 mg/kg per day).

Acyclovir-resistant strains ofHSV have been identified. Most of these strains have an altered substrate specificity for phosphorylating acyclovir. Thus, cross-resistance to famciclovir and valacyclovir is usually found. Occasionally, an isolate with altered thymidine kinase (TK) specificity arises and is sensitive to famciclovir but not to acyclovir. In some patients infected with TK-deficient virus, higher doses of acyclovir are associated with clearing of lesions. In others, clinical disease progresses despite high-dose therapy. Almost all clinically significant acyclovir resistance has been seen in immunocompromised patients, and HSV-2 isolates are more often resistant than HSV-1 strains. A study by the Centers for Disease Control and Prevention indicated that ~5% of isolates from HIV-positive persons exhibit some degree of in vitro resistance to acyclovir. Isolation of HSV from persisting lesions despite adequate dosages and blood levels of acyclovir should raise the suspicion of acyclovir resistance. Therapy with the antiviral drug foscarnet is useful (Chap. 181). Because of its toxicity and cost, this drug is usually reserved for patients with extensive mucocutaneous infections. Cidofovir is a nucleotide analogue and exists as a phosphonate or monophosphate form. Most TK-deficient strains of HSV are sensitive to cidofovir. Cidofovir ointment speeds healing of acyclovir-resistant lesions. No well-controlled trials of systemic cidofovir have been reported. True TK-negative variants of HSV appear to have a reduced capacity to spread because of altered neurovirulence -- a feature important in the relatively infrequent presence of such strains in immunocompetent populations, even with increasing use of antivirals.

PREVENTION

The large reservoir of persons with asymptomaticHSV-1 and HSV-2 infections indicates that the success of efforts to control HSV disease through suppressive antiviral chemotherapy and/or educational programs will be limited. Rather, control of HSV infection will require the prevention of infection -- a goal most likely to be attained by vaccination. Several candidate vaccines are under investigation, and the prevention of HSV infection has been assigned a high public health priority.

Barrier forms of contraception, especially condoms, decrease the likelihood of transmission ofHSVinfection, especially during periods of asymptomatic viral excretion. When lesions are present, HSV infection may be transmitted by skin-to-skin contact despite the use of a condom. Nevertheless, the available data suggest that consistent condom use is an effective means of reducing the risk of genital HSV-2 transmission. Prevention of neonatal HSV requires the prevention of acquisition of HSV in the third trimester of pregnancy. Identification of women or couples susceptible to acquisition of HSV in pregnancy through serologic screening is receiving increasing attention, and such screening is being used with increasing frequency.

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183. VARICELLA-ZOSTER VIRUS INFECTIONS - *Richard J. Whitley*

DEFINITION

Varicella-zoster virus (VZV) causes two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles). Chickenpox, a ubiquitous and extremely contagious infection, is usually a benign illness of childhood characterized by an exanthematous vesicular rash. With reactivation of latent VZV (which is most common after the sixth decade of life), herpes zoster presents as a dermatomal vesicular rash, usually associated with severe pain.

ETIOLOGY

A clinical association between varicella and herpes zoster has been recognized for nearly 100 years. Early in the twentieth century, similarities in the histopathologic features of skin lesions resulting from varicella and herpes zoster were demonstrated. Viral isolates from patients with chickenpox and herpes zoster produced similar alterations in tissue culture -- specifically, the appearance of eosinophilic intranuclear inclusions and multinucleated giant cells. These results suggested that the viruses were biologically similar. Restriction endonuclease analyses of viral DNA from a patient with chickenpox who subsequently developed herpes zoster verified the molecular identity of the two viruses responsible for these different clinical presentations.

VZVis a member of the family Herpesviridae, sharing with other members such structural characteristics as a lipid envelope surrounding a nucleocapsid with icosahedral symmetry, a total diameter of approximately 180 to 200 nm, and centrally located double-stranded DNA that is about 125,000 bp in length.

PATHOGENESIS AND PATHOLOGY

Primary Infection Transmission is most likely to take place by the respiratory route; the subsequent localized replication of the virus at an undefined site (presumably the nasopharynx) leads to seeding of the reticuloendothelial system and ultimately to the development of viremia. Viremia in patients with chickenpox is reflected in the diffuse and scattered nature of the skin lesions and can be verified in selected cases by the recovery ofVZV from the blood. Vesicles involve the corium and dermis, with degenerative changes characterized by ballooning, the presence of multinucleated giant cells, and eosinophilic intranuclear inclusions. Infection may involve localized blood vessels of the skin, resulting in necrosis and epidermal hemorrhage. With the evolution of disease, the vesicular fluid becomes cloudy because of the recruitment of polymorphonuclear leukocytes and the presence of degenerated cells and fibrin. Ultimately, the vesicles either rupture and release their fluid (which includes infectious virus) or are gradually reabsorbed.

Recurrent Infection The mechanism of reactivation ofVZV that results in herpes zoster is unknown. Presumably, the virus infects the dorsal root ganglia during chickenpox, where it remains latent until reactivated. Histopathologic examination of representative dorsal root ganglia during active herpes zoster demonstrates hemorrhage, edema, and lymphocytic infiltration.

Active replication ofVZV in other organs, such as the lung or the brain, can occur during either chickenpox or herpes zoster but is uncommon in the immunocompetent host. Pulmonary involvement is characterized by interstitial pneumonitis, multinucleated giant cell formation, intranuclear inclusions, and pulmonary hemorrhage. Central nervous system (CNS) infection leads to histopathologic evidence of perivascular cuffing similar to that encountered in measles and other viral encephalitides. Focal hemorrhagic necrosis of the brain, characteristic of herpes simplex virus encephalitis, is uncommon in VZV infection.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Chickenpox Humans are the only known reservoir forVZV. Chickenpox is highly contagious, with an attack rate of at least 90% among susceptible (seronegative) individuals. Persons of both sexes and all races are infected equally often. The virus is endemic in the population at large; however, it becomes epidemic among susceptible individuals during seasonal peaks -- namely, late winter and early spring in the temperate zone. Children between the ages of 5 and 9 are most commonly affected and account for 50% of all cases. Most other cases involve children aged 1 to 4 and those aged 10 to 14. Approximately 10% of the population of the United States over the age of 15 is susceptible to infection.

The incubation period of chickenpox ranges between 10 and 21 days but is usually between 14 and 17 days. Secondary attack rates in susceptible siblings within a household are between 70 and 90%. Patients are infectious approximately 48 h prior to the onset of the vesicular rash, during the period of vesicle formation (which generally lasts 4 to 5 days), and until all vesicles are crusted.

Clinically, chickenpox presents as a rash, low-grade fever, and malaise, although a few patients develop a prodrome 1 to 2 days before onset of the exanthem. In the immunocompetent patient, this is usually a benign illness that is associated with lassitude and with body temperatures of 37.8 to 39.4°C (100 to 103°F) of 3 to 5 days' duration. The skin lesions -- the hallmark of the infection -- include maculopapules, vesicles, and scabs in various stages of evolution (Plate IID-36,Fig. 183-CD1). These lesions, which evolve from maculopapules to vesicles over hours to days, appear on the trunk and face and rapidly spread to involve other areas of the body. Most are small and have an erythematous base with a diameter of 5 to 10 mm. Successive crops appear over a 2- to 4-day period. Lesions also can be found on the mucosa of the pharynx and/or the vagina. Their severity varies from one person to another. Some individuals have very few lesions, while others have as many as 2000. Younger children tend to have fewer vesicles than older individuals. Secondary and tertiary cases within families are associated with a relatively large number of vesicles. Immunocompromised patients -- both children and adults, particularly those with leukemia -- have lesions (often with a hemorrhagic base) that are more numerous and take longer to heal than those of immunocompetent patients. Immunocompromised individuals are also at greater risk for visceral complications, which occur in 30 to 50% of cases and are fatal 15% of the time.

The most common infectious complication of varicella is secondary bacterial superinfection of the skin, which is usually caused by *Streptococcus pyogenes* or

Staphylococcus aureus. This complication may result from excoriation of skin lesions after scratching. Gram's staining of skin lesions should help clarify the etiology of unusually erythematous and pustulated lesions.

The most common extracutaneous site of involvement in children is theCNS. The syndrome of acute cerebellar ataxia and meningeal irritation generally appears around 21 days after the onset of the rash and rarely develops in the preeruptive phase. The cerebrospinal fluid (CSF) contains lymphocytes and elevated levels of protein. CNS involvement is a benign complication ofVZVinfection in children and generally does not require hospitalization. Aseptic meningitis, encephalitis, transverse myelitis, Guillain-Barre syndrome, and Reye's syndrome also can occur. Encephalitis is reported in 0.1 to 0.2% of children with chickenpox. Other than supportive care, no specific therapy is available for patients with CNS involvement.

Varicella pneumonia is the most serious complication following chickenpox, developing more commonly in adults (up to 20% of cases) than in children. It usually has its onset 3 to 5 days into the illness and is associated with tachypnea, cough, dyspnea, and fever. Cyanosis, pleuritic chest pain, and hemoptysis are frequent. Roentgenographic evidence of disease consists of nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash; however, patients may have persistent fever and compromised pulmonary function for weeks.

Other complications of chickenpox include myocarditis, corneal lesions, nephritis, arthritis, bleeding diatheses, acute glomerulonephritis, and hepatitis. Hepatic involvement, distinct from Reye's syndrome and usually asymptomatic, is common in chickenpox and is usually characterized by elevated levels of liver enzymes, particularly aspartate and alanine aminotransferases.

Perinatal varicella is associated with a high mortality rate when maternal disease develops within 5 days before delivery or within 48 h thereafter. Because the newborn does not receive protective transplacental antibodies and has an immature immune system, the illness may be unusually severe. The reported mortality rate has been as high as 30% in this group. Congenital varicella, with clinical manifestations of limb hypoplasia, cicatricial skin lesions, and microcephaly at birth, is extremely uncommon.

Herpes Zoster Herpes zoster, a sporadic disease, is the consequence of reactivation of latentVZV from the dorsal root ganglia. Most patients have no history of recent exposure to other individuals with VZV infection. Herpes zoster occurs at all ages, but its incidence is highest (5 to 10 cases per 1000 persons) among individuals in the sixth through the eighth decades of life. Recurrent herpes zoster is exceedingly rare except in immunocompromised hosts, especially those with AIDS.

Herpes zoster, also called shingles, is characterized by a unilateral vesicular eruption within a dermatome, often associated with severe pain. The dermatomes from T3 to L3 are most frequently involved. If the ophthalmic branch of the trigeminal nerve is involved, zoster ophthalmicus results. The factors responsible for the reactivation ofVZV are not known. In children reactivation is usually benign, whereas in adults it can be debilitating. The continuum of pain from onset to resolution is known as *zoster-associated pain*. The onset of disease is heralded by pain within the dermatome

that may precede lesions by 48 to 72 h; an erythematous maculopapular rash evolves rapidly into vesicular lesions. In the normal host, these lesions may remain few in number and continue to form only for a period of 3 to 5 days. The total duration of disease is generally between 7 and 10 days; however, it may take as long as 2 to 4 weeks for the skin to return to normal. In a few patients, characteristic localization of pain to a dermatome with serologic evidence of herpes zoster has been reported in the absence of skin lesions. When branches of the trigeminal nerve are involved, lesions may appear on the face, in the mouth, in the eye, or on the tongue. In the Ramsay Hunt syndrome (Plate IID-35), pain and vesicles appear in the external auditory canal, and patients lose their sense of taste in the anterior two-thirds of the tongue while developing ipsilateral facial palsy. The geniculate ganglion of the sensory branch of the facial nerve is involved.

The most debilitating complication of herpes zoster, in both the normal and the immunocompromised host, is pain associated with acute neuritis and postherpetic neuralgia. Postherpetic neuralgia is uncommon in young individuals; however, at least 50% of patients over age 50 with zoster report some degree of pain in the involved dermatome months after the resolution of cutaneous disease. Changes in sensation in the dermatome, resulting in either hypo- or hyperesthesia, are common.

CNSinvolvement may follow localized herpes zoster. Many patients without signs of meningeal irritation haveCSFpleocytosis and moderately elevated levels of CSF protein. Symptomatic meningoencephalitis is characterized by headache, fever, photophobia, meningitis, and vomiting. A rare manifestation of CNS involvement is granulomatous angiitis with contralateral hemiplegia, which can be diagnosed by cerebral arteriography. Other neurologic manifestations include transverse myelitis with or without motor paralysis.

Like chickenpox, herpes zoster is more severe in the immunocompromised host than in the normal individual. Lesions continue to form for over a week, and scabbing is not complete in most cases until 3 weeks into the illness. Patients with Hodgkin's disease and non-Hodgkin's lymphoma are at greatest risk for progressive herpes zoster. Cutaneous dissemination (Plate IID-37,Fig. 183-CD2) develops in about 40% of these patients. Among patients with cutaneous dissemination (Fig. 183-CD3), the risk of pneumonitis, meningoencephalitis, hepatitis, and other serious complications is increased by 5 to 10%. However, even in immunocompromised patients, disseminated zoster is rarely fatal.

Patients who have received a bone marrow transplant are at particularly high risk ofVZVinfection. Thirty percent of cases of posttransplantation VZV infection occur within 1 year (50% of these within 9 months); 45% of the patients involved have cutaneous or visceral dissemination. The mortality rate in this situation is 10%. Postherpetic neuralgia, scarring, and bacterial superinfection are especially frequent in VZV infections occurring within 9 months of transplantation. Among infected patients, concomitant graft-versus-host disease increases the chance of dissemination and/or death.

DIFFERENTIAL DIAGNOSIS

The diagnosis of chickenpox is not difficult. The characteristic rash and a history of recent exposure should lead to a prompt diagnosis. Other viral infections that can mimic chickenpox include disseminated herpes simplex virus infection in patients with atopic dermatitis and the disseminated vesiculopapular lesions sometimes associated with coxsackievirus infection, echovirus infection, or atypical measles. However, these rashes are more commonly morbilliform with a hemorrhagic component rather than vesicular or vesiculopustular. Rickettsialpox can be confused with chickenpox; however, it can be distinguished easily by detection of the "herald spot" at the site of the mite bite and the development of a more pronounced headache. Serologic testing is also useful in differentiating rickettsialpox from varicella.

Unilateral vesicular lesions in a dermatomal pattern should lead rapidly to the diagnosis of herpes zoster, although the occurrence of shingles without a rash has been reported. Both herpes simplex virus infections and coxsackievirus infections can cause dermatomal vesicular lesions. Supportive diagnostic virology and fluorescent staining of skin scrapings with monoclonal antibodies are helpful in ensuring the proper diagnosis. In the prodromal stage of herpes zoster, the diagnosis can be exceedingly difficult and may be made only after lesions have appeared or by retrospective serologic assessment.

LABORATORY FINDINGS

Unequivocal confirmation of the diagnosis is possible only through the isolation ofVZV in susceptible tissue-culture cell lines, the demonstration of either seroconversion or a fourfold or greater rise in antibody titer between convalescent- and acute-phase serum specimens, or the detection of VZV DNA by polymerase chain reaction (PCR). A rapid impression can be obtained by a Tzanck smear, with scraping of the base of the lesions in an attempt to demonstrate multinucleated giant cells, although the sensitivity of this method is low (about 60%). PCR technology for the detection of viral DNA in vesicular fluid is available in a limited number of diagnostic laboratories. Direct immunofluorescent staining of cells from the lesion base or detection of viral antigens by other assays (such as the immunoperoxidase assay) is also useful, although these tests are not commercially available. The most frequently employed serologic tools for assessing host response are the immunofluorescent detection of antibodies to VZV membrane antigens, the fluorescent antibody to membrane antigen (FAMA) test, immune adherence hemagglutination, and enzyme-linked immunosorbent assay (ELISA). The FAMA test and the ELISA appear to be the most sensitive.

PROPHYLAXIS

While chickenpox in the otherwise healthy host is relatively benign, it can cause morbidity and death. Furthermore, the parents of a child with chickenpox often lose a significant amount of time from work. A live attenuated varicella vaccine has been licensed and is recommended for administration to all immunocompetent children and adults at risk of infection.

The immunocompromised individual is at significant risk for developing progressive varicella; modalities of prevention include passive immunization or experimental administration of the same live attenuated vaccine used in the immunocompetent child.

Immune prophylaxis can consist of the administration of specific zoster immune globulin (ZIG) derived from patients with herpes zoster, varicella-zoster immune globulin (VZIG), or the intravenous formulation of zoster immune plasma (ZIP). Both ZIG and VZIG should be given within 96 h (preferably within 72 h) of exposure to ensure efficacy. It is likely that ZIP can be given somewhat later. Indications for the administration of VZIG are summarized inTable 183-1.

TREATMENT

Medical management of chickenpox in the immunologically normal host is directed toward the prevention of avoidable complications. Obviously, good hygiene includes daily bathing and soaks. Secondary bacterial infection of the skin can be avoided by meticulous skin care, particularly with close cropping of fingernails. Pruritus can be decreased with topical dressings or the administration of antipruritic drugs. Tepid water baths and wet compresses are better than drying lotions for the relief of itching. Aluminum acetate soaks for the management of herpes zoster can be both soothing and cleansing. Administration of aspirin to children with chickenpox should be avoided because of the association of aspirin derivatives with the development of Reye's syndrome. Acyclovir therapy (800 mg by mouth five times daily for 5 to 7 days) is recommended for adolescents and adults with chickenpox of£24 h duration. Likewise, acyclovir therapy may be of benefit to children <12 years of age if initiated early in the disease (<24 h) at a dose of 20 mg/kg every 6 h.

Patients with herpes zoster benefit from oral antiviral therapy, as evidenced by accelerated healing of lesions and resolution of zoster-associated pain with acyclovir, valacyclovir, or famciclovir. Acyclovir, now off patent, is administered at a dosage of 800 mg five times daily for 7 to 10 days. Famciclovir, the prodrug of penciclovir, is at least as effective as acyclovir and perhaps more so. One study showed twofold faster resolution of postherpetic neuralgia in famciclovir-treated patients with zoster than in recipients of placebo. The dose is 500 mg by mouth three times daily for 7 days. Valacyclovir, the prodrug of acyclovir, accelerates healing and resolution of zoster-associated pain more promptly than acyclovir. The dose is 1 g by mouth three times daily for 5 to 7 days. Both famciclovir and valacyclovir offer the advantage of a lower dosing frequency than acyclovir.

In the immunocompromised host, both chickenpox and herpes zoster (including disseminated disease) should be treated with intravenous acyclovir, which reduces the occurrence of visceral complications but has no effect on healing of skin lesions or pain. The dose is 10 to 12.5 mg/kg every 8 h for 7 days. Oral acyclovir therapy is not recommended for the treatment ofVZVinfections in immunocompromised patients. Concomitant with the administration of intravenous acyclovir, it is desirable to attempt to wean these patients from immunosuppressive treatment.

Patients with varicella pneumonia may require removal of bronchial secretions and ventilatory support. Persons with zoster ophthalmicus should be referred immediately to an ophthalmologist. Therapy for this condition consists of the administration of analgesics for severe pain and the use of atropine. Acyclovir accelerates healing.

The management of acute neuritis and/or postherpetic neuralgia can be particularly

difficult. In addition to the judicious use of analgesics, ranging from nonnarcotics to narcotic derivatives, drugs such as gabapentin, amitriptyline hydrochloride, and fluphenazine hydrochloride have been reported to be beneficial for pain relief. In one study, glucocorticoid therapy administered early in the course of localized herpes zoster significantly accelerated such quality-of-life improvements as a return to usual activity and termination of analgesia. The dose of prednisone administered orally was 60 mg/d on days 1 through 7, 30 mg/d on days 8 through 14, and 15 mg/d on days 15 through 21. This regimen is appropriate only for relatively healthy elderly persons who have moderate or severe pain at presentation. Patients with osteoporosis, diabetes mellitus, glycosuria, or hypertension may not be appropriate candidates. Glucocorticoids should not be used without concomitant antiviral therapy.

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184. EPSTEIN-BARR VIRUS INFECTIONS, INCLUDING INFECTIOUS MONONUCLEOSIS - *Jeffrey I. Cohen*

DEFINITION

Epstein-Barr virus (EBV) is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis. EBV is also associated with several human tumors, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and -- in patients with immunodeficiencies (including AIDS) -- B cell lymphoma. The virus, a member of the family Herpesviridae, consists of a linear, double-stranded DNA core surrounded by an icosahedral nucleocapsid and by the viral envelope, which contains glycoproteins. The two types of EBV that are widely prevalent in nature are not distinguishable by conventional serologic tests.

EPIDEMIOLOGY

EBVinfections occur worldwide. These infections are most common in early childhood, with a second peak during late adolescence. By adulthood, more than 90% of individuals have been infected and have antibodies to the virus.IM is usually a disease of young adults. In lower socioeconomic groups and in areas of the world with lower standards of hygiene (e.g., developing countries), EBV tends to infect children at an early age, and symptomatic IM is uncommon. In areas with higher standards of hygiene (e.g., the United States), infection with EBV is often delayed until adulthood, and IM is more prevalent.

EBVis spread by contact with oral secretions. The virus is frequently transmitted from asymptomatic adults to infants and among young adults by transfer of saliva during kissing. Transmission by less intimate contact is rare. EBV has been transmitted by blood transfusion and by bone marrow transplantation. Studies indicate that more than 90% of asymptomatic seropositive individuals shed the virus in oropharyngeal secretions.

PATHOGENESIS

EBVis transmitted by salivary secretions. The virus infects the epithelium of the oropharynx and the salivary glands and is shed from these cells. While B cells may become infected after contact with epithelial cells, studies suggest that lymphocytes in the tonsillar crypts can be infected directly. The virus then spreads through the bloodstream. The proliferation and expansion of EBV-infected B cells along with reactive T cells duringIMresult in enlargement of lymphoid tissue. Polyclonal activation of B cells leads to the production of antibodies to host-cell and viral proteins. During the acute phase of IM, up to 1 in every 100 B cells in the peripheral blood is infected by EBV, while after recovery, about 1 in every million B cells is infected. During IM there is an inverted CD4+/CD8+ T cell ratio. The percentage of CD4+ T cells decreases, while there are large clonal expansions of CD8+ T cells; up to 40% of CD8+ T cells are directed against EBV antigens during acute infection. Data suggest that memory B cells, not epithelial cells, are the reservoir for EBV in the body: Shedding of EBV from the oropharynx stops but the virus persists in B cells when patients are treated with

acyclovir.

TheEBVreceptor (CD21), present on the surface of B cells and epithelial cells, is also the receptor for the C3d component of complement. EBV infection of epithelial cells results in viral replication and production of virions. When B cells are infected by EBV in vitro, they become transformed and can proliferate indefinitely. During latent infection of B cells, only the EBV nuclear antigens (EBNAs), latent membrane proteins (LMPs), and small EBV RNAs are expressed in vitro. EBV-transformed B cells secrete immunoglobulin; only a small fraction of cells produce virus.

Cellular immunity is more important than humoral immunity in controllingEBVinfection. In the initial phase of infection, suppressor T cells, natural killer cells, and nonspecific cytotoxic T cells are important in controlling the proliferation of EBV-infected B cells. Levels of markers of T cell activation and serum interferon g are elevated. Later in infection, HLA-restricted cytotoxic T cells that recognizeEBNAsand LMPsand destroy EBV-infected cells are generated. Studies have shown that one of the late genes expressed during EBV replication, *BCRF1*, is a homologue of interleukin 10 and can inhibit the production of interferong by mononuclear cells in vitro. In addition, EBNA-1 inhibits antigen processing.

If T cell immunity is compromised,EBV-infected B cells may begin to proliferate. When EBV is associated with lymphoma, virus-induced proliferation is but one step in a multistep process of neoplastic transformation. In many EBV-containing tumors, LMP-1 mimics members of the tumor necrosis factor receptor family (e.g., CD40), transmitting growth-proliferating signals.

CLINICAL MANIFESTATIONS

MostEBVinfections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis. In contrast, up to 75% of infections in adolescents present asIM.

Signs and Symptoms The incubation period forIM in young adults is about 4 to 6 weeks. A prodrome of fatigue, malaise, and myalgia may last for 1 to 2 weeks before the onset of fever, sore throat, and lymphadenopathy. Fever is usually low-grade and is most common in the first 2 weeks of the illness; however, it may persist for over a month. Common signs and symptoms are listed along with their frequencies inTable 184-1. Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks of the illness, while splenomegaly is more prominent during the second and third weeks. Lymphadenopathy most often affects the posterior cervical nodes but may be generalized. Enlarged lymph nodes are frequently tender and symmetric but are not fixed in place. Pharyngitis, often the most prominent sign, can be accompanied by enlargement of the tonsils with an exudate resembling that of streptococcal pharyngitis. A morbilliform or papular rash, usually on the arms or trunk, develops in about 5% of cases. Most patients treated with ampicillin develop a macular rash (Fig. 186-CD1); this rash is not predictive of future adverse reactions to penicillins. Erythema nodosum and erythema multiforme have also been described (Chap. 57). Most patients have symptoms for 2 to 4 weeks, but malaise and difficulty concentrating can persist for months.

SymptomaticIM is uncommon in infants and young children. IM in the elderly presents relatively often as nonspecific symptoms, including prolonged fever, fatigue, myalgia, and malaise; in contrast, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes are relatively rare in elderly patients.

Laboratory Findings The white blood cell count is usually elevated and peaks at 10,000 to 20,000/uL during the second or third week of illness. Lymphocytosis is usually demonstrable, with more than 10% atypical lymphocytes. The latter cells are enlarged lymphocytes that have abundant cytoplasm, vacuoles, and indentations of the cell membrane. CD8+ cells predominate among the atypical lymphocytes. Low-grade neutropenia and thrombocytopenia are common during the first month of illness. Liver function is abnormal in more than 90% of cases. Serum levels of aminotransferases and alkaline phosphatase are usually mildly elevated; the serum concentration of bilirubin is elevated in about 40% of cases.

Complications Most cases ofIM are self-limited. Deaths are very rare and most often are due to central nervous system (CNS) complications, splenic rupture, upper airway obstruction, or bacterial superinfection.

WhenCNScomplications develop, they usually do so during the first 2 weeks ofEBVinfection; in some patients, especially children, they are the only clinical manifestations ofIM. Heterophile antibodies and atypical lymphocytes may be absent. Meningitis and encephalitis are the most common neurologic abnormalities, and patients may present with headache, meningismus, or cerebellar ataxia; acute hemiplegia and psychosis have also been described. The cerebrospinal fluid (CSF) contains mainly lymphocytes, with occasional atypical lymphocytes. Most cases resolve without neurologic sequelae. Acute EBV infection has also been associated with cranial nerve palsies (especially ones involving cranial nerve VII), Guillain-Barre syndrome, acute transverse myelitis, and peripheral neuritis.

Autoimmune hemolytic anemia occurs in about 2% of cases during the first 2 weeks. In most cases the anemia is Coombs'-test positive, with cold agglutinins directed against the i red blood cell antigen. Most patients with hemolysis have mild anemia that lasts for 1 or 2 months, but some patients have severe disease with hemoglobinuria and jaundice. Nonspecific antibody responses may also include rheumatoid factor, antinuclear antibodies, anti-smooth muscle antibodies, antiplatelet antibodies, and cryoglobulins.IM has been associated with red-cell aplasia, severe granulocytopenia, thrombocytopenia, pancytopenia, and hemophagocytic syndrome. The spleen ruptures in fewer than 0.5% of cases. Splenic rupture is more common among males than among females and may be manifest as abdominal pain, referred shoulder pain, or hemodynamic compromise.

Hypertrophy of lymphoid tissue in the tonsils or adenoids can result in upper airway obstruction, as can inflammation and edema of the epiglottis, pharynx, or uvula. About 10% of patients withIMdevelop streptococcal pharyngitis after their initial sore throat resolves.

Other rare complications associated with acuteEBVinfection include hepatitis (which can

be fulminant), myocarditis or pericarditis with electrocardiographic changes, pneumonia with pleural effusion, interstitial nephritis, genital ulcerations, and vasculitis.

OTHER DISEASES ASSOCIATED WITH EBV INFECTION

EBV-associated lymphoproliferative disease has been described in patients with congenital or acquired immunodeficiency, including those with severe combined immunodeficiency or AIDS, recipients of bone marrow transplants, and recipients of organ transplants who are receiving immunosuppressive drugs (especially cyclosporine). Proliferating EBV-infected B cells infiltrate lymph nodes and multiple organs, and patients present with fever and lymphadenopathy or gastrointestinal symptoms. Pathologic studies show B cell hyperplasia or poly- or monoclonal lymphoma. The X-linked lymphoproliferative syndrome (Duncan's disease) is a recessive disorder of young boys who have a normal response to childhood infections but develop fatal lymphoproliferative disorders after infection with EBV. The gene mutated in this syndrome, SAP or SH2D1A, has been identified; its product binds to a protein that mediates interactions of B and T cells. Most patients with this syndrome die of acuteIM; others develop hypogammaglobulinemia, malignant B cell lymphomas, aplastic anemia, or agranulocytosis. IM has also proved fatal to some patients with no obvious preexisting immune abnormality.

Oral hairy leukoplakia (Plate IID-42) is an early manifestation of infection with HIV in adults (Chap. 309). Most patients present with raised, white corrugated lesions on the tongue (and occasionally on the buccal mucosa) that containEBV DNA. Children infected with HIV can develop lymphoid interstitial pneumonitis; EBV DNA is often found in lung tissue from these patients.

Patients with the chronic fatigue syndrome may have titers of antibody toEBV that are elevated but are not significantly different from those in healthy EBV-seropositive adults. While some patients have malaise and fatigue that persist for weeks or months afterIM, persistent EBV infection is not a cause of the chronic fatigue syndrome. Chronic active EBV infection is very rare and is distinct from the chronic fatigue syndrome. The affected patients have an illness lasting more than 6 months with markedly elevated titers of antibody to EBV and evidence of organ involvement, including hepatosplenomegaly, lymphadenopathy, and pneumonitis, uveitis, or neurologic disease.

EBVis associated with several malignancies. About 15% of cases of Burkitt's lymphoma in the United States and about 90% of those in Africa are associated with EBV (Chap. 112). African patients with Burkitt's lymphoma have high levels of antibody to EBV, and their tumor tissue usually contains viral DNA. EBV-containing Burkitt's lymphoma also occurs in patients with AIDS. Anaplastic nasopharyngeal carcinoma is uniformly associated with EBV; the affected tissues contain viral DNA and antigens. Patients with nasopharyngeal carcinoma often have elevated titers of antibody to EBV (Chap. 87).

EBVhas been associated with Hodgkin's disease, especially the mixed-cellularity type (Chap. 112). Patients with Hodgkin's disease often have elevated titers of antibody to EBV, and in about half of cases viral DNA and antigens are found in Reed-Sternberg cells. In some cases, EBV DNA has been detected in tonsillar carcinoma,

angioimmunoblastic lymphadenopathy, angiocentric nasal NK/T cell immunoproliferative lesions, T cell lymphoma, thymoma, gastric carcinoma, andCNSlymphoma from patients with no underlying immunodeficiency. Studies have demonstrated viral DNA in leiomyosarcomas from AIDS patients and in smooth-muscle tumors from organ transplant recipients. Virtually all CNS lymphomas in AIDS patients are associated with EBV.

DIAGNOSIS

Serologic Testing The heterophile test is used for the diagnosis ofIM in children and adults (Table 184-2). Heterophile antibody is an IgM antibody that does not bindEBVproteins. In the test for this antibody, human serum is absorbed with guinea pig kidney, and the heterophile titer is defined as the greatest serum dilution that agglutinates sheep, horse, or cow erythrocytes. A titer of 40-fold or greater is diagnostic of acute EBV infection in a patient who has symptoms compatible with IM and atypical lymphocytes. Tests for heterophile antibodies are positive in 40% of patients with IM during the first week of illness and in 80 to 90% during the third week. Therefore, repeated testing may be necessary, especially if the initial test is performed early. Tests usually remain positive for 3 months after the onset of illness, but heterophile antibodies can persist for up to 1 year. These antibodies usually are not detectable in children<5 years of age, in the elderly, or in patients presenting with symptoms not typical of IM. The commercially available monospot test for heterophile antibodies is somewhat more sensitive than the classic heterophile test. False-positive results in the monospot test are more common in children and in patients with other viral infections.

EBV-specific antibody testing is used for patients with suspected acute EBV infection who lack heterophile antibodies and for patients with atypical infections. Serologic tests are particularly useful in young children, who often do not develop heterophile antibodies. Titers of IgM and IgG antibodies to viral capsid antigen (VCA) are elevated in the serum of more than 90% of patients at the onset of disease. IgM antibody to VCA is useful for the diagnosis of acuteIMbecause it is present at elevated titers only during the first 2 months of the disease; in contrast, IgG antibody to VCA is often used to assess exposure to EBV in the past because it persists for life.

Antibodies to early antigens (EAs) are found either in a diffuse pattern in the nucleus and cytoplasm of infected cells (EA-D antibody) or restricted to the cytoplasm (EA-R antibody). These antibodies are detectable 3 to 4 weeks after the onset of symptoms in patients withIM. About 70% of individuals with IM, especially those with relatively severe disease, have EA-D antibodies during the course of their illness. These antibodies usually persist for only 3 to 6 months. Levels of EA-D antibodies are also elevated in patients with nasopharyngeal carcinoma or chronic activeEBVinfection. EA-R antibodies are only occasionally detected in patients with IM but are often found at elevated titers in patients with African Burkitt's lymphoma or chronic active EBV infection.

IgA antibodies toEBVantigens have proved useful for the identification of patients with nasopharyngeal carcinoma and of persons at high risk for the disease. Seroconversion toEBNApositivity is also useful for the diagnosis of acute infection with EBV. Antibodies to EBNA are detectable relatively late (3 to 6 weeks after the onset of symptoms) in nearly all cases of acute EBV infection and persist for the lifetime of the patient. These

antibodies may be lacking in immunodeficient patients and in those with chronic active EBV infection.

Other Studies Detection ofEBV DNA, RNA, or proteins has been valuable in demonstrating the association of the virus with various malignancies. The polymerase chain reaction has been used to detect EBV DNA in theCSF of some AIDS patients with lymphomas and to monitor the amount of EBV DNA in the blood of patients with lymphoproliferative disease. Culture of EBV from throat washings or blood is not helpful in the diagnosis of acute infection, since EBV commonly persists in the oropharynx and in B cells for the lifetime of the infected individual.

Differential Diagnosis The differential diagnosis ofIM and atypical lymphocytosis includes acute infection with cytomegalovirus, *Toxoplasma*, HIV, human herpesvirus 6, and hepatitis viruses as well as drug hypersensitivity reactions. Cytomegalovirus is the most common cause of heterophile-negative mononucleosis, usually involves older patients, and is associated with a lower frequency of sore throat, splenomegaly, and lymphadenopathy than IM due toEBV. Other diseases that share some of the features of IM include rubella, acute infectious lymphocytosis in children, and lymphoma or leukemia.

TREATMENT

Therapy for IMconsists of supportive measures, with rest and analgesia. Excessive physical activity during the first month should be avoided to reduce the possibility of splenic rupture. If splenic rupture occurs, splenectomy is required. Glucocorticoid therapy is not indicated for uncomplicated IM and in fact may predispose to bacterial superinfection. Prednisone (40 to 60 mg/d for 2 to 3 days, with subsequent tapering of the dose over 1 to 2 weeks) has been used for the prevention of airway obstruction in patients with severe tonsillar hypertrophy, for autoimmune hemolytic anemia, and for severe thrombocytopenia. Glucocorticoids have also been used in a few selected patients with severe malaise and fever and in patients with severeCNS or cardiac disease.

Acyclovir has had no significant clinical impact onIM in controlled trials. In one study, the combination of acyclovir and prednisolone had no significant effect on the duration of symptoms of IM. Acyclovir, at a dosage of 400 to 800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses) and some cases of chronic activeEBVdisease. This agent generally has not been beneficial for patients with lymphoproliferative syndromes. When possible, therapy for EBV lymphoproliferative disease should be directed toward the reduction of immunosuppressive medication. New therapies, including the use of interferona and the infusion of donor T cells or EBV-specific cytotoxic T cells, are being studied.

The isolation of patients withIM is unnecessary. Vaccines directed against the majorEBVglycoprotein have been effective in animal studies and are currently undergoing small-scale clinical trials.

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185. CYTOMEGALOVIRUS AND HUMAN HERPESVIRUS TYPES 6, 7, AND 8 - *Martin S. Hirsch*

CYTOMEGALOVIRUS

DEFINITION

Cytomegalovirus (CMV), which was initially isolated from patients with congenital cytomegalic inclusion disease, is now recognized as an important pathogen in all age groups. In addition to inducing severe birth defects, CMV causes a wide spectrum of disorders in older children and adults, ranging from an asymptomatic, subclinical infection to a mononucleosis syndrome in healthy individuals to disseminated disease in immunocompromised patients. Human CMV is one of several related species-specific viruses that cause similar diseases in various animals. All are associated with the production of characteristic enlarged cells -- hence the name *cytomegalovirus*.

CMVis a member of the b-herpesvirus group and has double-stranded DNA, a protein capsid, and a lipoprotein envelope. Like other herpesviruses, CMV demonstrates icosahedral symmetry, replicates in the cell nucleus, and can cause either a lytic and productive or a latent infection. CMV can be distinguished from other herpesviruses by certain biologic properties, such as host range and type of cytopathology induced. Viral replication is associated with the production of large intranuclear inclusions and smaller cytoplasmic inclusions. The virus appears to replicate in a variety of cell types in vivo; in tissue culture it grows preferentially in fibroblasts. Although there is little evidence that CMV is oncogenic in vivo, the virus does transform fibroblasts in rare instances, and genomic transforming fragments have been identified.

EPIDEMIOLOGY

CMVhas a worldwide distribution. Approximately 1% of newborns in the United States are infected with CMV, and the percentage is higher in many less developed countries. Communal living and poor personal hygiene facilitate early spread. Perinatal and early childhood infections are common. Virus may be present in milk, saliva, feces, and urine. Transmission of CMV has been identified among young children in day-care centers and has been traced from infected toddler to pregnant mother to developing fetus. When an infected child introduces CMV into a household, 50% of susceptible family members seroconvert within 6 months.

The virus is not readily spread by casual contact but requires repeated or prolonged intimate exposure for transmission. In late adolescence and young adulthood,CMV is often transmitted sexually, and asymptomatic viral carriage in semen or cervical secretions is common. CMV antibody is present at detectable levels in nearly 100% of female prostitutes and sexually active homosexual men. Sexually active adults may harbor several strains of CMV simultaneously. Transfusion of whole blood or certain blood products containing viable leukocytes may also transmit CMV, with a frequency of 0.14 to 10% per unit transfused.

Once infected, an individual probably carriesCMV for life. The infection usually remains latent. However, CMV reactivation syndromes develop frequently when T

lymphocyte-mediated immunity is compromised -- for example, after organ transplantation or in association with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, infection with HIV;Chap. 309). Most primary CMV infections in organ transplant recipients (Chap. 136) result from transmission of the virus in the graft itself. In CMV-seropositive transplant recipients, infection results from reactivation of latent virus or, less commonly, from reinfection by a new strain of CMV. CMV infection may be associated with coronary artery stenosis following heart transplantation or coronary angioplasty, but this association requires further validation.

PATHOGENESIS

CongenitalCMVinfection can result from either primary or reactivation infection of the mother. However, clinical disease in the fetus or newborn is almost exclusively related to primary maternal infection (Table 185-1). The factors determining the severity of congenital infection are unknown; a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease.

Primary infection in late childhood or adulthood is often associated with a vigorous T lymphocyte response that may contribute to the development of a mononucleosis syndrome similar to that observed following Epstein-Barr virus (EBV) infection (Chap. 184). The hallmark of such infection is the appearance of atypical lymphocytes in the peripheral blood; these cells are predominantly activated CD8+ T lymphocytes. Polyclonal activation of B cells by the virus contributes to the development of rheumatoid factors and other autoantibodies duringCMVmononucleosis.

Once acquired by symptomatic or asymptomatic primary infection,CMVpersists indefinitely in tissues of the host. The sites of persistent or latent infection are unclear but probably include multiple cell types and various organs. Transmission following blood transfusion or organ transplantation is due to silent infections in these tissues. Autopsy studies suggest that salivary glands and bowel may be areas of latent infection.

If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can be reactivated to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, following tissue transplantation) appears to be an ideal setting forCMVactivation and CMV-induced disease. Certain particularly potent suppressants of T cell immunity, such as antithymocyte globulin, are associated with a high rate of clinical CMV syndromes, which may follow either primary or reactivation infection. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens, such as *Pneumocystis carinii*. CMV and *P. carinii* are frequently found together in immunosuppressed patients with severe interstitial pneumonia. CMV may function as a cofactor to activate latent HIV infection.

PATHOLOGY

Cytomegalic cells in vivo (presumed to be infected epithelial cells) are two to four times larger than surrounding cells and often contain an 8- to 10-um intranuclear inclusion that is eccentrically placed and is surrounded by a clear halo, producing an "owl's eye"

appearance. Smaller granular cytoplasmic inclusions are demonstrated occasionally. Cytomegalic cells are found in a wide variety of organs, including salivary gland, lung, liver, kidney, intestine, pancreas, adrenal gland, and the central nervous system.

The cellular inflammatory response to infection consists of plasma cells, lymphocytes, and monocyte-macrophages. Granulomatous reactions occasionally develop, particularly in the liver. Immunopathologic reactions may contribute toCMVdisease. Immune complexes have been detected in infected infants, sometimes in association with CMV-related glomerulopathies. Immune-complex glomerulopathy has been observed in some CMV-infected patients after renal transplantation.

CLINICAL MANIFESTATIONS

Congenital CMV Infection Fetal infections range from inapparent to severe and disseminated. Cytomegalic inclusion disease develops in approximately 5% of infected fetuses and is seen almost exclusively in infants born to mothers who develop primary infections during pregnancy. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60 to 80% of cases). Microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity are reported in 30 to 50% of cases. Inguinal hernias and chorioretinitis are less common. Laboratory abnormalities include elevated alanine aminotransferase levels, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated cerebrospinal fluid protein levels. The prognosis for severely infected infants is poor; the mortality rate is 20 to 30%, and few of the patients who survive escape intellectual or hearing difficulties in later years. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, rubella, toxoplasmosis, infection with herpes simplex virus or enterovirus, and bacterial sepsis.

Most congenitalCMVinfections are clinically inapparent at birth. Between 5 and 25% of asymptomatically infected infants develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

Perinatal CMV Infection The newborn may acquireCMV at the time of delivery by passage through an infected birth canal or by postnatal contact with maternal milk or other secretions. Approximately 40 to 60% of infants who are breast-fed for longer than 1 month by seropositive mothers become infected. Iatrogenic transmission also can result from neonatal blood transfusion. Screening of blood products before they are transfused into low-birth-weight seronegative infants or into seronegative pregnant women decreases the risk of infection.

The great majority of infants infected at or after delivery remain asymptomatic. However, protracted interstitial pneumonitis has been associated with perinatally acquiredCMVinfection, particularly in premature infants, and occasionally has been accompanied by infection with *Chlamydia trachomatis*, *P. carinii*, or *Ureaplasma urealyticum*. Poor weight gain, adenopathy, rash, hepatitis, anemia, and atypical lymphocytosis may also be found, and CMV excretion often persists for months or years.

CMV Mononucleosis The most common clinical manifestation ofCMVinfection in

normal hosts beyond the neonatal period is a heterophil antibody-negative mononucleosis syndrome. This manifestation may develop spontaneously or may follow the transfusion of leukocyte-containing blood products. Although the syndrome occurs at all ages, it most often involves sexually active young adults. Incubation periods range from 20 to 60 days, and the illness generally lasts for 2 to 6 weeks. Prolonged high fevers, sometimes accompanied by chills, profound fatigue, and malaise, characterize this disorder. Myalgias, headache, and splenomegaly are frequent, but in CMV mononucleosis (as opposed to infectious mononucleosis caused byEBV), exudative pharyngitis and cervical lymphadenopathy are rare. Occasional patients develop rubelliform rashes, often after exposure to ampicillin. Less commonly observed are interstitial or segmental pneumonia, myocarditis, pleuritis, arthritis, and encephalitis. In rare cases, Guillain-Barre syndrome complicates CMV mononucleosis. The characteristic laboratory abnormality is relative lymphocytosis in peripheral blood, with more than 10% atypical lymphocytes. Total leukocyte counts may be low, normal, or markedly elevated. Although significant jaundice is uncommon, serum aminotransferase and alkaline phosphatase levels are often moderately elevated. Heterophil antibodies are absent; however, transient immunologic abnormalities are common and may include the presence of cryoglobulins, rheumatoid factors, cold agglutinins, and antinuclear antibodies. Hemolytic anemia, thrombocytopenia, and granulocytopenia complicate recovery in rare instances.

Most patients recover without sequelae, although postviral asthenia may persist for months. The excretion ofCMV in urine, genital secretions, and/or saliva often continues for months or years. Rarely, CMV infection is fatal in immunocompetent hosts; even when such patients survive, they can have recurrent episodes of fever and malaise that are sometimes associated with autonomic nervous system dysfunction (e.g., attacks of sweating or flushing).

CMV Infection in the Immunocompromised Host (See alsoTable 185-1) CMV appears to be the most common and important viral pathogen complicating organ transplantation (Chap. 136). In recipients of kidney, heart, lung, and liver transplants, CMV induces a variety of syndromes, including fever and leukopenia, hepatitis, pneumonitis, esophagitis, gastritis, colitis, and retinitis. CMV disease may be an independent risk factor for both graft loss and death. The period of maximal risk is between 1 and 4 months after transplantation, although retinitis may be a later complication. The risk of disease appears to be greater after primary infection than after reactivation. In addition, molecular studies indicate that seropositive transplant recipients are susceptible to reinfection with donor-derived, genotypically variant CMV, and such infection often results in disease. Reactivation infection, although frequent, is less likely than primary infection to be important clinically. Clinical disease is related to various factors, such as the degree of immunosuppression; patients receiving certain immunosuppressive agents, such as antithymocyte globulin, appear to be more likely to have severe infections than those receiving other agents, such as cyclosporine. The transplanted organ is particularly vulnerable as a target for CMV infection; thus, there is a tendency for CMV hepatitis to follow liver transplantation and for CMV pneumonitis to follow lung transplantation.

CMVpneumonia occurs in 15 to 20% of bone marrow transplant recipients, with a case-fatality rate of 84 to 88%. The risk is greatest between 5 and 13 weeks after

transplantation, and the several risk factors identified include certain types of immunosuppressive therapy, acute graft-versus-host disease, older age, viremia, and seropositivity before transplantation.

CMVis recognized as an important pathogen in patients with advanced HIV infection (Chap. 309), in whom it often causes retinitis or disseminated disease, particularly when peripheral-blood CD4+ cell counts fall below 50 to 100/uL. As treatment for underlying HIV infection has improved, the incidence of serious CMV infections (e.g., retinitis) has decreased. However, institution of highly active antiretroviral regimens sometimes leads to acute flare-ups of CMV retinitis during the first few weeks of therapy.

Syndromes produced byCMV in the immunocompromised host often begin with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgias or myalgias. Liver function abnormalities, leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. The development of tachypnea, hypoxia, and unproductive cough signals respiratory involvement. Radiologic examination of the lung often demonstrates bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly; localized segmental, nodular, or alveolar patterns are less common. The differential diagnosis includes infection with *P. carinii*; infections due to other viral, bacterial, or fungal pathogens; pulmonary hemorrhage; and injury secondary to irradiation or to treatment with cytotoxic drugs.

GastrointestinalCMVinvolvement may be localized or extensive and almost exclusively affects compromised hosts. Ulcers of the esophagus, stomach, small intestine, or colon may result in bleeding or perforation. CMV infection may lead to exacerbations of underlying ulcerative colitis. Hepatitis occurs frequently, particularly following liver transplantation, and CMV-associated acalculous cholecystitis and adrenalitis have been described.

CMVrarely causes meningoencephalitis in otherwise healthy individuals. Two forms of CMV encephalitis are seen in patients with AIDS. One resembles HIV encephalitis and presents as progressive dementia; the other is a ventriculoencephalitis characterized by cranial-nerve deficits, nystagmus, disorientation, lethargy, and ventriculomegaly. In immunocompromised patients, CMV can also cause subacute progressive polyradiculopathy, which is often reversible if recognized and treated promptly.

CMVretinitis is an important cause of blindness in immunocompromised patients, particularly patients with advanced AIDS (Chap. 309). Early lesions consist of small, opaque, white areas of granular retinal necrosis that spread in a centrifugal manner and are later accompanied by hemorrhages, vessel sheathing, and retinal edema (seePlate IV-2). CMV retinopathy must be distinguished from that due to other conditions, including toxoplasmosis, candidiasis, and herpes simplex virus infection.

FatalCMVinfections are often associated with persistent viremia and the involvement of multiple organ systems. Progressive pulmonary infiltrates, pancytopenia, hyperamylasemia, and hypotension are characteristic features that are frequently found in conjunction with a terminal bacterial, fungal, or protozoan superinfection. Extensive adrenal necrosis with CMV inclusions is often documented at autopsy, as is CMV

involvement of many other organs.

DIAGNOSIS

The diagnosis ofCMVinfection usually cannot be made reliably on clinical grounds alone. Isolation of the virus or detection of CMV antigens or DNA from appropriate clinical specimens, together with demonstration of a fourfold or greater rise in antibody titers or persistently elevated antibody titers, is the preferred diagnostic approach. Virus excretion or viremia is readily detected by culture of appropriate specimens on human fibroblast monolayers. If viral titers are high, as is frequently the case in congenital disseminated infection or in patients with AIDS, characteristic cytopathic effects may be detected within a few days. However, in some situations -- such as CMV mononucleosis -- viral titers are low, and cytopathic effects may take several weeks to appear. Many laboratories expedite diagnosis with an overnight tissue-culture method (shell vial assay) involving centrifugation and an immunocytochemical detection technique employing monoclonal antibodies to an immediate-early CMV antigen. Isolation of virus from urine or saliva does not, by itself, constitute proof of acute infection, since excretion from these sites may continue for months or years after illness. Detection of CMV viremia is a better predictor of acute infection.

Detection ofCMVantigens (pp65) in peripheral-blood leukocytes or of CMV DNA in blood or tissues may hasten the diagnosis of CMV disease in certain populations, including organ transplant recipients and persons with AIDS. Such assays may yield a positive result several days earlier than culture methods. The detection of CMV DNA in cerebrospinal fluid by the polymerase chain reaction is useful in the diagnosis of CMV encephalitis or polyradiculopathy.

A variety of serologic assays are available to detect increases in titers of antibody toCMVantigens. An increased antibody level may not be detectable for up to 4 weeks after primary infection, and titers often remain high for years after infection. For this reason, single-sample antibody determinations are of no value in assessing the acuteness of infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; circulating rheumatoid factors may result in occasional false-positive IgM tests.

TREATMENT

Several prophylactic measures are useful for the prevention ofCMVinfection in patients at high risk. The use of blood from seronegative donors or of blood that has been frozen, thawed, and deglycerolized greatly decreases the rate of transfusion-associated transmission of CMV. Similarly, matching of organ or bone marrow transplants by CMV serology, using organs only from seronegative donors for seronegative recipients, reduces rates of primary infection following transplantation. Both live attenuated and CMV subunit vaccines have been evaluated, but neither is close to approval for general use.

CMVimmune globulin has been reported to reduce rates of occurrence of CMV-associated syndromes and of fungal or parasitic superinfections among seronegative renal transplant recipients. Studies in bone marrow transplant recipients

have produced conflicting results. Prophylactic acyclovir has been demonstrated to reduce rates of CMV infection and disease in certain seronegative renal transplant recipients; acyclovir is not effective in the treatment of active CMV disease, however.

Ganciclovir is a guanosine derivative that has considerably more activity againstCMV than its congener acyclovir. After intracellular conversion by a viral phosphotransferase encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase. Several clinical studies have indicated response rates of 70 to 90% among patients with AIDS given ganciclovir for the treatment of CMV retinitis or colitis. In bone marrow transplant recipients with CMV pneumonia, ganciclovir is less effective when given alone, but it elicits a favorable clinical response 50 to 70% of the time when it is combined with CMV immune globulin. Prophylactic or suppressive ganciclovir may be useful in high-risk bone marrow or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation or who are CMV culture-positive afterward). In many patients with AIDS, persistently low CD4+ cell counts, and CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged maintenance regimens are recommended for such patients. Resistance to ganciclovir is common among patients treated for more than 3 months and is usually related to mutations in the CMV UL97 gene.

Ganciclovir therapy forCMVretinitis consists of a 14- to 21-day induction course (5 mg/kg intravenously twice a day) followed by a prolonged intravenous or oral maintenance regimen. For parenteral maintenance, the dose is 5 mg/kg daily or 6 mg/kg 5 days per week. Peripheral-blood neutropenia develops in 16 to 29% of treated patients but is often ameliorated by granulocyte or granulocyte-macrophage colony-stimulating factor. Oral ganciclovir at a high dose (3 g/d) can also be used for maintenance, although the blood levels achieved are insufficient for acute induction regimens. Although progression (as assessed by funduscopy) is more rapid with oral than with intravenous ganciclovir maintenance (mean time to progression, 68 vs. 96 days; $p = .03$), the ease of administration and reduced toxicity of the oral preparation may make it an acceptable alternative for some patients who do not have sight-threatening central retinitis. The use of oral ganciclovir as prophylaxis in high-risk AIDS patients (i.e., those with CD4+ cell counts of<100/uL) has been studied in two placebo-controlled trials, with somewhat contradictory results.

Foscarnet (sodium phosphonoformate) also acts againstCMVinfection by inhibiting viral DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant CMV isolates. A comparative trial of foscarnet and ganciclovir in 234 patients with AIDS and CMV retinitis demonstrated equivalent activity against retinitis but longer survival (12.6 vs. 8.5 months) in the foscarnet group. Although the reasons for the latter difference are unclear, the antiretroviral activity of foscarnet and the greater use of zidovudine by foscarnet recipients are strong possibilities. Foscarnet is less well tolerated than ganciclovir and causes considerable toxicity, including renal dysfunction, hypomagnesemia, hypokalemia, hypocalcemia, genital ulcers, dysuria, nausea, and paresthesia. Moreover, foscarnet administration requires the use of an infusion pump and close clinical monitoring. With aggressive hydration and dose adjustments for renal dysfunction, the toxicity of foscarnet can be reduced. The use of foscarnet should be avoided when a saline load cannot be tolerated (e.g., in cardiomyopathy). The approved

induction regimen is 60 mg/kg every 8 h for 2 weeks, although 90 mg/kg every 12 h is equally effective and no more toxic. Maintenance infusions should deliver 90 to 120 mg/kg once daily; no oral preparation is available. Foscarnet-resistant viruses may emerge during extended therapy.

Ganciclovir may also be administered via a slow-release pellet sutured into the eye. Although this intraocular device provides good local protection, contralateral eye disease and disseminated disease are not affected, and early retinal detachment is possible. A combination of intraocular and systemic therapy may be better than the intraocular implant alone.

Cidofovir is a nucleotide analogue with a long intracellular half-life that allows intermittent intravenous administration. Induction regimens of 5 mg/kg weekly for 2 weeks are followed by maintenance regimens of 3 to 5 mg/kg every 2 weeks. Cidofovir can cause severe nephrotoxicity through dose-dependent proximal tubular cell injury; however, this adverse effect can be ameliorated somewhat by saline hydration and probenecid.

HUMAN HERPESVIRUS TYPES 6, 7, AND 8

Human herpesvirus (HHV) type 6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. The virus has a worldwide distribution, and two genetically distinct variants (HHV-6A and HHV-6B) are now recognized.

Infection withHHV-6 frequently develops during infancy as maternal antibody wanes. Congenital infections have also been described. HHV-6 (mostly variant B) can cause exanthem subitum (Fig. 18-CD2) (roseola infantum), a common illness characterized by fever with subsequent rash. HHV-6 is also a major cause of febrile seizures without rash during infancy. In older age groups, HHV-6 has been associated with mononucleosis syndromes, focal encephalitis, and (in immunocompromised hosts) pneumonitis and disseminated disease. In transplant recipients, HHV-6 infection may be associated with graft dysfunction. As many as 80% of adults are seropositive for HHV-6. The virus may be transmitted by saliva and possibly by genital secretions. There is no established treatment or vaccine.

HHV-7 was isolated in 1990 from T lymphocytes from the peripheral blood of a healthy 26-year-old man. Other isolates have since been obtained. It appears that the virus is frequently acquired during childhood and is frequently present in the saliva of healthy adults. No human disease has yet been definitively linked to HHV-7, although some cases of exanthem subitum (Fig. 18-CD2) and other childhood febrile illnesses have been associated with HHV-7 infection. An association has been made between HHV-7 and pityriasis rosea, but further studies must confirm this relationship.

Unique herpesvirus-like DNA sequences were reported during 1994 and 1995 in tissues derived from Kaposi's sarcoma and body cavity-based lymphoma occurring in patients with AIDS. When subjected to representational-difference analyses, more than 90% of Kaposi's sarcoma tissue samples were found to contain these sequences, whereas appropriate control tissues did not. The same herpesvirus-like DNA sequences have

been reported in Kaposi's sarcoma tissue from non-AIDS patients, in a subgroup of AIDS-related B-cell body cavity-based lymphomas, and in lymph nodes from patients with multicentric Castleman's disease (a condition also known as angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymphoid hamartoma, and follicular lymphoreticuloma, which is especially aggressive and frequently fatal). Approximately 15% of non-Kaposi's sarcoma tissue specimens from patients with AIDS contain these herpesvirus-like sequences, which have also been found in semen from both AIDS and non-AIDS patients. The virus has been propagated in cell culture and namedHHV-8; it is also referred to as Kaposi's sarcoma-associated herpesvirus. Several serologic assays suggest a low rate of background positivity (0 to 29%) among HIV-negative blood donors but a high rate of positivity (>80%) among patients with Kaposi's sarcoma. The etiologic role of HHV-8 in Kaposi's sarcoma and other diseases remains to be established, although HHV-8 seroconversion during HIV infection appears to be highly predictive of the development of Kaposi's sarcoma.

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186. SMALLPOX, VACCINIA, AND OTHER POXVIRUSES - *Fred Wang*

Two poxviruses, smallpox virus and molluscum contagiosum virus, cause natural disease in humans, and other poxviruses are associated with zoonotic infections. Monkeypox virus and smallpox virus typically cause systemic disease with rash, whereas the other poxviruses cause localized skin lesions. Poxviruses are the only DNA viruses that replicate in the cytoplasm, where accumulated viral particles form eosinophilic inclusions, or Guarnieri bodies, visible by light microscopy. Many poxvirus genes interfere with different aspects of the host immune response and provide important insights into the pathogenesis and virulence of viral infection. Genetically engineered vaccinia and avipoxviruses offer great promise as potential vectors for vaccination against other diseases.

SMALLPOX

The last case of endemic smallpox was reported in 1977 from Somalia. In 1980 the World Health Organization officially declared that smallpox had been eliminated worldwide as a result of a global vaccination and eradication program. Important features that contributed to the unique success of this vaccine program included (1) universal interest in eliminating this costly disease with high morbidity and mortality, (2) the infection's long incubation period and low level of communicability, (3) the ease of diagnosis of skin lesions by characteristic histology or antigen detection, (4) the fact that humans were the sole reservoir of the infection, (5) the absence of a carrier state, and (6) the availability of an effective live-virus vaccine that could readily be delivered to less developed countries because of its resistance to chemicals, temperature changes, and drying. The only known remaining repositories of smallpox virus reside in two research laboratories (located in the United States and Russia), and the issue of whether these last samples should be maintained or destroyed remains controversial.

Before the eradication of smallpox, variola virus existed as two related strains: *variola major* (smallpox), with a case-mortality rate of 20 to 50%, and *variola minor* (alastrim), which caused a clinically milder form of smallpox with a mortality of <1%. The clinical presentation of smallpox is now primarily of historic note. However, the threat of biologic terrorism means that smallpox remains a remote possibility in the differential diagnosis of a vesicular exanthem. Fever and macular rash appear after an average incubation period of 12 days, with a progression to typical vesicular and pustular lesions over 1 to 2 weeks. Rash generally appears first on the face, oral mucosa, and arms, with relative sparing of the trunk. Smallpox lesions may be confused with common chickenpox (varicella-zoster) infection but tend to be more diffuse, peripheral, and uniform in their stage of development. Polymerase chain reaction promises to be more useful than traditional electron microscopy or virus isolation for confirming variola or other poxvirus infections.

VACCINIA

The origin of vaccinia virus -- the virus used for vaccination against smallpox -- is uncertain, but it was probably derived from cowpox virus, variola virus, or a hybrid of the two. It is now a laboratory virus with no natural host. Experience has proven the effectiveness of live vaccinia virus vaccine, although its efficacy and safety were not

established in controlled studies. Percutaneous administration of vaccinia virus vaccine results in protective cellular and humoral immune responses in >95% of primary vaccinees. Formation of a pustule and scab at the site of inoculation is indicative of immunity; because immunity wanes after 10 to 20 years, revaccination every 10 years is recommended for continued protection. Routine smallpox vaccination was discontinued in 1971 and has not been required for international travel since 1982. However, the development of recombinant vaccinia viruses for potential use in vaccines against other infectious agents or as immunotherapy against malignant diseases has led to the recommendation that laboratory and health care employees working directly with vaccinia virus vectors be considered for vaccination. Selected groups that may be exposed to poxviruses (e.g., some military personnel and individuals who work with animals) are also vaccinated.

The most frequent adverse complication of vaccination is inadvertent inoculation (usually autoinoculation) at other sites. More serious complications, which are more common among primary vaccinees and infants than among revaccinees and adults, include (1) generalized vaccinia in otherwise healthy individuals, which is generally self-limited; (2) eczema vaccinatum, which consists of disseminated cutaneous lesions in highly susceptible patients with eczema or other chronic skin diseases and is occasionally severe or even fatal; (3) progressive vaccinia (vaccinia necrosum), which is a severe, potentially fatal illness occurring in patients with immunodeficiency, whether congenital, acquired (e.g., via leukemia or lymphoma), iatrogenic (e.g., via chemotherapy or glucocorticoid treatment), or HIV induced; and (4) postinfectious encephalitis, which is rare (3 cases per million primary vaccinees) but can be fatal in 15 to 25% of cases and can leave 25% of patients with permanent neurologic sequelae. Since vaccinees can transmit vaccinia virus to susceptible individuals, vaccination is contraindicated if the proposed recipient or his or her household contacts have eczema, are immunocompromised, or are pregnant. Vaccinia immune globulin (0.6 mL/kg) derived from the plasma of vaccinated persons may be useful for the treatment of severe generalized vaccinia, eczema vaccinatum, progressive vaccinia, and ocular vaccinia resulting from inadvertent inoculation but is of no value for the treatment of postinfectious encephalitis.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is generally a benign disease characterized by pearly, flesh-colored, umbilicated skin lesions 2 to 5 mm in diameter (Plate IID-41,Fig. 186-CD1). A relative lack of inflammation and necrosis distinguishes these proliferative lesions from other poxvirus lesions. The infection can be transmitted by close contact, including sexual intercourse. Swimming pools are a common vector for transmission. Atopy and compromise of skin integrity can increase the risk of infection. Lesions can be found anywhere on the body except the palms and soles and may be associated with an eczematous rash. In most cases the disease is self-limited and has no systemic complications. Molluscum contagiosum develops especially often in association with the advanced stages of HIV infection, with a prevalence of 5 to 18% among HIV-infected patients (Chap. 309). The disease is often more generalized, severe, and persistent in AIDS patients than in other groups, frequently involving the face and upper body. Extensive molluscum contagiosum has also been reported in conjunction with other types of immunodeficiency.

The diagnosis of molluscum contagiosum can be made by histologic demonstration of cytoplasmic eosinophilic inclusions characteristic of poxvirus replication. This virus cannot be propagated in vitro, but electron microscopy and molecular studies can be used for its identification.

There is no specific systemic treatment for molluscum contagiosum, but a variety of techniques for physical ablation have been used. Molluscum contagiosum may respond to effective control of HIV infection with highly active antiretroviral therapy. Cidofovir is also being investigated for potential clinical use against molluscum contagiosum.

MONKEYPOX VIRUS AND OTHER POXVIRUSES

Monkeypox virus naturally infects nonhuman primates in the tropical rain forests of western and central Africa and can infect humans who come into direct contact with infected animals. Human disease is rare and is characterized by a systemic illness and vesicular rash similar to those of variola. A large outbreak of monkeypox occurred between February 1996 and October 1997 in central Africa, with a case-fatality ratio of 3%; a prolonged period of active cases, suggesting a potential for sustained person-to-person transmission; and a high proportion of younger patients, suggesting the possible consequences of discontinued smallpox vaccination. Clinical presentations were occasionally confused with the more common varicella-zoster virus infection.

Other poxviruses can cause localized vesicular lesions when humans come into direct contact with infected animals. These viruses include cowpox virus (rodents, cats); milkers' node virus (cows; Fig. 186-CD2); buffalopox virus (buffaloes); bovine papular stomatitis virus (cows); and orf virus (Fig. 186-CD3), which is also known as contagious pustular dermatitis virus (sheep, goats).

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187. PARVOVIRUS - *Neil R. Blacklow*

DEFINITION

The parvovirus group includes several species-specific viruses of animals. One parvovirus, designated B19, is known to be a human pathogen. B19 is a small (diameter, 20 to 25 nm), icosahedral, nonenveloped, single-stranded DNA virus with an outer capsid formed by two structural proteins. Individual virus particles contain DNA strands of positive or negative polarity. The virus is stable and retains infectivity after incubation at 60°C for 16 h. It has failed to grow in conventional cell culture lines and animal model systems but does replicate in vitro in erythroid progenitor cells derived from human bone marrow, umbilical cord, peripheral blood, or fetal liver sources.

During the 1980s, it was discovered that B19 causes a variety of disorders ranging from erythema infectiosum and acute arthropathy in otherwise healthy hosts to transient aplastic crisis and chronic anemia in compromised patients to fetal infection manifested by death or hydrops fetalis. Many of the severe manifestations of B19 viremia relate to the propensity of the virus to infect and lyse erythroid precursor cells in the bone marrow. The name B19 is derived from the code number of the human serum in which the virus was discovered.

PATHOGENESIS

Two studies of adult volunteers have provided a basis for understanding the pathogenesis of B19 infection, which has two phases. The first phase is characterized by viremia that develops approximately 6 days after intranasal inoculation of B19 into susceptible individuals who lack serum antibodies to the virus. The viremia lasts about 1 week; its clearance is correlated with the development of IgM antibodies to B19, which remain detectable for up to a few months. IgG antibodies develop several days later and persist indefinitely. Nonspecific systemic symptoms lasting 2 or 3 days occur early during the viremic phase; these symptoms include headache, malaise, myalgia, fever, chills, and pruritus and are accompanied by reticulocytopenia and excretion of the virus from the respiratory tract. Several days after the onset of symptoms, a clinically insignificant decline in hemoglobin concentration is noted; the decreased level is maintained for 7 to 10 days, during which time examination of bone marrow samples reveals a marked depletion of erythroid precursor cells. Transient mild lymphopenia, neutropenia, and a drop in platelet count also may be found. A second phase of illness begins around 17 or 18 days after virus inoculation (after the clearance of viremia, the cessation of viral shedding in throat secretions, and the resolution of reticulocytopenia). This illness mimics erythema infectiosum in adults, with 2 or 3 days of fine maculopapular rash accompanied by arthralgias and arthritis that last another 1 or 2 days. This phase occurs in the presence of rising serum titers of antibody to B19.

The studies just described indicate that B19 disease in the otherwise *healthy host*, manifested by self-limited erythema infectiosum and/or arthropathy, is almost certainly an immune-complex disorder. This concept is supported by the induction of erythema infectiosum through the infusion of immunoglobulins into chronically viremic patients. In contrast, B19 disease in the *compromised host* (chronic hemolytic disease or immunodeficiency syndromes) is often serious, resulting from the destruction by B19 of

erythroid precursor cells. Normal hosts can tolerate 7 to 10 days of shutoff of erythropoiesis; however, patients with hemolytic disease who require increased production of erythrocytes do not tolerate erythroid cell destruction and thus usually develop severe transient aplastic crisis. Patients who are immunodeficient may fail to clear B19 viremia, the results being persistent infection of red blood cells and chronic severe anemia. The fetus requires a higher level of red cell production than do adults and has an immature immune system; both these factors could explain B19-induced hydrops fetalis.

B19 binds specifically to a cellular receptor, erythrocyte P antigen; this specific binding explains the tropism of B19 for erythroid progenitor cells, particularly pronormoblasts and normoblasts. The few persons who lack P antigen cannot be infected with B19.

EPIDEMIOLOGY

Although B19 infections occur year-round, they appear most commonly as outbreaks of erythema infectiosum in schools during winter and spring months. Between 20 and 60% of children in outbreaks are symptomatic, and many are asymptomatically infected. Seroepidemiologic studies indicate that approximately half of adults possess serum antibodies to B19. Antibody prevalence (reflecting prior exposure and probable immunity to the virus) rises rapidly between the ages of 5 and 18 years and continues to increase with age -- a pattern probably indicating ongoing exposure during adulthood. B19 can be detected in throat swabbings, respiratory tract secretions, and serum, and its detection at these sites probably correlates with infectiousness. Thus, patients with transient aplastic crisis are highly infectious. Their infectivity has been firmly documented as the source of one well-defined nosocomial outbreak of erythema infectiosum among nurses. In contrast, individuals with erythema infectiosum are much less infectious. The usual route of viral transmission under natural conditions is unknown but may be respiratory or through direct contact. B19 can be transmitted during therapy with clotting factor concentrate, even after exposure to detergent, steam, or dry heat.

CLINICAL MANIFESTATIONS

Erythema Infectiosum (Fig. 187-CD1) Erythema infectiosum is the most common manifestation of B19 infection and occurs predominantly in children. This entity is also called *fifth disease* because it was classified in the late nineteenth century as the fifth in a series of six exanthems of childhood. Normally a mild illness, erythema infectiosum typically presents as a facial rash with a "slapped-cheek" appearance that is sometimes preceded by low-grade fever. The rash may develop quickly on the arms and legs and usually has a lacy, reticular, erythematous appearance (Plate IID-40). The trunk, palms, and soles are less commonly involved. Occasionally, the rash appears with maculopapular, morbilliform, vesicular, purpuric, or pruritic characteristics. The typical rash resolves in about a week but can recur intermittently for several weeks, particularly after stress, exercise, exposure to sunlight, bathing, or change in environmental temperature. Arthralgia and arthritis are uncommon among children but are frequent among adults, in whom the rash is often absent or nonspecific, with a lack of the characteristic facial erythema.

Arthropathy B19 infection in adults most commonly presents as acute arthralgias and arthritis, sometimes accompanied by rash. The arthritis is characteristically symmetric and peripheral, involving the wrists, hands, and knees most frequently. It normally resolves in about 3 weeks and is nondestructive. However, a small percentage of patients have arthritis persisting for months or even (in rare cases) for years. It is not known whether these individuals have persistent infection or an abnormal immune response to the virus.

Transient Aplastic Crisis B19 infection is the cause in most instances of transient aplastic crisis developing suddenly in patients with chronic hemolytic disease. Nearly all hemolytic conditions can be affected by B19 infection, including sickle cell disease, erythrocyte enzyme deficiencies, hereditary spherocytosis, thalassemias, paroxysmal nocturnal hemoglobinuria, and autoimmune hemolysis. B19-induced aplastic crisis also can occur in the setting of acute blood loss. Patients present with weakness, lethargy, pallor, and severe anemia, a syndrome often preceded by a few days of nonspecific symptoms. These patients have intense reticulocytopenia lasting 7 to 10 days, and their bone marrow contains no erythroid precursor cells despite a normal myeloid series. Transient aplastic crisis can produce life-threatening anemia and may require urgent transfusion therapy. Unlike patients with erythema infectiosum or arthropathy, those with transient aplastic crisis are viremic and can readily transmit B19 infection to other people.

Chronic Anemia in Immunodeficient Patients Immunodeficient patients may be unable to eliminate B19 infection, probably because they cannot produce adequate levels of virus-specific IgG antibodies. The result is persistent infection with destruction of erythroid precursor cells in the bone marrow and chronic transfusion-dependent anemia. This condition has been described occasionally in patients with immunodeficiency related to infection with HIV, congenital immunodeficiencies, and acute lymphoblastic leukemia during maintenance chemotherapy as well as in recipients of bone marrow, heart, liver, and renal transplants. In addition, some cases of idiopathic pure red-cell aplasia probably are caused by persistent B19 infection. B19-induced chronic anemia may be the presenting finding of an otherwise unrecognized immunodeficiency. Chronic anemia may fluctuate in intensity over time and may be cured or controlled by immunoglobulin therapy. Both the spectrum of immunodeficiencies associated with B19-induced chronic anemia and the frequency of the association remain to be determined.

Fetal and Congenital Infection Maternal B19 infections usually do not adversely affect the fetus. More often than not, in fact, the fetus remains uninfected. Therefore, couples in which the pregnant woman is infected should be counseled as to the relatively low risk of fetal infection. It is estimated that fewer than 10% of maternal B19 infections in the first 20 weeks of pregnancy lead to fetal death; when fetal death does occur, it is usually attributable to the development of nonimmune hydrops fetalis, wherein the fetus succumbs to severe anemia and congestive heart failure. In these instances, B19 can be detected in fetal tissues, with predominant infection of erythroblasts. Pregnant women with known exposure to B19 should have their serum monitored for IgM antibodies to the virus and for elevated levels of a-fetoprotein and human chorionic gonadotropin; ultrasonic examinations of the fetus for hydrops should also be conducted. Some hydropic fetuses survive B19 infection and appear normal at delivery.

Rarely, fetal infection with hydrops results in congenital anemia and hypogammaglobulinemia that is unresponsive to immunoglobulin therapy.

Possible Clinical Associations Case studies suggest a link -- as yet inconclusive -- between B19 and several rheumatic diseases, most notably rheumatoid arthritis but also vasculitis (including polyarteritis, Wegener's granulomatosis, and giant cell arteritis), lupus erythematosus, dermatomyositis, and juvenile rheumatoid arthritis. Other unproven associations include those involving multiple systems: cardiac (myocarditis), hematologic (hemophagocytic syndrome, idiopathic thrombocytopenic purpura), hepatic (fulminant hepatitis), neurologic (meningoencephalitis), and respiratory (pneumonia).

DIAGNOSIS

Diagnosis most commonly relies on measurements of B19-specific IgM and IgG antibodies, which can be detected with commercially available immunoassay kits. The virus, its DNA, or its antigens are also detected in the serum or infected tissues of some patients. Acute infection can be proven by B19-compatible symptoms and the presence of IgM antibodies or virus itself, whereas past infection is documented by IgG antibodies. Individuals with erythema infectiosum and acute arthropathy usually have IgM antibodies without detectable virus in serum. Those with transient aplastic crisis may have IgM antibodies but typically possess high titers of virus and its DNA in serum; the bone marrow of these patients shows characteristic giant pronormoblasts and hypoplasia. Immunodeficient patients with anemia often lack readily detectable antibodies but have viral particles and DNA in serum. Fetal infection may be recognized by hydrops fetalis and the presence of B19 DNA in amniotic fluid or fetal blood in association with maternal IgM antibodies to B19.

TREATMENT

Erythema infectiosum usually requires no treatment; the same is true for many cases of arthropathy. More severe cases of arthritis, particularly those involving chronic symptoms, can be treated with nonsteroidal anti-inflammatory agents. Transient aplastic crisis is usually treated with erythrocyte transfusions. In immunodeficient anemic patients, B19 infection should be treated with commercial intravenous immunoglobulin, which is known to contain IgG antibodies to B19. This therapy controls and may cure B19 infection.

PROPHYLAXIS

Prophylaxis of B19 infection with immunoglobulin should be considered for patients with chronic hemolysis or immunodeficiency and for pregnant women. The risk of infection for these persons may be reduced by hand washing before eating or after contact with respiratory or other secretions when B19 is known to be present in a community. Patients with transient aplastic crisis or chronic B19 infection (but not those with erythema infectiosum or arthropathy) pose a serious risk for nosocomial transmission of infection. They should be hospitalized in a private room with contact and respiratory isolation precautions. It is not known whether pre- or postexposure administration of immunoglobulin prevents infection. No vaccine for B19 is currently available; however, a baculovirus-infected insect cell line that expresses noninfectious immunogenic B19

capsid proteins is being evaluated to determine an optimal regimen for use as a vaccine.

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188. HUMAN PAPILLOMAVIRUSES - *Richard C. Reichman*

DEFINITION

Human papillomaviruses (HPVs) selectively infect the epithelium of the skin and mucous membranes. These infections may be asymptomatic, produce warts, or be associated with a variety of benign and malignant neoplasias.

ETIOLOGIC AGENT

Papillomaviruses are members of the *Papillomavirus* genus of the family Papovaviridae. They are nonenveloped, measure 50 to 55 nm in diameter, have icosahedral capsids composed of 72 capsomeres, and contain a double-stranded circular DNA genome of about 7900 base pairs. The genomic organization of all papillomaviruses is similar and consists of an early (E) region, a late (L) region, and a noncoding upstream regulatory region. OncogenicHPVtypes can immortalize human keratinocytes, and this activity has been mapped to products of early genes E6 and E7. E6 protein facilitates the degradation of the p53 tumor suppressor protein, and E7 protein binds the retinoblastoma gene product and related proteins. The E1 and E2 proteins modulate viral DNA replication and regulate gene expression. The L1 gene codes for the major capsid protein, which makes up 80% of the virion mass. L2 codes for a minor capsid protein. Type-specific conformational antigenic determinants are located on the virion surface. Papillomavirus types are distinguished from one another by the degree of nucleic acid sequence homology. Distinct types share fewer than 90% of their DNA sequences in L1. More than 80 types of HPV are recognized, and individual types are associated with specific clinical manifestations (Table 188-1). HPVs are species-specific and have not been propagated in tissue culture or in common experimental animals. However, HPV types 1, 6, 11, 16, 40, and 83 have been produced in human tissues implanted in immunodeficient mice.

EPIDEMIOLOGY

There are few good studies of the incidence or prevalence of warts in well-defined human populations. Common warts (verruca vulgaris) are found in as many as 25% of some groups and are most prevalent among young children. Plantar warts (verruca plantaris) are also widely prevalent; they occur most often among adolescents and young adults. Condyloma acuminatum (anogenital warts) is one of the most common sexually transmitted diseases in the United States.HPVinfection of the uterine cervix produces the squamous cell abnormalities most frequently detected on Papanicolaou smears.

Most genitalHPVinfections are transmitted through direct contact with infectious lesions. Close personal contact is also assumed to play a role in the transmission of most cutaneous warts; the importance of fomites in this setting is not clear. Minor trauma at the site of inoculation may facilitate transmission. Recurrent respiratory papillomatosis in young children is an uncommon disease that is acquired from maternal genital tract infection; in adults, the disease may be transmitted through orogenital sexual contact.

HPVinfection has been strongly associated with the development of dysplasia and

cancer of the uterine cervix. More than 95% of cervical cancers contain DNA of oncogenic (high-risk) HPV types, such as 16, 18, and 31. HPV DNA is also present in the precursor lesions of cervical cancer, known as cervical intraepithelial neoplasias. Such lesions containing DNA of oncogenic HPV types are more likely to progress than those associated with low-risk types, such as 6 and 11. HPV DNA is transcribed in tumor tissues; many epidemiologic studies have confirmed a relation between HPV infection (with or without cofactors) and the development of cervical cancer, although most cervical HPV infections are self-limited. Infection with specific HPV types has also been associated with squamous cell carcinomas and dysplasias of the penis, anus, vagina, and vulva. In patients with epidermodysplasia verruciformis, squamous cell cancers develop frequently at sites infected with specific HPV types, including 5 and 8.

Serologic studies with virus-like particles as antigens have demonstrated type-specific antibodies in most patients withHPVgenital tract infections.

CLINICAL MANIFESTATIONS

The clinical manifestations of HPVinfection depend on the location of the lesions and the type of virus. Common warts (Fig. 128-CD6) usually occur on the hands as flesh-colored to brown, exophytic, hyperkeratotic papules. Plantar warts (Fig. 188-CD1) may be quite painful; they can be differentiated from calluses by paring of the surface to reveal thrombosed capillaries. Flat warts (verruca plana;Fig. 188-CD2) are most common among children and occur on the face, neck, chest, and flexor surfaces of the forearms and legs.

Anogenital warts develop on the skin and mucosal surfaces of the external genitalia and perianal areas (Plate IID-55). Among circumcised men, warts are most commonly found on the penile shaft. Lesions commonly occur at the urethral meatus and may extend proximally. Perianal warts are common among homosexual men but develop in heterosexual men as well. In women, warts appear first at the posterior introitus and adjacent labia. They then spread to other parts of the vulva and commonly involve the vagina and cervix. These lesions may be present without external warts. The differential diagnosis of anogenital warts includes condylomata lata of secondary syphilis, molluscum contagiosum, hirsutoid papillomatosis (pearly penile papules), fibroepitheliomas, and a variety of benign and malignant mucocutaneous neoplasms. Respiratory papillomatosis in young children may be life-threatening and presents as hoarseness, stridor, or respiratory distress. The disease in adults is usually milder.

Immunosuppressed patients, particularly those undergoing organ transplantation, often develop pityriasis versicolor-like lesions, from which DNA of severalHPVtypes has been extracted. Occasionally, such lesions appear to undergo malignant transformation. Patients infected with HIV frequently have severe clinical manifestations of HPV infection and appear to be at unusually high risk for cervical and anal malignancies. HPV disease in patients with HIV infection is difficult to treat and often recurs.

Epidermodysplasia verruciformis is a rare autosomal recessive disease characterized by the inability to controlHPVinfection. Patients are often infected with unusual HPV types and frequently develop cutaneous squamous cell malignancies, particularly in sun-exposed areas. The lesions resemble flat warts or macules similar to those of

pityriasis versicolor.

The complications of warts include itching and occasionally bleeding. In rare cases warts become secondarily infected with bacteria or fungi. Large masses of warts may cause mechanical problems, such as obstruction of the birth canal. Dysplasias of the uterine cervix are generally asymptomatic until frank carcinoma develops. Patients with anogenitalHPVdisease may develop serious psychological symptoms due to anxiety or depression over this condition.

PATHOGENESIS

The incubation period ofHPVdisease is usually 3 to 4 months, with a range of 1 month to 2 years. All types of squamous epithelium can be infected by HPV, and the gross and histologic appearances of individual lesions vary with the site of infection and the type of virus. The replication of HPV begins with the infection of basal cells. As cellular differentiation proceeds, HPV DNA replicates and is transcribed. Ultimately, virions are assembled in the nucleus and released when keratinocytes are shed. This process is associated with proliferation of all epidermal layers except the basal layer and produces acanthosis, parakeratosis, and hyperkeratosis. Koilocytes, large round cells with pyknotic nuclei, appear in the granular layer. Histologically normal epithelium may contain HPV DNA, and residual DNA after treatment can be associated with recurrent disease.

EpisomalHPV DNA is present in the nuclei of infected cells in benign lesions caused by the virus. However, in severe dysplasias and cancers, HPV DNA is generally integrated, with disruption of the E1/E2 open reading frames. This disruption leads to upregulation of E6 and E7 and subsequent interference with cellular tumor suppressor proteins.

Host defense responses toHPVinfection are incompletely understood, and immune correlates of protection from infection and resolution of disease have not been established. Because patients with defects in cell-mediated immune responses, including transplant recipients and patients with HIV infection, frequently develop severe HPV disease, such responses are probably important for the control of virus replication. Histologic studies demonstrating an epidermal lymphomonocytic infiltrate in resolving warts suggest that local immunity may be of particular importance in the resolution of disease. HPV infection can also elicit a serologic response, and antibodies to the viral capsid have been found in sera from patients with anogenital warts, cutaneous warts, and respiratory papillomatosis. Antibodies to E-region proteins, most notably E7, have been detected among patients with cervical carcinoma. Vaccine studies in animals have shown that production of neutralizing antibodies can be associated with protection from papillomavirus infection.

DIAGNOSIS

Most warts that are visible to the naked eye can be diagnosed correctly by history and physical examination alone. The use of a colposcope is invaluable in assessing vaginal and cervical lesions and is helpful in the diagnosis of oral and cutaneousHPVdisease as well. Papanicolaou smears prepared from cervical scrapings often show cytologic evidence of HPV infection. Persistent or atypical lesions should be biopsied and

examined by routine histologic methods. The most sensitive and specific methods of virologic diagnosis entail the use of techniques such as the polymerase chain reaction or the hybrid capture assay to detect HPV nucleic acids and to identify specific virus types. Serologic techniques to diagnose HPV infection are not helpful in individual cases and are not widely available.

TREATMENT

Decisions regarding the initiation of therapy should be made with the knowledge that currently available modes of treatment are not completely effective and some have significant side effects. In addition, treatment may be expensive, and manyHPVlesions resolve spontaneously. Frequently used therapies include cryosurgery, application of caustic agents, electrodesiccation, surgical excision, and ablation with a laser. Topical antimetabolites such as 5-fluorouracil also have been used. Both failure and recurrence have been well documented with all of these methods of treatment. Cryosurgery is the initial treatment of choice for condyloma acuminatum. Topically applied podophyllum preparations as well as podofilox may also be used. Various interferon preparations have been used with modest success in the treatment of respiratory papillomatosis and condyloma acuminatum. A topically applied interferon inducer, imiquimod, is also of benefit in the treatment of condyloma acuminatum. The diagnosis and management of anogenital dysplasias and of internal anogenital warts require special skills and resources, and patients with such lesions should be referred to a qualified specialist.

No effective methods for the prevention ofHPVinfections are available at present other than the avoidance of contact with infectious lesions. Barrier methods of contraception may be helpful in preventing the transmission of condyloma acuminatum and other HPV-associated diseases of the genital tract. Vaccines consisting of virus-like particles can prevent papillomavirus disease in some animal models and have been shown to induce neutralizing antibodies in phase 1 studies in humans. More extensive clinical trials of these preparations are under way.

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SECTION 13 -DNA AND RNA RESPIRATORY VIRUSES

189. COMMON VIRAL RESPIRATORY INFECTIONS - *Raphael Dolin*

GENERAL CONSIDERATIONS

Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses. The incidence of acute respiratory disease in the United States is from 3 to 5.6 cases per person per year. The rates are highest among children under 1 year old (6.1 to 8.3 cases per year) and remain high until age 6, when a progressive decrease begins. Adults have 3 to 4 cases per person per year. Morbidity from acute respiratory illnesses accounts for 30 to 50% of time lost from work by adults and for 60 to 80% of time lost from school by children. The use of antibacterial agents to treat viral respiratory infections represents a major source of abuse of that category of drugs.

It has been estimated that two-thirds to three-fourths of cases of acute respiratory illnesses are caused by viruses. More than 200 antigenically distinct viruses from 8 different genera have been reported to cause acute respiratory illness, and it is likely that additional agents will be described in the future. The vast majority of these viral infections involve the upper respiratory tract, but lower respiratory tract disease can also develop, particularly in younger age groups and in certain epidemiologic settings.

The illnesses caused by respiratory viruses traditionally have been divided into multiple distinct syndromes, such as the "common cold," pharyngitis, croup (laryngotracheobronchitis), tracheitis, bronchiolitis, bronchitis, and pneumonia. Each of these general categories of illnesses has a certain epidemiologic and clinical profile; for example, croup occurs exclusively in very young children and has a characteristic clinical course. Some types of respiratory illnesses are more likely to be associated with certain viruses (e.g., the common cold with rhinoviruses), while others occupy characteristic epidemiologic niches (e.g., adenovirus infections in military recruits). The syndromes most commonly associated with infections with the major respiratory virus groups are summarized in Table 189-1. Most respiratory viruses clearly have the potential to cause more than one type of respiratory illness, and frequently features of several types of illness are found in the same patient. Moreover, the clinical illnesses induced by these viruses are rarely sufficiently distinctive to permit an etiologic diagnosis on clinical grounds alone, although the epidemiologic setting increases the likelihood that one group of viruses rather than another is involved. In general, laboratory methods must be relied on to establish a specific viral diagnosis.

This chapter reviews viral infections caused by five of the major groups of respiratory viruses: rhinoviruses, coronaviruses, respiratory syncytial viruses, parainfluenza viruses, and adenoviruses. Influenza viruses, which are a major cause of mortality as well as morbidity, are reviewed inChap. 190. Herpesviruses, which occasionally cause pharyngitis and which also cause lower respiratory tract disease in immunosuppressed patients, are reviewed inChap. 182. Enteroviruses, which account for occasional respiratory illnesses during the summer months, are reviewed inChap. 193.

RHINOVIRUS INFECTIONS

ETIOLOGIC AGENT

Rhinoviruses are members of the Picornaviridae family, small (15 to 30 nm) nonenveloped viruses that contain a single-stranded RNA genome. In contrast to other members of the picornavirus family, such as enteroviruses, rhinoviruses are acid-labile and are almost completely inactivated at pH £3. Rhinoviruses grow preferentially at 33° to 34°C -- the temperature of the human nasal passages -- rather than at the higher temperature (37°C) of the lower respiratory tract. One hundred distinct serotypes and one subtype of rhinovirus are recognized.

EPIDEMIOLOGY

Rhinoviruses are a major cause of the common cold and have been isolated from 15 to 40% of adults with common cold-like illnesses. Overall rates of infection with rhinoviruses are higher among infants and young children and decrease with increasing age. Rhinovirus infections occur throughout the year, with seasonal peaks in early fall and spring in temperate climates. Rhinovirus infections are most often introduced into families by preschool or grade-school children younger than 6 years old. Between 25 and 70% of initial illnesses in family settings are followed by secondary cases, with the highest attack rates among the youngest siblings at home. Attack rates also increase with family size.

Rhinoviruses appear to spread through direct contact with infected secretions, usually respiratory droplets. In some studies of volunteers, transmission was most efficient by hand-to-hand contact, with subsequent self-inoculation of the conjunctival or nasal mucosa. In other studies, transmission by large- or small-particle aerosol was demonstrated. Virus also can be recovered from plastic surfaces inoculated 1 to 3 h previously; this observation suggests that environmental surfaces contribute to transmission. In studies of married couples in which neither partner had detectable serum antibody, transmission was associated with prolonged contact (122 h or more) during a 7-day period. Transmission was infrequent unless virus was recoverable from the donor's hands and nasal mucosa, at least 1000 $TCID_{50}$ of virus was present in nasal washes from the donor, and the donor was at least moderately symptomatic with the "cold." Despite anecdotal observations, exposure to cold temperatures, fatigue, or sleep deprivation has not been associated with increased rates of rhinovirus-induced illness in volunteers.

Infection with rhinoviruses is worldwide in distribution. By the time they reach adulthood, nearly all individuals have neutralizing antibodies to multiple serotypes, although the prevalence of antibody to any one serotype varies widely. Multiple serotypes circulate simultaneously, and generally no single serotype or group of serotypes has been more prevalent than the others.

PATHOGENESIS

Rhinoviruses infect cells through attachment to specific cellular receptors; most serotypes attach to intercellular adhesion molecule 1, while a few use low-density lipoprotein as the cellular receptor. Relatively limited information is available on the

histopathology and pathogenesis of acute rhinovirus infections in humans. Examination of biopsy specimens obtained during experimentally induced and naturally occurring illness indicates that the nasal mucosa is edematous, is often hyperemic, and -- during acute illness -- is covered by a mucoid discharge. There is a mild infiltrate with inflammatory cells, including neutrophils, lymphocytes, plasma cells, and eosinophils. Mucus-secreting glands in the submucosa appear hyperactive; the nasal turbinates are engorged, a condition that may lead to obstruction of nearby openings of sinus cavities. Several mediators, such as bradykinin, lysylbradykinin, prostaglandins, histamine, and interleukins 1, 6, and 8, have been linked to the development of signs and symptoms in rhinovirus-induced colds.

The incubation period for rhinovirus illness is short, generally 1 or 2 days. Virus shedding coincides with the onset of illness or may begin shortly before symptoms develop. The mechanisms of immunity to rhinovirus are not well worked out. In some studies, the presence of homotypic antibody has been associated with significantly reduced rates of subsequent infection and illness, but data conflict regarding the relative importance of serum and local antibody in protection from rhinovirus infection.

CLINICAL MANIFESTATIONS

The most common clinical manifestations of rhinovirus infections are those of the common cold. Illness usually begins with rhinorrhea and sneezing accompanied by nasal congestion. The throat is frequently sore, and in some cases sore throat is the initial complaint. Systemic signs and symptoms, such as malaise and headache, are mild or absent, and fever is unusual. Illness generally lasts for 4 to 9 days and resolves spontaneously without sequelae. In children, bronchitis, bronchiolitis, and bronchopneumonia have been reported; nevertheless, it appears that rhinoviruses are not major causes of lower respiratory tract disease in children. Rhinoviruses may cause exacerbations of asthma and chronic pulmonary disease in adults. The vast majority of rhinovirus infections resolve without sequelae, but complications related to obstruction of the eustachian tubes or sinus ostia, including otitis media or acute sinusitis, can develop.

DIAGNOSIS

Although rhinoviruses are the most frequently recognized cause of the common cold, similar illnesses are caused by a variety of other viruses, and the etiologic diagnosis cannot be made on clinical grounds alone. Rather, rhinovirus infection is diagnosed by isolation of the virus from nasal washes or nasal secretions in tissue culture. In practice, this procedure is rarely undertaken because of the benign, self-limited nature of the illness. Given the many serotypes of rhinovirus, diagnosis by serum antibody tests is currently impractical. Likewise, common laboratory tests, such as white cell count and sedimentation rate, are not helpful.

TREATMENT

Rhinovirus infections are generally mild and self-limited, so treatment is not usually necessary. Therapy in the form of antihistamines and nonsteroidal anti-inflammatory drugs may be beneficial in patients with particularly pronounced symptoms, and

reduction of activity is prudent in instances of significant discomfort or fatigability. Antibacterial agents should be used only if bacterial complications such as otitis media or sinusitis develop. Specific antiviral therapy is not available. Application of interferon sprays intranasally has been effective in the prophylaxis of rhinovirus infections but is also associated with local irritation of the nasal mucosa. Prevention of rhinovirus infection by antibodies directed against rhinovirus receptors or by the soluble purified receptors themselves is under study. Experimental vaccines to certain rhinovirus serotypes have been prepared, but their usefulness is questionable because of the myriad serotypes and the uncertainty about mechanisms of immunity. Thorough hand washing, environmental decontamination, and protection against autoinoculation may help to reduce rates of transmission of infection.

CORONAVIRUS INFECTIONS

ETIOLOGIC AGENT

Coronaviruses are pleomorphic, single-stranded RNA viruses that measure 80 to 160 nm in diameter. The name derives from the crownlike appearance produced by the club-shaped projections that stud the viral envelope. Coronaviruses that infect humans fall into two distinct antigenic groups (I and II), which are represented by prototype isolates 229E and OC43. Coronaviruses are fastidious and are difficult to culture in vitro. Some strains will grow only in human tracheal organ cultures rather than in tissue culture.

EPIDEMIOLOGY

Only limited seroepidemiologic studies of coronavirus infections have been conducted. Seroprevalence studies of strains 229E and OC43 have demonstrated the presence of serum antibodies at rates ranging from 12% to>80% in various populations. Overall, coronaviruses account for 10 to 20% of common colds. Coronavirus infections appear to be particularly prevalent in late fall, winter, and early spring -- times when rhinovirus infections are less common. A cyclical pattern has been suggested for outbreaks of infection with strains OC43 and 229E, with outbreaks occurring every 2 to 4 years.

CLINICAL MANIFESTATIONS

The clinical features of illness caused by coronaviruses are similar to those of illness caused by rhinoviruses. In studies of volunteers, the mean incubation period of illness induced by coronaviruses (3 days) is somewhat longer than that of illness caused by rhinoviruses, and the duration of illness is somewhat shorter (mean, 6 to 7 days). In some studies, the amount of nasal discharge was somewhat greater in colds induced by coronaviruses than in those induced by rhinoviruses. Coronaviruses have been recovered from infants with pneumonia and from military recruits with lower respiratory tract disease and have been associated with worsening of chronic bronchitis. However, the overall significance of coronaviruses in lower respiratory tract disease in humans remains unclear.

TREATMENT

The approach to the treatment of common colds caused by coronaviruses is similar to that discussed above for rhinovirus-induced illnesses. Because of uncertainty regarding the number and relative importance of coronavirus subgroups and the mechanisms of immunity, vaccines against coronaviruses have not been developed.

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

ETIOLOGIC AGENT

Respiratory syncytial virus (RSV) is a member of the Paramyxoviridae family and comprises the genus *Pneumovirus*. RSV, an enveloped virus approximately 150 to 300 nm in diameter, is so named because its replication in vitro leads to the fusion of neighboring cells into large multinucleated syncytia. The single-stranded RNA genome codes for 10 virus-specific proteins. Viral RNA is contained in a helical nucleocapsid surrounded by a lipid envelope bearing two glycoproteins: the G protein, by which the virus attaches to cells, and the F (fusion) protein, which facilitates entry of the virus into the cell by fusing host and viral membranes. RSV was once considered to be of a single antigenic type, but two distinct groups (A and B) and multiple subtypes within each group have now been described. Antigenic diversity is reflected by differences in the G protein, while the F protein is highly conserved. The epidemiologic significance of the antigenic diversity is under investigation. Both antigenic groups can circulate simultaneously in outbreaks, although the relative proportions of each vary.

EPIDEMIOLOGY

RSVis the major respiratory pathogen of young children and the foremost cause of lower respiratory disease in infants. Infection with RSV is seen throughout the world in annual epidemics that occur in late fall, winter, or spring and last up to 5 months. The virus is rarely encountered during the summer. Rates of illness are highest among infants between 1 and 6 months of age, peaking between 2 and 3 months of age. The attack rates among susceptible infants and children are extraordinarily high, approaching 100% in settings such as day-care centers where large numbers of susceptible infants are present. RSV accounts for 20 to 25% of hospital admissions of young infants and children for pneumonia and for up to 75% of cases of bronchiolitis in this age group. It has been estimated that more than half of infants who are at risk will become infected during an RSV epidemic.

In older children and adults, reinfection withRSV is frequent but disease is milder than in infancy. A common cold-like syndrome is the illness most commonly associated with RSV infection in adults. Severe lower respiratory tract disease with pneumonitis can occur in elderly (often institutionalized) adults and in patients with immunocompromising disorders or treatment, including recipients of bone-marrow and solid-organ transplants. RSV is also an important nosocomial pathogen; during an outbreak, it can infect pediatric patients and up to 25 to 50% of the staff on pediatric wards. The spread of virus among families is efficient: up to 40% of siblings may become infected when RSV is introduced into the family setting.

RSVis transmitted primarily by close contact with contaminated fingers or fomites and by self-inoculation of the conjunctiva or anterior nares. Virus also may be spread by

coarse aerosols produced by coughing or sneezing, but it is inefficiently spread by fine-particle aerosols. The incubation period is ~4 to 6 days, and virus shedding may last for ³2 weeks in children and for shorter periods in adults.

PATHOGENESIS

Little is known about the histopathology of minorRSVinfection. Severe bronchiolitis or pneumonia is characterized by necrosis of the bronchiolar epithelium and a peribronchiolar infiltrate of lymphocytes and mononuclear cells. Interalveolar thickening and filling of alveolar spaces with fluid can also be found. The characteristics of the immune response to RSV are not well elucidated. Because reinfection occurs frequently and is often associated with illness, the immunity that develops after single episodes of infection clearly is not complete or long-lasting. However, the cumulative effect of multiple reinfections is to temper subsequent disease and to provide some temporary measure of protection against infection. Studies of experimentally induced disease in healthy volunteers indicate that the presence of nasal IgA neutralizing antibody correlates more closely with protection than does the presence of serum antibody. Studies in infants, however, suggest that maternally acquired antibody provides some protection from lower respiratory tract disease, although illness can be severe even in infants who have moderate levels of maternally derived serum antibody. The relatively severe disease observed in immunosuppressed patients and experimental animal models indicates that cell-mediated immunity is an important mechanism of host defense against RSV. Evidence suggests that class I MHC-restricted cytotoxic T cells may be particularly important in this regard.

CLINICAL MANIFESTATIONS

RSVinfection leads to a wide spectrum of respiratory illnesses. In infants, 25 to 40% of infections result in lower respiratory tract involvement, including pneumonia, bronchiolitis, and tracheobronchitis. In this age group, illness begins most frequently with rhinorrhea, low-grade fever, and mild systemic symptoms, often accompanied by cough and wheezing. Most patients recover gradually over 1 to 2 weeks. In more severe illness, tachypnea and dyspnea develop, and eventually frank hypoxia, cyanosis, and apnea can ensue. Physical examination may reveal diffuse wheezing, rhonchi, and rales. Chest radiography shows hyperexpansion, peribronchial thickening, and variable infiltrates ranging from diffuse interstitial infiltrates to segmental or lobar consolidation. Illness may be particularly severe in children born prematurely and in those with congenital cardiac disease, bronchopulmonary dysplasia, nephrotic syndrome, or immunosuppression. One study documented a 37% mortality rate for infants with RSV pneumonia and congenital cardiac disease.

In adults, the most common symptoms ofRSVinfection are those of the common cold, with rhinorrhea, sore throat, and cough. Illness is occasionally associated with moderate systemic symptoms such as malaise, headache, and fever. RSV also has been reported to cause lower respiratory tract disease with fever in adults, including severe pneumonia in the elderly. RSV pneumonia can be a significant cause of morbidity and mortality in patients (particularly children) undergoing bone-marrow and solid-organ transplantation.

LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis ofRSVinfection can be suspected on the basis of a suggestive epidemiologic setting -- that is, severe illness among infants during an outbreak of RSV in the community. Infections in older children and adults cannot be differentiated with certainty from those caused by other respiratory viruses. The specific diagnosis is established by isolation of RSV from respiratory secretions, including sputum, throat swabs, or nasopharyngeal washes. Virus is detected in tissue culture and is identified specifically through immunologic reactions detected by immunofluorescence, enzyme-linked immunosorbent assay (ELISA), or other techniques. Immunofluorescence microscopy of nasal scrapings or washings provides a rapid diagnosis. Serologic tests that depend on fourfold or greater rises in complement-fixing or neutralizing antibody titers are useful for diagnosis in older children and adults but are less sensitive in children under 4 months of age. ELISA is more sensitive than complement-fixation or neutralization tests in the detection of serum antibody. Serologic diagnosis requires comparison of acute- and convalescent-phase serum specimens and is therefore not useful during acute illness.

TREATMENT

Treatment of upper respiratory tractRSVinfection is aimed primarily at the alleviation of symptoms and is similar to that for other viral infections of the upper respiratory tract. For lower respiratory tract infections, respiratory therapy, including hydration, suctioning of secretions, and administration of humidified oxygen and antibronchospastic agents, is given as needed. In severe hypoxia, intubation and ventilatory assistance may be required. Studies of infants with RSV infection who were given aerosolized ribavirin, a nucleoside analogue active in vitro against RSV, have demonstrated a beneficial effect on the resolution of lower respiratory tract illness, including alleviation of blood-gas abnormalities. Treatment with ribavirin is recommended for infants who are severely ill or who are at high risk for complications of RSV infection; included are premature infants and those with bronchopulmonary dysplasia, congenital heart disease, or immunosuppression. The effects of ribavirin in adults with RSV pneumonia have not been established. The monthly administration of human immunoglobulin with high titers of antibody to RSV (RSVIG) or of a chimeric mouse-human IgG antibody to RSV (palivizumab) has been approved as prophylaxis against RSV for children younger than 2 years of age who have bronchopulmonary dysplasia or were born prematurely.

Considerable interest exists in the development of vaccines againstRSV. Inactivated whole-virus vaccines have been ineffective; in one study, they actually potentiated the disease in infants. Other approaches include immunization with purified F and G surface glycoproteins of RSV or generation of stable, live attenuated virus vaccines. In settings such as pediatric wards where rates of transmission are high, barrier methods for the protection of hands and conjunctivae may be useful in reducing the spread of virus.

PARAINFLUENZA VIRUS INFECTIONS

ETIOLOGIC AGENT

Parainfluenza viruses belong to the Paramyxoviridae family, are 150 to 250 nm in diameter, are enveloped, and contain a single-stranded RNA genome. The envelope is

studded with two glycoproteins: one possesses both hemagglutinin and neuraminidase activity and the other contains fusion activity. The viral RNA genome is enclosed in a helical nucleocapsid and codes for seven or eight virus-specific proteins. All four distinct serotypes of parainfluenza viruses share certain antigens with other members of the Paramyxoviridae family, including mumps and Newcastle disease viruses.

EPIDEMIOLOGY

Parainfluenza viruses are distributed throughout the world; infection with type 4 (subtypes 4A and 4B) has been reported less widely, probably because type 4 is more difficult to grow in tissue culture. Infection is acquired in early childhood, so that by 8 years of age most children have antibodies to serotypes 1, 2, and 3. Types 1 and 2 cause epidemics during the fall, primarily in odd-numbered years. Type 3 infection has been detected during all seasons of the year, but epidemics have occurred annually in the spring.

The contribution of parainfluenza infections to respiratory disease varies with both the location and the year. In studies conducted in the United States, parainfluenza virus infections have accounted for 4.3 to 22% of respiratory illnesses in children. In adults, parainfluenza infections are generally mild and account for fewer than 5% of respiratory illnesses. The major importance of parainfluenza viruses is as a cause of respiratory illness in young children, in whom they rank second only toRSV as causes of lower respiratory tract illness. Parainfluenza virus type 1 is the most frequent cause of croup (laryngotracheobronchitis) in children, while serotype 2 causes similar, although generally less severe, disease. Type 3 is an important cause of bronchiolitis and pneumonia in infants, while illnesses associated with type 4 have generally been mild. Unlike types 1 and 2, type 3 frequently causes illness during the first month of life, when passively acquired maternal antibody is still present. Parainfluenza viruses are spread through infected respiratory secretions, primarily by person-to-person contact and/or by large droplets. The incubation period has varied from 3 to 6 days in experimental infections but may be somewhat shorter for naturally occurring disease in children.

PATHOGENESIS

Immunity to parainfluenza viruses is incompletely understood, but evidence suggests that immunity to infections with serotypes 1 and 2 is mediated by local IgA antibodies in the respiratory tract. Passively acquired serum neutralizing antibodies also confer some protection against infection with types 1, 2, and -- to a lesser degree -- 3. Studies in experimental animal models and in immunosuppressed patients suggest that cell-mediated immunity may also be important in parainfluenza virus infections.

CLINICAL MANIFESTATIONS

Parainfluenza virus infections occur most frequently among children, in whom initial infection with serotype 1, 2, or 3 is associated with an acute febrile illness 50 to 80% of the time. Children may present with coryza, sore throat, hoarseness, and cough that may or may not be croupy. In severe croup, fever persists, with worsening coryza and sore throat. A brassy or barking cough may progress to frank stridor. Most children recover over the next 1 or 2 days, although progressive airway obstruction and hypoxia

ensue occasionally. If bronchiolitis or pneumonia develops, progressive cough accompanied by wheezing, tachypnea, and intercostal retractions may occur. In this setting, sputum production increases modestly. Physical examination shows nasopharyngeal discharge and oropharyngeal injection, along with rhonchi, wheezes, or coarse breath sounds. Chest x-rays can show air trapping and occasionally interstitial infiltrates.

In older children and adults, parainfluenza infections tend to be milder, presenting most frequently as a common cold or as hoarseness, with or without cough. Lower respiratory tract involvement in older children and adults is uncommon, but tracheobronchitis in adults has been reported. Severe, prolonged, and even fatal parainfluenza infection has been reported in children and adults with severe immunosuppression, including bone-marrow and solid-organ transplant recipients.

LABORATORY FINDINGS AND DIAGNOSIS

The clinical syndromes caused by parainfluenza viruses (with the possible exception of croup in young children) are not sufficiently distinctive to be diagnosed on clinical grounds alone. A specific diagnosis is established by detection of virus in respiratory tract secretions, throat swabs, or nasopharyngeal washings. Virus is detected by growth in tissue culture (either by hemagglutination or by a cytopathic effect), by immunofluorescence of viral antigens in exfoliated cells from the respiratory tract, or by ELISA. Polymerase chain reaction assays have also been developed. Serologic diagnosis is based on a fourfold or greater rise in antibody titer, as detected by hemagglutination inhibition or by complement-fixation or neutralization tests in acute- and convalescent-phase specimens. However, as frequent heterotypic responses occur among the parainfluenza serotypes, the serotype causing illness often cannot be identified by serologic techniques alone.

Acute epiglottitis caused by *Haemophilus influenzae* type b must be differentiated from viral croup. Influenza A virus also is a common cause of croup during epidemic periods.

TREATMENT

For upper respiratory tract illness, symptoms can be treated as discussed for other viral respiratory tract illnesses. If complications such as sinusitis, otitis, or superimposed bacterial bronchitis develop, appropriate antibiotics should be administered. Mild cases of croup should be treated with bed rest and moist air generated by vaporizers. More severe cases require hospitalization and close observation for the development of respiratory distress. If acute respiratory distress develops, humidified oxygen and intermittent racemic epinephrine are usually administered. Aerosolized or systemically administered glucocorticoids are beneficial; the latter have a more profound effect. No specific antiviral therapy is available, although ribavirin is active against parainfluenza viruses in vitro and anecdotal reports describe its use clinically. Effective vaccines against parainfluenza viruses have not been developed.

ADENOVIRUS INFECTIONS

ETIOLOGIC AGENT

Adenoviruses are complex DNA viruses that measure 70 to 80 nm in diameter. Human adenoviruses belong to the genus *Mastadenovirus*, which includes at least 47 serotypes. Adenoviruses have a characteristic morphology consisting of an icosahedral shell composed of 20 equilateral triangular faces and 12 vertices. The protein coat (capsid) consists of hexon subunits with group-specific and type-specific antigenic determinants and penton subunits at each vertex primarily containing group-specific antigens. A fiber with a knob at the end projects from each penton; this fiber contains type-specific and some group-specific antigens. Human adenoviruses have been divided into six subgenera (A through F) on the basis of the homology of DNA genomes and other properties. The adenovirus genome is a linear double-stranded DNA that codes for structural and nonstructural polypeptides. The replicative cycle of adenovirus may result either in lytic infection of cells or in the establishment of a latent infection (primarily involving lymphoid cells). Some adenovirus types can induce oncogenic transformation, and tumor formation has been observed in rodents; however, despite intensive investigation, adenoviruses have not been associated with tumors in humans.

EPIDEMIOLOGY

Adenovirus infections most frequently affect infants and children. Infections occur throughout the year but are most common from fall to spring. Adenoviruses account for 3 to 5% of acute respiratory infections in children but for fewer than 2% of respiratory illnesses in civilian adults. Nearly 100% of adults have serum antibody to multiple serotypes -- a finding indicating that infection is common in childhood. Types 1, 2, 3, and 5 are the most frequent isolates from children. Certain adenovirus serotypes -- particularly 4 and 7 but also 3, 14, and 21 -- are associated with outbreaks of acute respiratory disease in military recruits in winter and spring. Adenovirus infection can be transmitted by inhalation of aerosolized virus, by inoculation of virus into conjunctival sacs, and probably by the fecal-oral route as well. Type-specific antibody generally develops after infection and is associated with protection against infection with the same serotype.

CLINICAL MANIFESTATIONS

In children, adenoviruses cause a variety of clinical syndromes. The most common is an acute upper respiratory tract infection, with prominent rhinitis. On occasion, lower respiratory tract disease, including bronchiolitis and pneumonia, also develops. Adenoviruses, particularly types 3 and 7, cause pharyngoconjunctival fever, a characteristic acute febrile illness of children that occurs in outbreaks, most often in summer camps. The syndrome is marked by bilateral conjunctivitis in which the bulbar and palpebral conjunctivae have a granular appearance. Low-grade fever is frequently present for the first 3 to 5 days, and rhinitis, sore throat, and cervical adenopathy develop. The illness generally lasts for 1 to 2 weeks and resolves spontaneously. Febrile pharyngitis without conjunctivitis also has been associated with adenovirus infection. Adenoviruses have been isolated from cases of whooping cough with or without *Bordetella pertussis;* the significance of adenovirus in that disease is unknown.

In adults, the most frequently reported illness has been acute respiratory disease caused by adenovirus types 4 and 7 in military recruits. This illness is marked by a

prominent sore throat and the gradual onset of fever, which often reaches 39°C (102.2°F) on the second or third day of illness. Cough is almost always present, and coryza and regional lymphadenopathy are frequently seen. Physical examination may show pharyngeal edema, injection, and tonsillar enlargement with little or no exudate. If pneumonia has developed, auscultation and x-ray of the chest may indicate areas of patchy infiltration.

Adenoviruses have been associated with a number of non-respiratory tract diseases, including acute diarrheal illness caused by types 40 and 41 in young children and hemorrhagic cystitis caused by types 11 and 21. Epidemic keratoconjunctivitis, caused most frequently by types 8, 19, and 37, has been associated with contaminated common sources such as ophthalmic solutions and roller towels. Adenoviruses also have been implicated in disseminated disease and pneumonia in immunosuppressed patients, including recipients of solid-organ or bone-marrow transplants and patients with AIDS. In the latter group, high-numbered and intermediate serotypes have been isolated, usually in the setting of low CD4+ counts, but their isolation frequently has not been clearly linked to disease manifestations. Adenovirus nucleic acids have been detected in myocardial cells from patients with "idiopathic" myocardiopathies, and adenoviruses have been suggested as causative agents in some cases.

LABORATORY FINDINGS AND DIAGNOSIS

Adenovirus infection should be suspected in the epidemiologic setting of acute respiratory disease in military recruits and in certain of the clinical syndromes (such as pharyngoconjunctival fever or epidemic keratoconjunctivitis) in which outbreaks of characteristic illnesses occur. In most cases, however, illnesses caused by adenovirus infection cannot be differentiated from those caused by a number of other viral respiratory agents and *Mycoplasma pneumoniae*. A definitive diagnosis of adenovirus infection is established by culture or detection of the virus by means of ELISA or nucleic acid hybridization from sites such as the conjunctiva and oropharynx or from sputum, urine, or stool. Virus may be detected in tissue culture by cytopathic changes and specifically identified by immunofluorescence or other immunologic techniques. Adenovirus types 40 and 41, which have been associated with diarrheal disease in children, require special tissue-culture cells for isolation, and these serotypes are most commonly detected by direct ELISA of stool. Serum antibody rises can be demonstrated by complement-fixation or neutralization tests, ELISA, radioimmunoassay, or (for those adenoviruses that hemagglutinate red cells) hemagglutination inhibition tests.

TREATMENT

Only symptom-based treatment and supportive therapy are available for adenovirus infections, and no clinically useful antiviral compounds have been identified. Live vaccines have been developed against adenovirus types 4 and 7 and have been used to control illness in military recruits. These vaccines consist of live, unattenuated virus administered in enteric-coated capsules. Infection of the gastrointestinal tract with types 4 and 7 does not cause disease but stimulates local and systemic antibodies that are protective against subsequent acute respiratory disease due to those serotypes. Vaccines prepared from purified subunits of adenovirus are being investigated. Adenoviruses are also being studied as live-virus vectors for the delivery of vaccine

antigens and for gene therapy.

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190. INFLUENZA - *Raphael Dolin*

DEFINITION

Influenza is an acute respiratory illness caused by infection with influenza viruses. The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness. Outbreaks of illness of variable extent and severity occur nearly every winter. Such outbreaks result in significant morbidity in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.

ETIOLOGIC AGENT

Influenza viruses are members of the Orthomyxoviridae family. Influenza A and B viruses constitute one genus, and influenza C viruses make up the other. The designation of influenza viruses as type A, B, or C is based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens. Influenza A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (H) and neuraminidase (N) antigens (see below); individual strains are designated according to the site of origin, isolate number, year of isolation, and subtype -- for example, influenza A/Sydney/5/97 (H3N2). Influenza B and C viruses are similarly designated, but H and N antigens from these viruses do not receive subtype designations, since intratypic variations in influenza B antigens are less extensive than those in influenza A viruses and may not occur with influenza C virus.

Most of the information on the molecular biology of influenza viruses has come from studies of influenza A viruses; less is known about the replicative cycle of influenza B and C viruses. Morphologically, influenza viruses A, B, and C are similar. The virions are irregularly shaped spherical particles, 80 to 120 nm in diameter, and have a lipid envelope from the surface of which the H and N glycoproteins project (Fig. 190-1). The hemagglutinin is the site by which virus binds to cell receptors, whereas the neuraminidase degrades the receptor and probably plays a role in the release of virus from infected cells after replication has taken place. Influenza viruses enter cells by receptor-mediated endocytosis, forming a virus-containing endosome. The viral hemagglutinin mediates fusion of the endosomal membrane with the virus envelope, and viral nucleocapsids are subsequently released into the cytoplasm. Antibodies to the H antigen are the major determinants of immunity to influenza virus, while those to the N antigen limit viral spread and contribute to reduction of the infection. The inner surface of the lipid envelope contains the M proteins M1 and M2, the functions of which are incompletely understood but which may be involved in virus assembly and in stabilization of the lipid envelope. The virion also contains theNPantigen, which is associated with the viral genome, as well as three polymerase (P) proteins that are essential for transcription and synthesis of viral RNA. Two nonstructural (NS) proteins of unknown function are also present in infected cells.

The genomes of influenza A and B viruses consist of eight single-stranded RNA segments, which code for the structural and nonstructural proteins. Because the genome is segmented, the opportunity for reassortment of genes during infection is

high, and reassortment occurs frequently during infection of cells with more than one influenza A virus.

EPIDEMIOLOGY

Influenza outbreaks are recorded virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals, usually every 1 to 3 years. Except for the past two decades, global epidemics or pandemics have occurred approximately every 10 to 15 years since the 1918-1919 pandemic (Table 190-1).

The most extensive and severe outbreaks are caused by influenza A viruses. In part, this predominance is a result of the remarkable propensity of the H and N antigens of influenza A virus to undergo periodic antigenic variation. Major antigenic variations are referred to as *antigenic shifts*, which may be associated with pandemics and are restricted to influenza A viruses. Minor variations are called *antigenic drifts*. These antigenic changes may involve the hemagglutinin alone or both the hemagglutinin and the neuraminidase. In human infections, three major antigenic subtypes of hemagglutinins (H1, H2, and H3) and two of neuraminidases (N1 and N2) have been recognized. The hemagglutinins formerly designated as H0 and Hsw are now classified as variants of H1. An example of an antigenic shift involving both the hemagglutinin and the neuraminidase is that of 1957, when the predominant influenza A virus subtype shifted from H1N1 to H2N2; this shift resulted in a severe pandemic, with an estimated 70,000 excess deaths (i.e., deaths in excess of the number expected without an influenza epidemic) in the United States alone. In 1968, an antigenic shift involving only the hemagglutinin occurred (H2N2 to H3N2); the subsequent pandemic was less severe than that of 1957. In 1977, an H1N1 virus emerged and caused a pandemic that primarily affected younger individuals (i.e., those born after 1957). As can be seen in Table 190-1, H1N1 viruses circulated from 1918 to 1956; thus, individuals born prior to 1957 would be expected to have some degree of immunity to H1N1 viruses. During most outbreaks of influenza A, a single subtype has circulated at a time. However, since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity. In some outbreaks, influenza B viruses have also circulated simultaneously with influenza A viruses.

The origin of pandemic strains is unknown. Given the marked differences between the primary structures of the hemagglutinins of different subtypes of influenza A viruses (H1, H2, and H3), it seems unlikely that antigenic shifts result from spontaneous mutations in the hemagglutinin gene. Because the segmented genome of influenza viruses may result in high rates of reassortment, it has been suggested that pandemic strains may emerge by reassortment of genes between human and animal viruses. There was concern that such reassortment might have occurred in 1997 in Hong Kong, where cases of infection caused by influenza virus A/H5N1 were detected in humans during an extensive outbreak of avian influenza A/H5N1 in poultry. However, only a few cases of A/H5N1 influenza in humans were documented, and the infection did not spread into the community. Influenza B viruses do not have an animal reservoir and do not undergo antigenic shifts, although they do undergo antigenic drift.

Pandemics provide the most dramatic evidence of the impact of influenza. However, illnesses that occur between pandemics account for greater total mortality and

morbidity, albeit over a longer period. From 1972 through the present, influenza has been associated with at least 20,000 excess deaths during more than half of the interpandemic epidemics in the United States; more than 40,000 influenza-associated deaths occurred in each of three of these epidemics. Influenza A viruses that circulate between pandemics demonstrate antigenic drifts in the H antigen. These antigenic drifts apparently result from point mutations involving the RNA segment that codes for the hemagglutinin. Epidemiologically significant strains -- that is, those with the potential to cause widespread outbreaks -- exhibit changes in amino acids in at least two of the major antigenic sites in the hemagglutinin molecule. Since two point mutations are unlikely to occur simultaneously, it is believed that antigenic drifts result from point mutations occurring sequentially during the spread of virus from person to person. Antigenic drifts have been reported nearly annually since 1977 for H1N1 viruses and since 1968 for H3N2 viruses.

Influenza A epidemics begin abruptly, peak over a 2- to 3-week period, generally last for 2 to 3 months, and often subside almost as rapidly as they began. The first indication of influenza activity in a community is an increase in the number of children with febrile respiratory illnesses who present for medical attention. This increase is followed by increases in rates of influenza-like illnesses among adults and eventually by an increase in hospital admissions for patients with pneumonia, worsening of congestive heart failure, and exacerbations of chronic pulmonary disease. Rates of absence from work and school also rise at this time. An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Attack rates have been highly variable from outbreak to outbreak but most commonly are in the range of 10 to 20% of the general population. During the pandemic of 1957, it was estimated that the attack rate of clinical influenza exceeded 50% in urban populations and that an additional 25% or more of individuals in these populations may have been subclinically infected with influenza A virus. Among institutionalized populations and in semiclosed settings with a large number of susceptible individuals, even higher attack rates have been reported.

Epidemics of influenza occur almost exclusively during the winter months in the temperate zones of the northern and southern hemispheres. In those locations, it is highly unusual to detect influenza A virus at other times, although serologic rises or even outbreaks have been noted rarely during warm-weather months. In contrast, influenza virus infections occur throughout the year in the tropics. Where or how influenza A virus persists between outbreaks in temperate zones is unknown. It is possible that influenza A viruses are maintained in the human population on a worldwide basis by person-to-person transmission and that large population clusters support a low level of interepidemic transmission. Alternatively, human strains may persist in animal reservoirs. Convincing evidence to support either explanation is not available. In the modern era, rapid transportation may contribute to the transmission of viruses among widespread geographic locales.

The factors that result in the inception and termination of outbreaks of influenza are incompletely understood. A major determinant of the extent and severity of an outbreak is the level of immunity in the population at risk. With the emergence of an antigenically novel influenza virus to which little or no antibody is present in a community, extensive outbreaks may occur. When the absence of antibody is worldwide, epidemic disease

may spread around the globe, resulting in a pandemic. Such pandemic waves can continue for several years, until immunity in the population reaches a high level. In the years following pandemic influenza, antigenic drifts among influenza viruses result in outbreaks of variable severity in populations with high levels of immunity to the pandemic strain that circulated earlier. This situation persists until another antigenically novel pandemic strain emerges. On the other hand, outbreaks sometimes end despite the persistence of a large pool of susceptible individuals in the population.

Occasionally, the emergence of a significantly different antigenic variant will result only in a localized outbreak. The swine influenza outbreak of 1976 in the United States, caused by an A/H1N1 virus antigenically similar to the virus that circulated in 1918-1919, may be an example, although this outbreak may have represented simply the introduction of a swine influenza virus into a crowded human population without spread beyond that setting. The cluster of human infections with influenza A/H5N1 in Hong Kong in 1997 may also be an example of this phenomenon. It has been suggested that certain viruses, such as recently circulating A/H1N1 strains, may be intrinsically less virulent and cause less severe disease than other variants, even in immunologically virgin subjects. If so, then other (undefined) factors besides the level of preexisting immunity must play a role in the epidemiology of influenza.

Influenza B virus causes outbreaks that are generally less extensive and are associated with less severe disease than those caused by influenza A virus. The hemagglutinin and neuraminidase of influenza B virus undergo less frequent and less extensive variation than those of influenza A viruses; this characteristic may account, in part, for the lesser extent of disease. Influenza B outbreaks are seen most frequently in schools and military camps, although outbreaks in institutions in which elderly individuals reside have also been noted on occasion. The most serious complication of influenza B virus infection is Reye's syndrome (Chap. 300). Influenza C virus has only infrequently been associated with human disease, although the wide prevalence of serum antibody to this virus indicates that asymptomatic infection may be common.

The morbidity and mortality caused by influenza outbreaks continue to be substantial. Most individuals who die in this setting have underlying diseases that place them at high risk for complications of influenza. Excess hospitalizations for adults with high-risk medical conditions have ranged from 20 to 1000 per 100,000 during recent outbreaks of influenza. The most prominent high-risk conditions are chronic cardiac and pulmonary diseases as well as old age. Mortality among individuals with chronic metabolic, renal, and certain immunosuppressive diseases has also been elevated, although lower than that among patients with chronic cardiopulmonary diseases. The morbidity attributable to influenza in the general population is considerable. For each of three outbreaks in the United States that were studied during the 1960s, estimated direct and indirect economic costs ranged from $1.5 to $3.5 billion; today such costs would obviously be much greater.

PATHOGENESIS

The initial event in influenza is infection of the respiratory epithelium with influenza virus acquired from respiratory secretions of acutely infected individuals. In all likelihood, transmission occurs via aerosols generated by coughs and sneezes, although

hand-to-hand contact, other personal contact, and even fomite transmission may take place. Experimental evidence suggests that infection by a small-particle aerosol (particle diameter,<10 um) is more efficient than that by larger droplets. Initially, viral infection involves the ciliated columnar epithelial cells, but it also may involve other respiratory tract cells, including alveolar cells, mucous gland cells, and macrophages. In infected cells, virus replicates within 4 to 6 h, after which infectious virus is released to infect adjacent or nearby cells. In this way, infection spreads from a few foci to a large number of respiratory cells over several hours. In experimentally induced infection, the incubation period of illness has ranged from 18 to 72 h, depending on the size of the virus inoculum. Histopathologic study reveals degenerative changes, including granulation, vacuolization, swelling, and pyknotic nuclei, in infected ciliated cells. The cells eventually become necrotic and desquamate; in some areas, previously columnar epithelium is replaced by flattened and metaplastic epithelial cells. The severity of illness is correlated with the quantity of virus shed in secretions; thus, the degree of viral replication itself may be an important factor in pathogenesis. Despite the frequent development of systemic signs and symptoms such as fever, headache, and myalgias, influenza virus has only rarely been detected in extrapulmonary sites (including the bloodstream). Evidence suggests that the pathogenesis of systemic symptoms in influenza may be related to the induction of certain cytokines, particularly tumor necrosis factor a and interleukin 6.

The host response to influenza infections involves a complex interplay of humoral antibody, local antibody, cell-mediated immunity, interferon, and other host defenses. Serum antibody responses, which can be detected by the second week after primary infection, are measured by a variety of techniques: hemagglutination inhibition (HI), complement fixation (CF), neutralization, enzyme-linked immunosorbent assay (ELISA), and antineuraminidase antibody assay. Antibodies directed against the hemagglutinin appear to be the most important mediators of immunity; in several studies, HI titers of $^{3}40$ have been associated with protection from infection. Secretory antibodies produced in the respiratory tract are predominantly of the IgA class and also play a major role in protection against infection. Secretory antibody neutralization titers of$^{3}4$ have also been associated with protection. A variety of cell-mediated immune responses, both antigen-specific and antigen-nonspecific, can be detected early after infection and depend on the prior immune status of the host. These responses include T-cell proliferative, T-cell cytotoxic, and natural killer cell activity. Interferons have been detected in respiratory secretions shortly after the shedding of virus has begun, and rises in interferon titers coincide with decreases in virus shedding.

The host defense factors responsible for cessation of virus shedding and resolution of illness have not been defined specifically. Virus shedding generally stops within 2 to 5 days after symptoms first appear, at a time when serum and local antibody responses often are not detectable by conventional techniques (although antibody rises may be detected earlier by use of highly sensitive techniques, particularly in individuals with previous immunity to the virus). It has been suggested that interferon, cell-mediated immune responses, and/or nonspecific inflammatory responses are important in the resolution of illness.

MANIFESTATIONS

Influenza has most frequently been described as an illness characterized by the abrupt onset of systemic symptoms, such as headache, feverishness, chills, myalgia, or malaise, and accompanying respiratory tract signs, particularly cough and sore throat. In many cases, the onset is so abrupt that patients can recall the precise time they became ill. A typical case of naturally occurring influenza is depicted in Fig. 190-2. However, the spectrum of clinical presentations is wide, ranging from a mild, afebrile respiratory illness similar to the common cold (with either a gradual or an abrupt onset) to severe prostration with relatively few respiratory signs and symptoms. In most of the cases that come to a physician's attention, the patient has a fever, with temperatures of 38° to 41°C (100.4° to 105.8°F). A rapid temperature rise within the first 24 h of illness is generally followed by a gradual defervescence over a 2- to 3-day period, although, on occasion, fever may last for as long as a week. Patients report a feverish feeling and chilliness, but true rigors are rare. Headache, either generalized or frontal, is often particularly troublesome. Myalgias may involve any part of the body but are most common in the legs and lumbosacral area. Arthralgias may also develop.

Respiratory complaints often become more prominent as systemic symptoms subside. Many patients have a sore throat or persistent cough, which may last for a week or more and which is often accompanied by substernal discomfort. Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eyes.

Physical findings are usually minimal in cases of uncomplicated influenza. Early in the illness, the patient appears flushed and the skin is hot and dry, although diaphoresis and mottled extremities are sometimes evident, particularly in older patients. Examination of the pharynx may yield surprisingly unremarkable results despite a severe sore throat, but injection of the mucous membranes and postnasal discharge are apparent in some cases. Mild cervical lymphadenopathy may be noted, especially in younger individuals. The results of chest examination are largely negative in uncomplicated influenza, although rhonchi, wheezes, and scattered rales have been reported with variable frequency in different outbreaks. Frank dyspnea, hyperpnea, cyanosis, diffuse rales, and signs of consolidation are indicative of pulmonary complications. Patients with apparently uncomplicated influenza have been reported to have a variety of mild ventilatory defects and increased alveolar-capillary diffusion gradients; thus, subclinical pulmonary involvement may be more frequent than is appreciated.

In uncomplicated influenza, the acute illness generally resolves over a 2- to 5-day period, and most patients have largely recovered in 1 week. In a significant minority (particularly the elderly), however, symptoms of weakness or lassitude (postinfluenzal asthenia) may persist for several weeks and may prove troublesome for persons who wish to resume their full level of activity promptly. The pathogenetic basis for this asthenia is unknown, although pulmonary function abnormalities may persist for several weeks after uncomplicated influenza.

COMPLICATIONS

The most common complication of influenza is pneumonia: "primary" influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia. Primary influenza viral pneumonia is the least common but most severe of the

pneumonic complications. It presents as acute influenza that does not resolve but instead progresses relentlessly, with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales may be noted, and chest x-ray findings consistent with diffuse interstitial infiltrates and/or acute respiratory distress syndrome may be present. In such cases, arterial blood-gas determinations show marked hypoxia. Viral cultures of respiratory secretions and lung parenchyma, especially if samples are taken early in illness, yield high titers of virus. In fatal cases of primary viral pneumonia, histopathologic examination reveals a marked inflammatory reaction in the alveolar septa, with edema and infiltration by lymphocytes, macrophages, occasional plasma cells, and variable numbers of neutrophils. Fibrin thrombi in alveolar capillaries, along with necrosis and hemorrhage, have also been noted. Eosinophilic hyaline membranes can be found lining alveoli and alveolar ducts.

Primary influenza viral pneumonia has a predilection for individuals with cardiac disease, particularly those with mitral stenosis (Fig. 190-CD1), but has also been reported in otherwise healthy young adults as well as in older individuals with chronic pulmonary disorders. In some epidemics of influenza (notably those of 1918 and 1957), pregnancy increased the risk of primary influenza pneumonia.

Secondary bacterial pneumonia follows acute influenza. Improvement of the patient's condition over 2 to 3 days is followed by a reappearance of fever along with clinical signs and symptoms of bacterial pneumonia, including cough, production of purulent sputum, and physical and x-ray signs of consolidation. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* -- organisms that can colonize the nasopharynx and that cause infection in the wake of changes in bronchopulmonary defenses. The etiology can often be determined by Gram's staining and culture of an appropriately obtained sputum specimen. Secondary bacterial pneumonia occurs most frequently in high-risk individuals with chronic pulmonary and cardiac disease and in elderly individuals. Patients with secondary bacterial pneumonia often respond to antibiotic therapy when it is instituted promptly.

Perhaps the most common pneumonic complications during outbreaks of influenza have mixed features of viral and bacterial pneumonia. Patients may experience a gradual progression of their acute illness or may show transient improvement followed by clinical exacerbation, with eventual manifestation of the clinical features of bacterial pneumonia. Sputum cultures may contain both influenza A virus and one of the bacterial pathogens described above. Patchy infiltrates or areas of consolidation may be detected by physical examination and chest x-ray. Patients with mixed viral and bacterial pneumonia generally have less widespread involvement of the lung than those with primary viral pneumonia, and their bacterial infections may respond to appropriate antibiotics. Mixed viral and bacterial pneumonia occurs primarily in patients with chronic cardiovascular and pulmonary diseases.

Other pulmonary complications associated with influenza include worsening of chronic obstructive pulmonary disease and exacerbation of chronic bronchitis and asthma. In children, influenza infection may present as croup.

In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur. These include *Reye's syndrome*, a serious complication in children that is associated with influenza B and to a lesser extent with influenza A virus infection as well as with varicella-zoster virus infection. An epidemiologic association between Reye's syndrome and aspirin therapy for the antecedent viral infection has been noted, and the incidence of Reye's syndrome has decreased markedly with widespread warnings regarding the use of aspirin by children with acute viral respiratory infections. A detailed description of Reye's syndrome is found in Chap. 300.

Myositis, rhabdomyolysis, and myoglobinuria are occasional complications of influenza infection. Although myalgias are exceedingly common in influenza, true myositis is rare. Patients with acute myositis have exquisite tenderness of the affected muscles, most commonly in the legs, and may not be able to tolerate even the slightest pressure, such as the touch of bedsheets. In the most severe cases, there is frank swelling and bogginess of muscles. Serum levels of creatine phosphokinase and aldolase are markedly elevated, and an occasional patient has developed renal failure from myoglobinuria. The pathogenesis of influenza-associated myositis is also unclear, although the presence of influenza virus in affected muscles has been reported.

Myocarditis and pericarditis were reported in association with influenza virus infection during the 1918-1919 pandemic; these reports were based largely on histopathologic findings, and these complications have been reported only infrequently since that time. Electrocardiographic changes during acute influenza are common among patients who have cardiac disease but have been ascribed most often to exacerbations of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus.

Central nervous system (CNS) diseases, including encephalitis, transverse myelitis, and Guillain-Barre syndrome, have been reported during influenza. The etiologic relationship of influenza virus to such CNS illnesses remains unestablished. Toxic shock syndrome caused by *S. aureus* infection following acute influenza infection has also been reported (Chap. 139).

In addition to complications involving the specific organ systems described above, influenza outbreaks include a number of cases in which elderly and other high-risk individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function -- changes that occasionally are irreversible and lead to death. These fatalities contribute to the overall excess mortality associated with influenza A outbreaks.

LABORATORY FINDINGS AND DIAGNOSIS

Laboratory diagnosis is accomplished during acute influenza by isolation of the virus from throat swabs, nasopharyngeal washes, or sputum. Virus is usually detected in tissue culture or less commonly is found in the amniotic cavity of chick embryos within 48 to 72 h after inoculation. The rapid viral diagnostic tests now available detect viral nucleoprotein or neuraminidase with high specificity and sensitivities of 57 to 81% compared with tissue culture. Viral nucleic acids have been detected in clinical samples by reverse transcriptase polymerase chain reaction. The type of influenza virus (A or B)

may be determined by either immunofluorescence orHItechniques, and the hemagglutinin subtype of influenza A virus (H1, H2, or H3) may be identified by HI with use of subtype-specific antisera. Serologic methods for diagnosis require comparison of antibody titers in sera obtained during the acute illness with those in sera obtained 10 to 14 days after the onset of illness and are useful primarily in retrospect. Fourfold or greater titer rises as detected by HI orCF or significant rises as measured byELISAare diagnostic of acute infection. CF tests are generally less sensitive than other serologic techniques, but, as they detect type-specific antigens, they may be particularly useful when subtype-specific reagents are not available.

Other laboratory tests are generally not helpful in making a specific diagnosis of influenza virus infection. Leukocyte counts are variable, frequently being low early in illness and normal or slightly elevated later. Severe leukopenia has been described in overwhelming viral or bacterial infection, while leukocytosis with more than 15,000 cells/uL raises the suspicion of secondary bacterial infection.

DIFFERENTIAL DIAGNOSIS

On clinical grounds alone, an individual case of influenza may be difficult to differentiate from an acute respiratory illness caused by any of a variety of respiratory viruses or by *Mycoplasma pneumoniae*. Severe streptococcal pharyngitis or early bacterial pneumonia may mimic acute influenza, although bacterial pneumonias generally do not run a self-limited course. Purulent sputum in which a bacterial pathogen can be detected by Gram's staining is an important diagnostic feature in bacterial pneumonia. The fact that influenza occurs in characteristic outbreaks during the winter months may facilitate a clinical diagnosis. When local health authorities indicate that influenza is present in the community, an acute febrile respiratory illness can be attributed to influenza with a high degree of certainty, particularly if the typical features of abrupt onset and systemic symptoms are present.

TREATMENT

In uncomplicated cases of influenza, symptom-based therapy with acetaminophen for the relief of headache, myalgia, and fever may be considered, but the use of salicylates should be avoided in children below 18 years of age because of the possible association of salicylates with Reye's syndrome. Since cough is ordinarily self-limited, treatment with cough suppressants generally is not indicated, although codeine-containing compounds may be employed if the cough is particularly troublesome. Patients should be advised to rest and maintain hydration during acute illness and should return to full activity only gradually after the illness has resolved, especially if the illness has been severe.

Specific antiviral therapy is available for influenza: amantadine and rimantadine for influenza A and the neuraminidase inhibitors zanamivir and oseltamivir for both influenza A and influenza B. If begun within 48 h of the onset of illness, treatment with amantadine or rimantadine has reduced the duration of systemic and respiratory symptoms of influenza by ~50%. From 5 to 10% of individuals who receive amantadine experience mildCNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty in concentrating. These side effects disappear promptly upon cessation of the drug.

Rimantadine appears to be equally efficacious and is associated with less frequent CNS side effects than is amantadine. In adults, the usual dose of amantadine or rimantadine is 200 mg/d for 3 to 7 days. Since both drugs are excreted via the kidney, the dose should be reduced to£100 mg/d in elderly patients and patients with renal insufficiency. Zanamivir, inhaled orally at a dose of 10 mg twice a day for 5 days, or oseltamivir, ingested orally at a dose of 75 mg twice a day for 5 days, has reduced the duration of signs and symptoms of influenza by 1 to 1.5 days if treatment is started within 2 days of the onset of illness. Zanamivir may exacerbate bronchospasm in asthmatic patients, and oseltamivir has been associated with nausea and vomiting, whose frequency can be reduced by drug administration with food. Currently, only amantadine and zanamivir are approved in the United States for treatment of children (the latter for use in children³7 years old). Ribavirin, a nucleoside analogue with activity against a variety of viral agents, has been reported to be effective against both influenza A and influenza B virus infections when administered as an aerosol, although it is relatively ineffective when administered orally.

Studies demonstrating the therapeutic efficacy of antiviral compounds in influenza have primarily involved young adults with uncomplicated disease; it is not known whether such compounds are effective in the treatment of complications such as influenza pneumonia. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit, with aggressive respiratory and hemodynamic support as needed. Bypass membrane oxygenators have been employed in this setting with variable results. When an acute respiratory distress syndrome develops, fluids must be administered cautiously, with close monitoring of blood gases and hemodynamic function.

Antibacterial drugs should be reserved for the therapy of bacterial complications of acute influenza, such as secondary bacterial pneumonia. The choice of antibiotics should be guided by Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum or transtracheal aspirates. If the etiology of a case of bacterial pneumonia is unclear from an examination of respiratory secretions, empirical antibiotics effective against the most common bacterial pathogens in this setting (*S. pneumoniae*, *S. aureus*, and *H. influenzae*) should be selected (Chaps. 138,139, and149).

PROPHYLAXIS

The major public health measure for prevention of influenza has been the use of inactivated influenza vaccines derived from influenza A and B viruses that circulated during the previous influenza season. If the vaccine virus and the currently circulating viruses are closely related, 50 to 80% protection against influenza would be expected. Presently available vaccines have been highly purified and are associated with few reactions. Up to 5% of individuals experience low-grade fever and mild systemic symptoms 8 to 24 h after vaccination, and up to one-third develop mild redness or tenderness at the vaccination site. Since the vaccine is produced in eggs, individuals with true hypersensitivity to egg products either should be desensitized or should not be vaccinated. Although the 1976 swine influenza vaccine appears to have been associated with an increased frequency of Guillain-Barre syndrome, influenza vaccines administered since 1976 generally have not been. Possible exceptions were noted

during the 1992-1993 and 1993-1994 influenza seasons, when there may have been an excess risk of Guillain-Barre syndrome of slightly more than one case per million among vaccine recipients. However, the overall health risk following influenza outweighs the potential risk associated with vaccination. Investigational live attenuated ("cold-adapted") influenza A and B vaccines also have been developed and have been highly effective in preventing influenza in studies in adults and children. Such vaccines are administered intranasally and stimulate local antibody production more efficiently than conventional inactivated vaccines.

The U.S. Public Health Service recommends influenza vaccination for any individual>6 months of age who is at an increased risk for complications of influenza. Included are individuals with chronic cardiovascular or pulmonary disorders (including asthma) and residents of nursing homes and other chronic-care facilities. Other populations for whom the vaccine is recommended include healthy individuals >65 years of age and individuals who have required regular medical attention for diabetes mellitus, renal disease, hemoglobinopathies, or immunosuppression. Individuals who provide care for high-risk patients or who come into frequent contact with such patients, including household members, should also receive vaccine to reduce the likelihood of transmission of infection. Vaccination is recommended for women who will be in the second or third trimester of pregnancy during the influenza season and for individuals 6 months to 18 years of age who are receiving long-term aspirin therapy and may be at risk for Reye's syndrome. Since commercially available vaccines are inactivated ("killed"), they may be administered safely to immunocompromised patients. Influenza vaccination is not associated with exacerbations of chronic nervous-system diseases such as multiple sclerosis. Vaccine should be administered early in the autumn before influenza outbreaks occur and should be repeated annually to maintain immunity against the most current influenza virus strains.

Of the vaccines currently available (inactivated whole-virus vaccine, subvirion vaccine, and purified surface-antigen vaccine), only the "split-virus" preparations (i.e., the subvirion and purified surface-antigen vaccines) should be given to children<13 years old, since the whole-virus preparations have been associated with higher rates of adverse reactions in this age group.

Studies have shown amantadine and rimantadine to be 70 to 100% effective in the prophylaxis of illness associated with influenza A virus infection. Such prophylaxis is most likely to be used for high-risk individuals who have not received influenza vaccine or in a situation where the vaccines previously administered are relatively ineffective because of antigenic changes in the circulating virus. During an outbreak, amantadine or rimantadine can be administered simultaneously with inactivated vaccine, since neither drug interferes with an immune response to the vaccine. In fact, there is evidence that the protective effects of amantadine and vaccine may be additive. Amantadine has also been employed to control nosocomial outbreaks of influenza A. For prophylaxis, administration of amantadine or rimantadine should be instituted promptly when influenza A activity is detected and must be continued daily for the duration of the outbreak. The dosage most frequently employed has been 200 mg/d for adults, but the dose should be reduced for patients with renal insufficiency and for the elderly. Viruses resistant to both amantadine and rimantadine can emerge quickly after therapy with these drugs, and the possible transmission of these resistant viruses has

been reported. The neuraminidase inhibitors zanamivir and oseltamivir have also been reported to be highly effective in the prophylaxis of influenza A and offer the advantage of efficacy against influenza B as well. They are currently under review for use as prophylaxis. As with amantadine and rimantadine, the neuraminidase inhibitors must be administered daily to maintain prophylaxis.

(Bibliography omitted in Palm version)

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SECTION 14 -RNA VIRUSES

191. THE HUMAN RETROVIRUSES - *Anthony S. Fauci*, *Dan L. Longo*

The retroviruses, which make up a large family (Retroviridae), infect mainly vertebrates. They have a unique replication cycle whereby their genetic information is encoded by RNA rather than DNA. Retroviruses contain an RNA-dependent DNA polymerase (a reverse transcriptase) that directs the synthesis of a DNA form of the viral genome after infection of a host cell. The designation *retrovirus* denotes that information in the form of RNA is transcribed into DNA in the host cell -- a sequence that overturned a central dogma of molecular biology: that information passes unidirectionally from DNA to RNA to protein. The observation that RNA was the source of genetic information in the causative agents of certain animal tumors led to a number of paradigm-shifting biologic insights regarding not only the direction of genetic-information passage but also the viral etiology of certain cancers and the concept of oncogenes as normal host genes scavenged and altered by a viral vector.

The family Retroviridae includes three subfamilies (Table 191-1): Oncovirinae, of which human T-cell lymphotropic virus (HTLV) type I is the most important in humans; Lentivirinae, of which HIV is the most important in humans; and Spumavirinae, the "foamy" viruses, named for the pathologic appearance of infected cells. A number of spumaviruses have been isolated from humans; however, they are not associated with any known disease and therefore are not discussed further in this chapter.

The wide variety of interactions of a retrovirus with its host range from completely benign events (e.g., silent carriage of endogenous retroviral sequences in the germ-line genome of many animal species) to rapidly fatal infections (e.g., exogenous infection with an oncogenic virus such as Rous sarcoma virus in chickens). The ability of retroviruses to acquire and alter the structure and function of host cell sequences has revolutionized our understanding of molecular carcinogenesis. The viruses can insert into the germ-line genome of the host cell and behave as a transposable or movable genetic element. They can activate or inactivate genes near the site of integration into the genome. They can rapidly alter their own genome by recombination and mutation under selective environmental stimuli.

Most human viral diseases occur as a consequence of either tissue destruction by the virus itself or the host's response to the virus. Although these mechanisms are operative in retroviral infections, retroviruses have additional mechanisms of inducing disease, including the malignant transformation of an infected cell and the induction of an immunodeficiency state that leads to opportunistic diseases (infections and neoplasms; Chap. 309).

STRUCTURE AND LIFE CYCLE

Despite the wide range of biologic consequences of retroviral infection, all retroviruses are similar in structure, genome organization, and mode of replication. Retroviruses are 70 to 130 nm in diameter and have a lipid-containing envelope surrounding an icosahedral capsid with a dense inner core. The core contains two identical copies of the single-stranded RNA genome. The RNA molecules are 8 to 10 kb long and are

complexed with reverse transcriptase and tRNA. Other viral proteins, such as integrase, are also components of the virion particle. The RNA has features usually found in mRNA: a cap site at the 5¢ end of the molecule, which is important in the initiation of mRNA translation, and a polyadenylation site at the 3¢ end, which influences mRNA turnover (i.e., messages with shorter polyA tails turn over faster than messages with longer polyA tails). However, the retroviral RNA is not translated; instead it is transcribed into DNA. The DNA form of the retroviral genome is called a *provirus*.

The replication cycle of retroviruses proceeds in two phases (Fig. 191-1). In the first phase, the virus enters the cytoplasm after binding to a specific cell-surface receptor (with HIV, a cell-surface coreceptor is also utilized for binding and entry); the viral RNA and reverse transcriptase synthesize a double-stranded DNA version of the RNA template; and the provirus moves into the nucleus and integrates into the host cell genome. This proviral integration is permanent. Although some animal retroviruses integrate into a single specific site of the host genome in every infected cell, the four known pathogenic human retroviruses (HTLV-I, HTLV-II, HIV-1, and HIV-2) integrate randomly. This first phase of replication depends entirely on gene products in the virus. The second phase includes the synthesis and processing of viral genomes, mRNAs, and proteins using host cell machinery, often under the influence of viral gene products. Virions are assembled and released from the cell by budding from the membrane; host cell membrane proteins are frequently incorporated into the envelope of the virus. Proviral integration occurs during the S phase of the cell cycle; thus, in general, nondividing cells are resistant to retroviral infection. Only the lentiviruses are able to infect nondividing cells. Once a host is infected, it is infected for life.

Retroviral genomes include both coding and noncoding sequences (Fig. 191-2). In general, noncoding sequences are important recognition signals for DNA or RNA synthesis or processing events and are located in the 5¢ and 3¢ terminal regions of the genome. All retroviral genomes are terminally redundant, containing identical sequences called *long terminal repeats* (LTRs). The ends of the retroviral RNA genome differ slightly in sequence from the integrated retroviral DNA. In the latter, the LTR sequences are repeated in both the 5¢ and the 3¢ terminus of the virus. The LTRs contain sequences involved in initiating the expression of the viral proteins, the integration of the provirus, and the polyadenylation of viral RNAs. The primer binding site, which is critical for the initiation of reverse transcription, and the viral packaging sequences are located outside the LTR sequences. The coding regions include the *gag* (group-specific antigen, core protein), *pol* (RNA-dependent DNA polymerase), and *env* (envelope) genes. The *gag* gene encodes a precursor polyprotein that is cleaved to form three to five capsid proteins; a fraction of the Gag precursor proteins also contain a protease responsible for cleaving the Gag and Pol polyproteins. A Gag-Pol polyprotein gives rise to the protease that is responsible for cleaving the Gag-Pol polyprotein. The *pol* gene encodes three proteins: the reverse transcriptase, the integrase, and the protease. The reverse transcriptase functions to copy the viral RNA into the double-stranded DNA provirus, which can attach to the host cell DNA via the action of integrase. The protease functions to cleave the Gag-Pol polyprotein into smaller protein products. The *env* gene encodes the envelope glycoproteins: one protein that binds to specific surface receptors and determines what cell types can be infected and a smaller transmembrane protein that anchors the complex to the envelope. The cartoon in Fig. 191-3 shows how the retroviral gene products make up the virus structure.

HTLVs have a region between *env* and the 3¢LTR that encodes at least two proteins in overlapping reading frames; Tax, a 40-kD protein that does not bind to DNA but induces the expression of host cell transcription factors that alter host cell gene expression; and Rex, a 27-kD protein that regulates the expression of viral mRNAs. These two proteins are produced from messages that are similar but that are spliced differently from overlapping but distinct exons.

The lentiviruses in general, and HIV-1 and -2 in particular, contain a larger genome than other pathogenic retroviruses. They contain an untranslated region between *pol* and *env* that encodes portions of several proteins, varying with the reading frame into which the mRNA is spliced. Tat is a 14-kD protein that augments the expression of virus from theLTR. The Rev protein of HIV-1, similar to the Rex protein ofHTLV, regulates RNA splicing and/or RNA transport. The Nef protein downregulates CD4, the cellular receptor for HIV; alters host T cell activation pathways; and enhances viral infectivity. The Vif protein is necessary for the proper assembly of the HIV nucleoprotein core in many types of cells; without Vif, proviral DNA is not efficiently produced in these infected cells. Vpr, Vpu (HIV-1 only), and Vpx (HIV-2 only) are viral proteins encoded by translation of the same message in different reading frames. As noted above, oncogenic retroviruses depend on cell proliferation for their replication; lentiviruses can infect nondividing cells, largely owing to effects mediated by Vpr. Vpr facilitates transport of the provirus into the nucleus and can induce other cellular changes, such as G2 growth arrest and differentiation of some target cells. Vpx is structurally related to Vpr, but its functions are not fully defined. Vpu promotes the degradation of CD4 in the endoplasmic reticulum and stimulates the release of virions from infected cells.

Retroviruses can be either exogenously acquired by infection with a virion capable of replication or transmitted in the germ line as endogenous virus. Endogenous retroviruses are often replication-defective. The human genome contains endogenous retroviral sequences, but there are no known replication-competent endogenous retroviruses in humans.

In general, viruses that contain only the *gag*, *pol*, and *env* genes either are not pathogenic or take a long time to induce disease because the pathogenesis of neoplastic transformation relies on the chance integration of the provirus at a spot in the genome that will result in the expression of a cellular gene (proto-oncogene) that becomes transforming by virtue of its unregulated expression. For example, avian leukosis virus causes B cell leukemia by inducing the expression of *myc*. Some retroviruses possess captured and altered cellular genes near their integration site, and these viral oncogenes are capable of transforming the infected host cell. Viruses that have oncogenes often have lost a portion of their genome that is required for replication. Such viruses need helper viruses to reproduce, a feature that may explain why these acute transforming retroviruses are rare in nature. All human retroviruses identified to date are exogenous and are not acutely transforming (that is, they lack a transforming oncogene).

These remarkable properties of retroviruses have led to experimental efforts to use them as vectors to insert specific genes into particular cell types, a process known as *gene therapy* or *gene transfer*. The process could be used to repair a genetic defect or

to introduce a new property that could be used therapeutically; for example, a gene (e.g., thymidine kinase) that would make a tumor cell susceptible to killing by a drug (e.g., ganciclovir) could be inserted. One source of concern about the use of retroviral vectors in humans is that replication-competent viruses might rescue endogenous retroviral replication, with unpredictable results. This concern is not merely hypothetical: The detection of proteins encoded by endogenous retroviral sequences on the surface of cancer cells implies that the genetic events leading to the cancer were able to activate the synthesis of these usually silent genes.

HUMAN T-CELL LYMPHOTROPIC VIRUS

HTLV-I was isolated in 1980 from a T-cell lymphoma cell line from a patient originally thought to have cutaneous T cell lymphoma. Later it became clear that the patient had a distinct form of lymphoma (originally reported in Japan) called *adult T cell leukemia/lymphoma* (ATL). Serologic data have determined that HTLV-I is the cause of at least two important diseases: ATL and tropical spastic paraparesis, also called *HTLV-I-associated myelopathy* (HAM). HTLV-I may also play a role in infective dermatitis and uveitis syndromes.

Two years after the isolation ofHTLV-I, HTLV-II was isolated from a patient with an unusual form of hairy cell leukemia that affected T cells. Although early epidemiologic studies of HTLV-II failed to reveal a consistent disease association, more recent studies suggest an association of HTLV-II with human disease (see "Associated Diseases" under "Features of HTLV-II Infection," below), particularly among injection drug users.

BIOLOGY AND MOLECULAR BIOLOGY

Because the biology ofHTLV-I and that of HTLV-II are similar, the following discussion will focus on HTLV-I.

The cellular receptor forHTLV-I has not yet been identified, but it maps to chromosome 17. Generally, only T cells are productively infected, but infection of B cells and other cell types is occasionally detected. The most common outcome of HTLV-I infection is latent carriage of randomly integrated provirus in CD4+ T cells. HTLV-I does not contain an oncogene and does not insert into a unique site in the genome. Indeed, most infected cells express no viral gene products. The only viral gene product that is routinely expressed in tumor cells transformed by HTLV-I in vivo is *tax*, and even *tax* is not expressed in the tumor cells of manyATLpatients. Cells transformed in vitro, by contrast, actively transcribe HTLV-I RNA and produce infectious virions. Most HTLV-I-transformed cell lines are the result of the infection of a normal host T cell in vitro. It is difficult to establish cell lines derived from authentic ATL cells.

Although *tax* does not itself bind to DNA, it does induce the expression of a wide range of host-cell gene products, including transcription factors (especially *c-rel*, *ets*-1 and -2, and members of the *fos/jun* family), cytokines [e.g., interleukin (IL) 2, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor (TNF)], and membrane proteins and receptors [major histocompatibility (MHC) molecules and IL-2 receptor a]. The genes activated by *tax* are generally controlled by transcription factors of the *c-rel* and cyclic AMP response element binding (CREB) protein families. It

is unclear how this induction of host gene expression leads to neoplastic transformation. Induction of a cytokine-autocrine loop has been proposed; however, IL-2 is not the crucial cytokine. The involvement of IL-4, IL-7, and IL-15 has been proposed.

In light of the irregular expression of *tax* inATLcells, it has been suggested that *tax* is important in the early phases of transformation but is not essential for the maintenance of the transformed state. As is clear from the epidemiology ofHTLV-I infection, transformation of an infected cell is a rare event and may depend on heterogeneous second, third, or fourth genetic hits. No consistent chromosomal abnormalities have been described inATL; however, individual cases with *p53* mutations and translocations involving the T cell receptor genes on chromosome 14 have been reported. *Tax* may repress certain DNA repair enzymes, permitting the accumulation of genetic damage that would normally be repaired. However, the molecular pathogenesis of HTLV-I-induced neoplasia is not fully understood.

FEATURES OF HTLV-I INFECTION

Epidemiology HTLV-I infection is transmitted in at least three ways: from mother to child, especially in breast milk; through sexual activity, more commonly from men to women; and through the blood -- via contaminated transfusions or contaminated needles. The virus is most commonly transmitted perinatally. Compared with HIV, which can be transmitted in cell-free form, HTLV-I is less infectious, and its transmission usually requires cell-to-cell contact.

HTLV-I is endemic in southwestern Japan and Okinawa, where more than 1 million persons are infected. Antibodies to HTLV-I are present in the serum of up to 35% of Okinawans, 10% of residents of the Japanese island of Kyushu, and<1% of persons in nonendemic regions of Japan. Despite this high prevalence of infection, only about 500 cases ofATL are diagnosed in this area each year. Clusters of infection have been noted in other areas of the Orient, such as Taiwan; in the Caribbean basin, including northeastern South America; in central Africa; in Italy; in Israel; in the Arctic; and in the southeastern part of the United States.

A progressive spastic or ataxic myelopathy that develops in an individual who isHTLV-I positive (i.e., who has serum antibodies to HTLV-I) is likely to be due to direct nervous system infection with the virus; a similar disorder may result from infection with HIV or HTLV-II. In rare instances, patients withHAM are seronegative but have detectable antibody to HTLV-I in the cerebrospinal fluid (CSF).

The cumulative lifetime risk of developingATL is 2% amongHTLV-I-infected patients; a similar risk is projected forHAM. The distribution of the two diseases overlaps the distribution of HTLV-I, with>95% of affected patients showing serologic evidence of HTLV-I infection. The latent period between infection and the emergence of disease is 20 to 30 years for ATL. For HAM, the median latency period is about 3.3 years (range, 4 months to 30 years). The development of ATL is rare among persons infected by blood products; however, ~20% of patients with HAM acquire HTLV-I from contaminated blood.

Associated Diseases

ATL Four clinical types ofHTLV-I-induced neoplasia have been described: acute, lymphomatous, chronic, and smoldering. All of these tumors are monoclonal proliferations of CD4+post-thymic T cells with clonal proviral integrations and clonal T-cell receptor gene rearrangements.

About 60% of patients who develop malignancy have classic *acute*ATL, which is characterized by a short clinical prodrome (~2 weeks between the first symptoms and the diagnosis) and an aggressive natural history (median survival period, 6 months). The clinical picture is dominated by rapidly progressive skin lesions, pulmonary involvement, hypercalcemia, and lymphocytosis with cells containing lobulated or "flower-shaped" nuclei (seePlate V-40). The malignant cells have monoclonal proviral integrations and express CD4, CD3, and CD25 (low-affinityIL-2 receptors) on their surface. Serum levels of CD25 can be used as a tumor marker. Anemia and thrombocytopenia are rare. The skin lesions may be difficult to distinguish from those in mycosis fungoides. Lytic bone lesions, which are common, do not contain tumor cells but rather are composed of osteolytic cells, usually without osteoblastic activity. Despite the leukemic picture, bone marrow involvement is patchy in most cases.

The hypercalcemia ofATL is multifactorial; the tumor cells produce osteoclast-activating factors (TNF-a,IL-1, lymphotoxin) and can also produce a parathyroid hormone-like molecule. The affected patients have an underlying immunodeficiency that makes them susceptible to opportunistic infections similar to those seen in patients with AIDS (Chap. 309). The pathogenesis of the immunodeficiency is unclear. Pulmonary infiltrates in ATL patients reflect leukemic infiltration half the time and opportunistic infections with organisms such as *Pneumocystis carinii* and other fungi the other half. Gastrointestinal symptoms are nearly always related to opportunistic infection. Serum concentrations of lactate dehydrogenase (LDH) and alkaline phosphatase are often elevated. About 10% of patients have leptomeningeal involvement leading to weakness, altered mental status, paresthesia, and/or headache. Unlike other forms of central nervous system (CNS) lymphoma, ATL may be accompanied by normalCSFprotein levels. The diagnosis depends on finding ATL cells in the CSF (Chap. 112).

The *lymphomatous* type ofATLoccurs in ~20% of patients and is similar to the acute form in its natural history and clinical course, except that circulating abnormal cells are rare and lymphadenopathy is evident. The histology of the lymphoma is variable but does not influence the natural history. In general, the diagnosis is suspected on the basis of the patient's birthplace and the presence of skin lesions and hypercalcemia. The diagnosis is confirmed by the detection of antibodies toHTLV-I in serum.

Patients with the *chronic* form of ATLgenerally have normal serum levels of calcium andLDH and no involvement of theCNS, bone, or gastrointestinal tract. The median duration of survival for these patients is 2 years. In some cases, chronic ATL progresses to the acute form of the disease.

Fewer than 5% of patients have the *smoldering* form ofATL. In this form, the malignant cells have monoclonal proviral integration;<5% of peripheral-blood cells exhibit typical morphologic abnormalities; hypercalcemia, adenopathy, and hepatosplenomegaly do not develop; theCNS, the bones, and the gastrointestinal tract are not involved; and skin

and pulmonary lesions may be present. The median survival period of this small subset of patients appears to be ³5 years.

HAM (Tropical Spastic Paraparesis) In contrast toATL, in which there is a slight predominance of male patients,HAMaffects females disproportionately.HAMresembles multiple sclerosis in certain ways (Chap. 371). The onset is insidious. Symptoms include weakness or stiffness in one or both legs, back pain, and urinary incontinence. Sensory changes are usually mild, but peripheral neuropathy may develop. The disease generally takes the form of slowly progressive and unremitting thoracic myelopathy; one-third of patients are bedridden within 10 years of diagnosis, and one-half are unable to walk unassisted by this point. Patients display spastic paraparesis or paraplegia with hyperreflexia, ankle clonus, and extensor plantar responses. Cognitive function is usually spared; cranial nerve abnormalities are unusual.

Magnetic resonance imaging (MRI) reveals lesions in both the white matter and the paraventricular regions of the brain as well as in the spinal cord. Pathologic examination of the spinal cord shows symmetric degeneration of the lateral columns, including the corticospinal tracts; some cases involve the posterior columns as well. The spinal meninges and cord parenchyma contain an inflammatory infiltrate with myelin destruction.

HTLV-I is not usually found in cells of theCNS but may be detected in a small population of lymphocytes present in theCSF. In general, HTLV-I replication is greater inHAM than in ATL, and patients with HAM have a stronger immune response to the virus. Antibodies to HTLV-I are present in the serum and appear to be produced in the CSF ofHAMpatients, where titers are often higher than in the serum. The pathophysiology of HAM may involve the induction of autoimmune destruction of neural cells by T cells with specificity for viral components such as Tax or Env proteins. One theory is that susceptibility to HAM may be related to the presence of human leukocyte antigen (HLA) alleles capable of presenting viral antigens in a fashion that leads to autoimmunity. Insufficient data are available to confirm an HLA association.

Other putative HTLV-I-related diseases In areas whereHTLV-I is endemic, diverse inflammatory and autoimmune diseases have been attributed to the virus, including uveitis, dermatitis, pneumonitis, rheumatoid arthritis, and polymyositis. However, a causal relationship between HTLV-I and these illnesses has not been rigorously established.

Prevention Women in endemic areas should not breast-feed their children, and blood donors should be screened for serum antibodies toHTLV-I. As in the prevention of HIV infection, the practice of safe sex and the avoidance of needle sharing are important.

TREATMENT

For the small number of patients who developHTLV-I-related disease, therapies are not curative. In patients with the acute and lymphomatous types ofATL, the disease progresses rapidly. Hypercalcemia is generally controlled by glucocorticoid administration and cytotoxic therapy directed against the neoplasm. The tumor is highly responsive to combination chemotherapy that is employed against other forms of

lymphoma; however, patients are susceptible to overwhelming bacterial and opportunistic infections, and ATL relapses within 4 to 10 months after remission in most patients. The combination of interferona and zidovudine may extend survival. Because viral replication is not clearly associated with ATL progression, zidovudine is probably effective through its cytotoxic effects (as a chain-terminating thymidine analogue) rather than its antiviral effects. An experimental approach using an yttrium 90-labeled antibody to theIL-2 receptor appears promising but is not widely available. Patients with the chronic or smoldering form of ATL may be managed with an expectant approach: Treat any infections, and watch and wait for signs of progression to acute disease.

Patients withHAM may obtain some benefit from the use of glucocorticoids to reduce inflammation. Antiretroviral regimens have not been effective. In one study, danazol (200 mg tid) produced significant neurologic improvement in five of six treated patients, with resolution of urinary incontinence in two cases, decreased spasticity in three, and the restoration of the ability to walk after confinement to a wheelchair in two. Physical therapy and rehabilitation are important components of management.

FEATURES OF HTLV-II INFECTION

Epidemiology HTLV-II is endemic in certain Native American tribes. It is generally considered to be a New World virus that was brought from Asia to the Americas 10,000 to 40,000 years ago during the migration of infected populations across the Bering land bridge.

The mode of transmission ofHTLV-II is probably the same as that of HTLV-I (see above). HTLV-II may be less readily transmitted sexually than HTLV-I.

Studies of large cohorts of injection drug users with serologic assays that reliably distinguishHTLV-I from HTLV-II indicate that the vast majority of HTLV-positive subjects are infected with HTLV-II. The seroprevalence of HTLV in a cohort of 7841 injection drug users from drug treatment centers in Baltimore, Chicago, Los Angeles, New Jersey (Asbury Park and Trenton), New York City (Brooklyn and Harlem), Philadelphia, and San Antonio was 20.9%, with>97% of cases due to HTLV-II. The seroprevalence of HTLV-II was higher in the Southwest and the Midwest than in the Northeast. In contrast, the seroprevalence of HIV-1 was higher in the Northeast than in the Southwest or the Midwest. Approximately 3% of the cohort members were infected with both HTLV-II and HIV-1. The seroprevalence of HTLV-II increased linearly with age. Women were significantly more likely to be infected with HTLV-II than were men; the virus is thought to be more efficiently transmitted from male to female than from female to male.

Associated Diseases AlthoughHTLV-II was isolated from a patient with a T cell variant of hairy cell leukemia, this virus has not been consistently associated with a particular disease and in fact has been thought of as "a virus searching for a disease." However, evidence is accumulating that HTLV-II may play a role in certain neurologic, hematologic, and dermatologic diseases. These data require confirmation, particularly in light of the previous confusion regarding the relative prevalences of HTLV-I and HTLV-II among injection drug users.

Prevention Avoidance of needle sharing, safe-sex practices, screening of blood (by

assays forHTLV-I, which also detect HTLV-II), and avoidance of breast-feeding by infected women are important principles in the prevention of spread of HTLV-II.

HUMAN IMMUNODEFICIENCY VIRUS

HIV-1 and HIV-2 are members of the lentivirus subfamily of Retroviridae and are the only lentiviruses known to infect humans. The lentiviruses are slow-acting by comparison with viruses that cause acute infection (e.g., influenza virus) but not by comparison with other retroviruses. The features of acute primary infection with HIV resemble those of more classic acute infections. The characteristic chronicity of HIV disease is consistent with the designation *lentivirus*.**For a detailed discussion of HIV, see Chap. 309.*

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192. VIRAL GASTROENTERITIS - *Harry B. Greenberg*

In less developed countries, acute infectious diarrheal disease is a leading cause of morbidity in all age groups and of mortality in infants and young children. In developed countries, acute diarrheal illness remains an important cause of morbidity among both children and adults. Two distinct groups of viruses -- the rotaviruses and the enteric caliciviruses, such as Norwalk virus -- as well as a variety of bacterial pathogens (Chap. 131) have emerged as important etiologic agents of gastroenteritis. The rotaviruses are primarily pathogens of young children. The Norwalk and related enteric caliciviruses affect adults as well as children. Several important gastrointestinal viruses are characterized inTable 192-1 and depicted inFig. 192-1.

ROTAVIRUS

Classification and Characterization Rotaviruses are members of the Reoviridae family. The rotavirus virion consists of a 100-nm triple-shelled icosahedral capsid surrounding a genome composed of 11 segments of double-stranded RNA. Several genetically distinct groups of rotaviruses (groups A, B, C, etc.) have been identified, but group A strains account for the great majority of illnesses in humans. With only one exception, the rotavirus gene segments are monocistronic. The virus has two surface proteins (VP4 and VP7), both of which are involved in viral neutralization. The major internal capsid protein (VP6) is the target of cross-reactive antibody to different virus strains. This protein also appears to induce protective immunity, although the mechanism is not clear. Because rotaviruses have a segmented genome, they are capable of undergoing gene reassortment at high frequency. The role of gene reassortment in generating rotavirus antigenic diversity is not known. In immunocompetent humans and animals, rotavirus infection is characterized by replication that is localized almost exclusively in the epithelial cells of the small intestine.

Epidemiology Rotavirus infection occurs worldwide. By the age of 3 years, virtually every individual has been infected by rotaviruses at least once. Most rotavirus infections are subclinical or cause mild gastrointestinal illnesses that do not require hospitalization. The first infection is the most likely to be symptomatic; subsequent infections are often mild or asymptomatic. In areas with a temperate climate, rotavirus infection is seasonal, occurring in the colder winter months. In the United States, the annual seasonal rotavirus epidemic tends to spread from west to east, starting in California and ending in New England. In tropical areas, rotavirus infection tends to occur throughout the year, with some increase in incidence during the cooler rainy season.

Rotaviruses are the single most important cause of severe dehydrating diarrhea in infants and children<3 years old in both developed and less developed countries; they account for 25 to 50% of all cases of diarrhea requiring hospitalization or intensive rehydration therapy. During a rotavirus outbreak in a temperate climate, this percentage can be as high as 80%. In the United States, between 5 and 10% of all diarrheal episodes among children under the age of 5 years are caused by rotavirus. Infection due to rotavirus accounts for ~500,000 physician visits per year in the United States. Although severe rotavirus infections are confined primarily to infants and young children, these agents are frequently associated with mild diarrhea in adults, particularly family members of affected infants, geriatric patients, and immunocompromised hosts. They

are responsible for up to 10% of cases of traveler's diarrhea (Chap. 131). Rotaviruses also may cause occasional cases of acute and chronic diarrhea in patients with AIDS.

Rotavirus serotypes have been defined by the antigenicity of both VP4 (P serotype) and VP7 (G serotype). At least 14 distinct G serotypes of rotavirus have been described, but only four types are commonly encountered in the United States. At least 20 P serotypes have been identified to date, of which only two are common among children in this country. The relationship of the frequency of infection with these multiple serotypes to host immune status is unclear. It does appear, however, that infection with one or two serotypes induces some degree of heterotypic immunity to severe disease.

A large variety of mammalian and avian species can be infected by rotavirus, but these animal rotavirus strains do not frequently cause disease in humans. Rotaviruses are shed in very large numbers in the stool (up to 10_{10}particles per gram of feces). Although transmission presumably takes place via the fecal-oral route, rotavirus infection spreads with great efficacy in developed as well as less developed countries.

Pathophysiology Rotavirus infects and kills the mature villus tip cells of the small intestine. The mature epithelial cells are replaced by immature absorptive cells that cannot absorb carbohydrates or other nutrients efficiently. Rotavirus infection thus leads to osmotic diarrhea due to nutrient malabsorption. Changes in intracellular cyclic adenosine monophosphate or guanosine monophosphate are not involved in the etiology of rotavirus diarrhea. Rotavirus also encodes a nonstructural protein (NSP4) that appears to function as an enterotoxin during infection. It is not known whether immunity to NSP4 plays a role in protection or disease resolution.

Manifestations The manifestations of rotavirus infection range from subclinical infection through mild diarrhea to severe, occasionally fatal dehydrating illness. Most information concerning the signs and symptoms of rotavirus infection has been derived from studies of hospitalized young children. The onset of illness is usually abrupt. More than 80% of affected children develop vomiting followed by diarrhea. About one-third of hospitalized children have a temperature of>39°C (>102.2°F). Mucus is commonly found in the stool, but white and red blood cells are present in the stool in fewer than 15% of cases.

Rotavirus infection frequently occurs in conjunction with respiratory tract symptoms, but there is little evidence to indicate that rotavirus replicates in the respiratory tract. Rotavirus infection has been observed in association with a wide variety of other clinical syndromes, including sudden infant death syndrome, Reye's syndrome, encephalitis, aseptic meningitis, pneumonia, exanthema subitum, Kawasaki's syndrome, necrotizing enterocolitis, intussusception, Schonlein-Henoch purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, and Crohn's disease. The etiologic relationship between these clinical syndromes and rotavirus infection is probably coincidental rather than causal. Rotavirus infection may be especially severe or even fatal in immunocompromised children.

Clinical Immunity Relative immunity to rotavirus illness is acquired early in childhood, after one or two natural infections. Subclinical infections in neonates have been shown to protect these children against severe rotavirus gastroenteritis for up to 3 years. Immunity is not complete, and adults with low levels of antibody can be symptomatically

infected. Local humoral immunity appears to be the critical determinant in protection, and cellular immune mechanisms seem to be involved as well.

Diagnosis Because rotavirus is shed in large amounts in the stool, detection is relatively easy. Various specific and highly sensitive commercial immunoassays are available to detect rotavirus antigen in fecal specimens. DNA probe diagnosis appears to be sensitive and specific, as do polymerase chain reaction (PCR)-based assays, but these detection methods have been used primarily for research purposes. No particular signs or symptoms are pathognomonic for rotavirus infection, but this infection is more frequently associated with severe dehydration than are infections caused by other enteric bacterial or viral pathogens.

TREATMENT

Although rotavirus diarrhea appears to be caused primarily by intestinal epithelial-cell lysis and death, it can be adequately managed with standard oral rehydration therapy. Only rarely is intravenous rehydration required. Since rotavirus infections have persisted in developed countries with advanced sanitation facilities and widely available clean water, it is unlikely that these infections will prove to be preventable by hygienic measures alone. Progress with a number of candidate live attenuated vaccines suggests that prevention through vaccination may be feasible. In 1998, a multivalent rotavirus vaccine was licensed for use in children under the age of 6 months in the United States. The vaccine virus was a live attenuated animal rotavirus containing genes encoding the four human G serotypes most common in the United States. The licensed vaccine was administered orally as three doses and was highly effective in preventing severe rotavirus illness. Reports of intussusception associated with the administration of rotavirus vaccine have been published; further studies are required to define the relative risk. However, because of the apparent association with intussusception, this first rotavirus vaccine has been withdrawn from use.

NORWALK AND RELATED ENTERIC CALICIVIRUSES

Classification and Characterization Various round 27- to 32-nm particles, some with clearly defined ultrastructure, have been identified in the stools of individuals with acute nonbacterial gastroenteritis. In the past, these agents have been difficult to classify because they are shed in the stool in small amounts for only a few days and have not been adapted to cell culture or to animal models. The Norwalk virus is the most extensively studied and best-characterized member of this group of enteric caliciviruses, which also includes such serologically or genetically distinct viruses as Hawaii virus, Snow Mountain virus, Southampton virus, Lordsdale virus, Mexico virus, Sapporo virus, and a number of agents described as calicivirus-like. Molecular biologic studies have shown that all these viruses have a protein structure similar to that of typical caliciviruses, with a single structural protein of ~60 kDa. The genomes of Norwalk virus and numerous related viruses have been cloned and sequenced. The genomes are plus-stranded RNA molecules of ~7.5 kb. On the basis of these molecular biologic studies, the human enteric caliciviruses can be divided into two groups: the Norwalk-like viruses (NLVs) and the Sapporo-like viruses (SLVs). The SLVs have a more typical calicivirus-like ultrastructure and cause diarrhea in young children. Unlike the NLVs, the SLVs may not cause frequent epidemics in adults.

Epidemiology Infection withNLVs is common year-round, with a clear winter peak. The seasonality ofSLVs has not yet been widely studied. More than 80% of adults in both developed and less developed countries have antibodies to these viruses. Antibody is acquired at a younger age among children in less developed countries than among those in developed areas; this observation is consistent with the assumption that NLVs are spread by the fecal-oral route. In the United States, the NLVs are responsible for ~90% of all epidemics of nonbacterial gastroenteritis. These agents have been incriminated in a variety of food-borne epidemics, and transmission vehicles have included oysters, green salad, and chocolate icing. The NLVs are common causes of waterborne epidemics of gastroenteritis and have been shown to be etiologic agents in nursing home, cruise ship, and institutional (summer camp and school) outbreaks. NLVs are also responsible for a small proportion of cases of traveler's diarrhea. NLV infection is a common cause of mild to moderate childhood diarrhea.

In less developed countries, the role of NLVinfection in the etiology of diarrhea in adults has not been thoroughly investigated. Preliminary studies indicate that NLVs can cause mild diarrhea in young children, but they do not appear to cause severe illness in infants in either developed or less developed countries.

Pathophysiology Information concerning the pathologic changes induced by the enteric caliciviruses is based almost entirely on a few studies of volunteers during the 1970s and 1980s. After infection with Norwalk or Hawaii virus, the architecture of the proximal small intestine is altered, with villus shortening, crypt hyperplasia, and infiltration of the lamina propria by polymorphonuclear and mononuclear cells. No changes are observed in the stomach or colon. The cells in which viral replication takes place have not been identified. The histologic alterations are accompanied by mild steatorrhea, carbohydrate malabsorption, and decreased levels of some brush border enzymes. No changes in adenylate cyclase activity have been observed.

Manifestations Norwalk illness has an incubation period of 18 to 72 h. The disease is characterized by the abrupt onset of nausea and abdominal cramps followed by vomiting and/or diarrhea. Vomiting is reported more frequently for children than for adults. Low-grade fever [>37.5° C (>99.5° F)] develops in about half of affected individuals. Headache, myalgias, and abdominal pain are common. The white blood cell count is normal; rarely, there is leukocytosis with relative lymphopenia. Red and white blood cells are not found in the stool. The illness is usually mild and self-limited, lasting 24 to 48 h.

Clinical Immunity Most people in developed countries do not have long-term resistance (i.e., that lasting³2 years) to Norwalk reinfection. Short-term (several-month) immunity -- at least to homotypic challenge -- does appear to develop. In volunteers challenged with Norwalk agent, there is a paradoxical relationship between the level of antibody toNLVs and susceptibility to illness: Low levels of Norwalk antibody in the serum and intestine are associated with clinical resistance to illness. It appears, therefore, that immune mechanisms are not the primary determinants of long-term protection from NLVs. Immunity to theSLVs may be more durable.

Diagnosis, Treatment, and Prevention Enzyme-linked immunosorbent assays

andPCR-based assays have been developed forNLVs and several other 27- to 32-nm gastroenteritis agents. However, these assays are not yet widely available, and their utility for general diagnosis has not been tested. Because Norwalk illness is acute and self-limited, treatment is not usually required. In the rare case of severe vomiting or diarrhea, oral or intravenous rehydration is indicated. Because long-term immunity to the NLVs does not usually follow natural infection, the role of vaccination may be limited to specific settings (e.g., the military). Recombinant NLV particles have been produced and are capable of inducing an immune response when administered orally to volunteers.

MISCELLANEOUS ENTERIC VIRAL PATHOGENS

Enteric adenoviruses are a minor cause of diarrheal illness in infants and children, accounting for 10% of cases. These viruses differ from other adenovirus strains in a variety of ways, including neutralization serotype, restriction endonuclease digestion pattern, and ability to grow in tissue culture. The role of enteric adenovirus illness in adults or in persons in less developed countries is not known.

Several strains of antigenically distinct rotaviruses, presently called *atypical rotaviruses* or *groups B and C rotaviruses*, have been identified as the cause of occasional episodes of diarrhea in humans and animals.

Preliminary epidemiologic studies have indicated that *astroviruses* are a fairly frequent cause of mild to moderate diarrhea in young children in developed and less developed countries, accounting for about one-quarter to one-half as much illness as group A rotaviruses. Moreover, preliminary data indicate that astroviruses are a common cause of diarrhea in immunocompromised hosts, such as bone marrow transplant recipients and patients with AIDS. Astroviruses are 27 to 32 nm in diameter, have a characteristic icosahedral ultrastructure, and contain a plus-stranded RNA genome with a size of ~7.0 kb and a unique genomic organization. At least seven distinct serotypes have been identified. The current availability of sensitive and specific diagnostic assays should allow more complete assessment of the importance of these agents.

Coronaviruses are frequent causes of diarrheal disease in a variety of animals. Using electron microscopy, several investigators have identified putative coronavirus-like particles in the stools of patients with diarrhea. In most cases, however, these particles do not have the typical morphologic features of coronaviruses and may represent bacterial breakdown products or cellular fragments.

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193. ENTEROVIRUSES AND REOVIRUSES - *Jeffrey I. Cohen*

ENTEROVIRUSES

CLASSIFICATION AND CHARACTERIZATION

Enteroviruses are so named because of their ability to multiply in the gastrointestinal tract. Despite their name, these viruses are not a prominent cause of gastroenteritis. Enteroviruses encompass 64 human serotypes: 3 serotypes of poliovirus, 23 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 28 serotypes of echovirus, and enteroviruses 68 through 71.

Human enteroviruses contain a single-stranded RNA genome surrounded by an icosahedral capsid comprising four viral proteins. These viruses have no lipid envelope and are stable in acidic environments, including the stomach. They are resistant to inactivation by standard disinfectants (e.g., alcohol, detergents) and can persist for days at room temperature.

PATHOGENESIS AND IMMUNITY

Much of what is known about the pathogenesis of enteroviruses has been derived from studies of poliovirus infection. After ingestion, poliovirus is thought to infect epithelial cells in the mucosa of the gastrointestinal tract and then to spread to and replicate in the submucosal lymphoid tissue of the tonsils and Peyer's patches. The virus next spreads to the regional lymph nodes, a viremic phase ensues, and the virus replicates in organs of the reticuloendothelial system. In some cases, a second viremia occurs and the virus replicates further in various tissues, sometimes causing symptomatic disease.

It is uncertain whether poliovirus reaches the central nervous system (CNS) during viremia or whether it also spreads via peripheral nerves. Since viremia precedes the onset of neurologic disease in humans and in experimentally infected chimpanzees, it has been assumed that the virus enters the CNS via the bloodstream. The poliovirus receptor is a member of the immunoglobulin superfamily. Poliovirus infection is limited to primates, largely because of the ability of their cells to express the viral receptor. Studies demonstrating the poliovirus receptor in the end-plate region of muscle at the neuromuscular junction suggest that if the virus enters the muscle during viremia, it could travel across the neuromuscular junction up the axon to the anterior horn cells. Studies of monkeys or transgenic mice expressing the poliovirus receptor show that, after intramuscular injection, poliovirus does not reach the spinal cord if the sciatic nerve is cut. Taken together, these findings suggest that poliovirus can spread directly from muscle to the CNS by neural pathways. The receptor for echovirus types 1 and 8 is VLA-2 integrin, that for echovirus 7 is CD55, and that for coxsackievirus B is CAR (also used by adenovirus).

Poliovirus can usually be cultured from the blood 3 to 5 days after infection, before the development of neutralizing antibodies. While viral replication at secondary sites begins to slow 1 week after infection, it continues in the gastrointestinal tract. Poliovirus is shed from the oropharynx for up to 3 weeks after infection and from the gastrointestinal tract for as long as 12 weeks; immunodeficient patients can shed poliovirus for more than 1

year. During replication in the gastrointestinal tract, attenuated oral poliovirus can mutate, reverting to a more neurovirulent phenotype within a few days. The clinical significance of this increased neurovirulence is unknown.

Humoral and secretory immunity in the gastrointestinal tract is important for the control of enterovirus infections. Enteroviruses induce specific IgM, which usually persists for< 6 months, and specific IgG, which persists for life. Capsid protein VP1 is the predominant target of neutralizing antibody, which generally confers lifelong protection against subsequent disease caused by the same serotype but does not prevent infection or virus shedding. Enteroviruses also induce cellular immunity, but the importance of this mechanism in limiting infection is uncertain. Patients with impaired cellular immunity are not known to develop unusually severe disease when infected with enteroviruses. In contrast, the severe infections in patients with agammaglobulinemia emphasize the importance of humoral immunity in controlling enterovirus infections. IgA antibodies are important in reducing poliovirus replication in and shedding from the gastrointestinal tract. Breast milk contains IgA specific for enteroviruses and can protect humans from infection.

EPIDEMIOLOGY

Enteroviruses have a worldwide distribution. More than 50% of nonpoliovirus enterovirus infections and more than 90% of poliovirus infections are subclinical. When symptoms do develop, they are usually nonspecific and occur in conjunction with fever; only a minority of infections are associated with specific clinical syndromes. The incubation period for most enterovirus infections ranges from 2 to 14 days but usually is less than a week.

Enterovirus infection is more common in socioeconomically disadvantaged areas, especially in those where conditions are crowded and in tropical areas where hygiene is poor. Infection is most common among infants and young children; serious illness develops most often during the first few days of life and in older children and adults. In developing countries, where children are infected at an early age, poliovirus infection has less often been associated with paralysis; in countries with better hygiene, older children and adults are more likely to be seronegative, become infected, and develop paralysis. Passively acquired maternal antibody reduces the risk of symptomatic infection in neonates. Young children are the most frequent shedders of enteroviruses and are usually the index cases in family outbreaks. In temperate climates, enterovirus infections occur most often in the summer and fall; no seasonal pattern is apparent in the tropics.

Most enteroviruses are transmitted primarily by the fecal-oral route from fecally contaminated fingers or inanimate objects. Patients are most infectious shortly before and after the onset of symptomatic disease, when virus is present in the stool and throat. The ingestion of virus-contaminated food or water can also cause disease. Certain enteroviruses (such as enterovirus 70, which causes acute hemorrhagic conjunctivitis) can be transmitted by direct inoculation from the fingers to the eye. Airborne transmission is important for some viruses that cause respiratory tract disease, such as coxsackievirus A21. Enteroviruses can be transmitted across the placenta from mother to fetus, causing severe disease in the newborn. The transmission of

enteroviruses through blood transfusions or insect bites has not been documented. Nosocomial spread of coxsackievirus and echovirus has taken place in hospital nurseries.

DIAGNOSIS

Isolation of enterovirus in cell culture is the most common procedure for the diagnosis of infection. While cultures of stool, nasopharyngeal, or throat samples from patients with enterovirus diseases are often positive, isolation of the virus from these sites does not prove that it is directly associated with disease because these sites are frequently colonized for weeks in patients with subclinical infections. Isolation of virus from the throat is more likely to be associated with disease than isolation from the stool since virus is shed for shorter periods from the throat. Cultures of cerebrospinal fluid (CSF), serum, fluid from body cavities, or tissues are positive less frequently, but a positive result is indicative of disease caused by enterovirus. In some cases the virus can be isolated only from the blood or only from the CSF; therefore, it is important to culture multiple sites. Cultures are more likely to be positive earlier than later in the course of infection. Most human enteroviruses can be detected within a week after inoculation of cell cultures. Cultures may be negative because of the presence of neutralizing antibody, lack of susceptibility of the cells used, or inappropriate handling of the specimen. Coxsackievirus A may require inoculation into special cell-culture lines or into suckling mice.

Identification of the serotype of an enterovirus is useful primarily for epidemiologic studies and, with a few exceptions, has little clinical utility. It is important to identify serious infections with enterovirus during epidemics and to distinguish the vaccine strain of poliovirus from the other enteroviruses in the throat or in the feces. Stool and throat samples for culture as well as acute- and convalescent-phase serum specimens should be obtained from all patients with suspected poliomyelitis. In the absence of a positiveCSFculture, a positive culture of stool obtained within the first 2 weeks after the onset of symptoms is most often used to confirm the diagnosis of poliomyelitis. If poliovirus is isolated, it should be sent to the Centers for Disease Control and Prevention (CDC) in Atlanta for identification as either a wild-type or a vaccine virus.

The polymerase chain reaction (PCR) has been used to amplify viral nucleic acid fromCSF, serum, urine, throat swabs, and tissues. A single pair of PCR primers can detect more than 92% of the serotypes that infect humans. With the proper controls, PCR of the CSF is highly sensitive (³95%) and specific (>80%) and is more rapid than culture. PCR of serum is also highly sensitive and specific in the diagnosis of disseminated disease. PCR may be particularly helpful for the diagnosis and follow-up of enterovirus disease in immunodeficient patients receiving immunoglobulin therapy, whose viral cultures may be negative. Antigen detection and hybridization of enterovirus sequences in human tissues with a specific probe are additional options, but these techniques are generally less sensitive than PCR.

Serologic diagnosis of enterovirus infection is limited by the large number of serotypes and the lack of a common antigen. Demonstration of seroconversion may be useful in rare cases for confirmation of culture results, but serologic testing is usually limited to epidemiologic studies. Serum should be collected and frozen soon after the onset of

disease and again about 4 weeks later. Measurement of neutralizing titers is the most accurate method for antibody determination; measurement of complement-fixation titers is usually less sensitive. Titers of virus-specific IgM are elevated in both acute and chronic infection.

TREATMENT

Most enterovirus infections are mild and resolve spontaneously; however, intensive supportive care may be needed for cardiac, hepatic, orCNSdisease. Intravenous, intrathecal, or intraventricular immunoglobulin has been used with apparent success for the treatment of chronic enterovirus meningoencephalitis and dermatomyositis in patients with hypo- or agammaglobulinemia. The disease may stabilize or resolve during therapy; however, some patients decline inexorably despite therapy. Intravenous administration of immunoglobulin with high titers of antibody to the infecting virus has been successful in the treatment of some cases of life-threatening infection in neonates, who may not have maternally acquired antibody. In one trial involving neonates with enterovirus infections, immunoglobulin containing very high titers of antibody to the infecting virus reduced rates of viremia; however, the study was too small to show a substantial clinical benefit. Oral pleconaril, a capsid-binding antiviral agent, reduced symptoms in a placebo-controlled trial of enteroviral aseptic meningitis and in a challenge study with coxsackievirus. This drug is available for compassionate use in patients with certain severe enterovirus infections. Glucocorticoids are contraindicated.

Good hand-washing practices and the use of gowns and gloves are important in limiting nosocomial transmission of enteroviruses during epidemics. Enteric precautions are indicated for 7 days after the onset of enterovirus infections.

POLIOVIRUS

Manifestations Most infections with poliovirus are asymptomatic. After an incubation period of 3 to 6 days, about 5% of patients present with a minor illness (abortive poliomyelitis) manifested by fever, malaise, sore throat, anorexia, myalgias, and headache. This condition usually resolves in 3 days. About 1% of patients present with aseptic meningitis (nonparalytic poliomyelitis). Examination ofCSFreveals lymphocytic pleocytosis, a normal glucose level, and a normal or slightly elevated protein level; CSF polymorphonuclear leukocytes may be present early. In some patients, especially children, malaise and fever precede the onset of aseptic meningitis.

The least common presentation is that of paralytic disease. After one or several days, signs of aseptic meningitis are followed by severe back, neck, and muscle pain and by the rapid or gradual development of motor weakness. In some cases the disease appears to be biphasic, with aseptic meningitis followed first by apparent recovery but then (1 or 2 days later) by the return of fever and the development of paralysis; this form is more common among children than among adults. Weakness is generally asymmetric, is proximal more than distal, and may involve the legs (most commonly); the arms; or the abdominal, thoracic, or bulbar muscles. Paralysis develops during the febrile phase of the illness and usually does not progress after defervescence. Urinary retention may also occur. Examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas. Transient hyperreflexia

sometimes precedes the loss of reflexes. Patients frequently report sensory symptoms, but objective sensory testing usually yields normal results. Bulbar paralysis may lead to dysphagia, difficulty in handling secretions, or dysphonia. Respiratory insufficiency due to aspiration, involvement of the respiratory center in the medulla, or paralysis of the phrenic or intercostal nerves may develop, and severe medullary involvement may lead to circulatory collapse. Most patients with paralysis recover some function weeks to months after infection. About two-thirds of patients have residual neurologic sequelae.

Paralytic disease is more common among older individuals, pregnant women, and persons exercising strenuously or undergoing trauma at the time ofCNSsymptoms. Tonsillectomy predisposes to bulbar poliomyelitis, and intramuscular injections increase the risk of paralysis in the involved limb(s).

At present, the only cases of poliomyelitis in the United States are due to live poliovirus vaccine; of the four cases reported in the United States in 1997 and 1998, three occurred in recipients of the first or second dose of oral poliovirus vaccine (OPV), and one occurred in an adult contact of a recipient of OPV. The median interval from vaccination to the onset of symptoms is usually 3 weeks. About 5% of the cases of poliomyelitis associated with vaccine occur in members of the community who have had no known direct contact with vaccinees. About 15% of all cases of vaccine-associated poliomyelitis involve immunodeficient children or adults, most of whom have hypo- or agammaglobulinemia. In these patients the median interval between vaccination and the onset of symptoms is 6 weeks, but disease can develop up to 6 months after vaccination. The risk of developing poliomyelitis after oral vaccination is estimated at 1 case per 2.5 million doses administered. The risk of developing paralytic disease after oral vaccination is about 2000 times higher among immunodeficient patients than among immunocompetent children.

The *postpolio syndrome* presents as a new onset of weakness, fatigue, fasciculations, and pain with additional atrophy of the muscle group involved during the initial paralytic disease 20 to 40 years earlier. The syndrome is more common among women and with increasing time after acute disease. The onset is insidious, and weakness occasionally extends to muscles that were not involved during the initial illness. The prognosis is generally good; progression to further weakness is usually slow, with plateau periods that range from 1 to 10 years. The postpolio syndrome is thought to be due to progressive dysfunction and loss of motor neurons that compensated for the neurons lost during the original infection and not to persistent or reactivated poliovirus infection.

Prevention and Eradication (See also Chap. 122) After a peak of 57,879 cases of poliomyelitis in the United States in 1952, the introduction of inactivated vaccine in 1955 and of oral vaccine in 1961 ultimately eradicated disease due to wild-type poliovirus in the western hemisphere. Such disease has not been documented in the United States since 1979, when cases occurred among religious groups who had declined immunization. In the western hemisphere, paralysis due to wild-type poliovirus was last documented in 1991.

In 1988, the World Health Organization adopted a resolution to eradicate poliomyelitis by the year 2000. From 1988 to 1997, the number of cases worldwide decreased by 89%, with about 6227 cases reported from 46 countries in 1998. More than 80% of the

world's cases of confirmed polio in 1998 occurred in India, Pakistan, Bangladesh, and Nigeria. Polio is a source of concern for unimmunized or partially immunized travelers to these regions. Outbreaks of polio in Europe and North America have been traced to cases imported from the Indian subcontinent. Clearly, global eradication of polio is necessary to eliminate the risk of importation of wild-type virus. Outbreaks are thought to have been facilitated by suboptimal rates of vaccination, isolated pockets of unvaccinated children, poor sanitation and crowding, improper vaccine-storage conditions, and a reduced level of response to one of the serotypes in the vaccine.

For the development of liveOPVcontaining all three poliovirus serotypes, wild-type virus was attenuated by passage in monkey kidney cell cultures. OPV strains differ from the wild-type strains in a limited number of nucleotide changes (i.e., fewer than 60). Multiple doses are required to ensure infection and development of immunity to all three serotypes. While intramuscular injections of other vaccines (live or attenuated) can be given concurrently with OPV, unnecessary intramuscular injections should be avoided during the first month after vaccination because they increase the risk of vaccine-associated paralysis. Inactivated poliovirus vaccine is generated by formalin inactivation of the three serotypes of live poliovirus. Since 1988 an enhanced-potency inactivated poliovirus vaccine (IPV) has been available in the United States.

OPVand IPVinduce antibodies that persist for at least 5 years. Both vaccines induce IgG and IgA antibodies. Compared with recipients of IPV, recipients of OPV shed less virus and less frequently develop reinfection with wild-type virus after exposure to poliovirus. Although IPV is safe and efficacious, OPV offers the advantages of ease of administration, lower cost, and induction of intestinal immunity resulting in a reduction in the risk of community transmission of wild-type virus. Because of progress toward global eradication of polio (with a reduced risk of imported cases) and the continued occurrence of cases of vaccine-associated polio, theCDCrecommended in 1997 that children receive a sequential schedule of two doses of IPV followed by two doses of OPV or a four-dose schedule of IPV alone. To further reduce the risk of vaccine-associated polio, the Advisory Committee for Immunization Practices recommended (in June 1999) an all-IPV regimen for childhood poliovirus vaccination. Beginning in January 2000, children should receive IPV at 2, 4, and 6 to 18 months and 4 to 6 years of age. OPV will be used only in special circumstances: (1) for mass immunization campaigns to control outbreaks of polio; (2) for vaccination of unimmunized children who will be traveling to a polio-endemic area within 4 weeks; and (3) for children whose parents do not accept an all-IPV regimen. The latter children should receive at least two doses of IPV before receiving OPV. The risk of vaccine-associated polio should be discussed before administering OPV. Recommendations for vaccination of adults are listed inTable 193-1.

COXSACKIEVIRUS, ECHOVIRUS, AND OTHER ENTEROVIRUSES

An estimated 5 to 10 million cases of symptomatic enterovirus disease occur in the United States each year. Enteroviruses are the most common cause of aseptic meningitis and nonspecific febrile illnesses of neonates. Certain clinical syndromes are more likely to be caused by certain serotypes (Table 193-2), but there is much overlap. From 1970 to 1983, 70% of enterovirus infections were caused by only 10 of the 64 human serotypes. Echoviruses 9 and 11 alone accounted for 24% of recognized

enterovirus infections; echoviruses 4, 6, and 30 and coxsackieviruses A9 and B2 through B5 accounted for 46%.

Nonspecific Febrile Illness (Summer Grippe) The most common clinical manifestation of enterovirus infection is a nonspecific febrile illness. After an incubation period of 3 to 6 days, patients present with an acute onset of fever, malaise, and headache. Occasional cases are associated with upper respiratory symptoms, and some cases include nausea and vomiting. Symptoms often last for 3 to 4 days, and most cases resolve in a week. While infections with other respiratory viruses occur more often from late fall to early spring, enterovirus febrile illness frequently occurs in the summer and early fall.

Generalized Disease of the Newborn Most serious enterovirus infections in infants develop during the first week of life, although severe disease can occur up to 3 months of age. Neonates often present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy. Laboratory abnormalities include leukocytosis with a left shift, thrombocytopenia, elevated values in liver function tests, andCSFpleocytosis. The illness can be complicated by myocarditis and hypotension, fulminant hepatitis and disseminated intravascular coagulation, meningitis or meningoencephalitis, or pneumonia. It may be difficult to distinguish enterovirus infection from bacterial sepsis, although a history of a recent virus-like illness in the mother provides a clue.

Aseptic Meningitis and Encephalitis Enteroviruses are the cause of up to 90% of cases of aseptic meningitis in children and young adults in which an etiologic agent can be identified. Patients with aseptic meningitis typically present with an acute onset of fever, chills, headache, photophobia, and pain on eye movement. Nausea and vomiting are also common. Examination reveals meningismus without localizing neurologic signs; drowsiness or irritability may also be apparent. In some cases, a febrile illness may be reported that remits but returns several days later in conjunction with signs of meningitis. Other systemic manifestations may provide clues to an enteroviral cause, including diarrhea, myalgias, rash, pleurodynia, myocarditis, and herpangina. Examination of theCSFinvariably reveals pleocytosis; early in the course, polymorphonuclear leukocytes may be present or even predominant, raising the possibility of bacterial or other nonviral causes of meningitis. Partially treated bacterial meningitis may be particularly difficult to exclude in some instances. A useful rule is that the CSF cell count in enteroviral meningitis shows a shift to lymphocytic predominance within 24 h of presentation, and the total count generally does not exceed 1000 cells/uL. Additional CSF findings consist of a normal glucose content and a normal or only slightly elevated (by£100 mg/mL) level of protein. Enteroviruses and mumps virus may produce a similar picture of meningitis; a low CSF glucose level suggests mumps, whereas a normal CSF glucose level and transient CSF polymorphonuclear pleocytosis suggest enterovirus infection. Symptoms ordinarily resolve within a week, although CSF abnormalities can persist for several weeks. Enteroviral meningitis is often more severe in adults than in children. Neurologic sequelae are rare, and most patients have an excellent prognosis.

Enteroviral encephalitis is much less common than enteroviral aseptic meningitis. Occasional highly inflammatory cases of enteroviral meningitis may be complicated by a mild form of encephalitis that is recognized on the basis of progressive lethargy,

disorientation, and sometimes seizures. Less commonly, severe primary encephalitis may develop. It is estimated that 10 to 20% of cases of viral encephalitis are due to enteroviruses. Immunocompetent patients generally have a good prognosis.

Patients with hypo- or agammaglobulinemia or severe combined immunodeficiency may develop chronic meningitis or encephalitis; about half of these patients have a dermatomyositis-like syndrome, with peripheral edema, rash, and myositis. They may also have chronic hepatitis. Patients may develop neurologic disease while receiving gamma globulin replacement therapy. Echoviruses (especially echovirus 11) are the most common pathogens in this situation.

Paralytic disease due to enteroviruses other than poliovirus occurs sporadically and is usually less severe than poliomyelitis. Most cases are due to enterovirus 70 or 71 or to coxsackievirus A7 or A9. Guillain-Barre syndrome is also associated with enterovirus infection. While some studies have suggested a link between enteroviruses and the chronic fatigue syndrome, most recent studies have not demonstrated such an association.

Pleurodynia (Bornholm Disease) Patients with pleurodynia present with an acute onset of fever and spasms of pleuritic chest or upper abdominal pain. Chest pain is more frequent in adults, and abdominal pain is more common in children. Paroxysms of severe, knifelike pain usually last 15 to 30 min and are associated with diaphoresis and tachypnea. Fever peaks within an hour after the onset of paroxysms and subsides when pain resolves. The involved muscles are tender to palpation, and a pleural rub may be detected. The white blood cell count and chest x-ray are usually normal. Most cases are due to coxsackievirus B and occur during epidemics. Symptoms resolve in a few days, and recurrences are rare. Treatment includes the administration of nonsteroidal anti-inflammatory agents or the application of heat to the affected muscles.

Myocarditis and Pericarditis Enteroviruses are estimated to cause up to one-third of cases of acute myocarditis. Coxsackievirus B and its RNA have been detected in pericardial fluid and myocardial tissue in some cases of acute myocarditis and pericarditis. Most cases of enteroviral myocarditis or pericarditis occur in newborns, adolescents, or young adults. More than two-thirds of patients are male. Patients often present with an upper respiratory tract infection that is followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure. A pericardial friction rub is documented in half of cases, and the electrocardiogram shows ST segment elevations or ST- and T-wave abnormalities. Serum levels of myocardial enzymes are often elevated. Neonates commonly have severe disease, while most older children and adults recover completely. Up to 10% of cases progress to chronic dilated cardiomyopathy. Chronic constrictive pericarditis may also be a sequela.

Exanthems Enterovirus infection is the leading cause of exanthems in children in the summer and fall. While exanthems are associated with many enteroviruses, certain types have been linked to specific syndromes. Echoviruses 9 and 16 have frequently been associated with exanthem and fever. Rashes may be discrete (rubelliform) or confluent (morbilliform), beginning on the face and spreading to the trunk and extremities. Echovirus 9 is the most common cause of rubelliform rash. Unlike the rash of rubella, the enteroviral rash occurs in the summer and is not associated with

lymphadenopathy. Roseola-like rashes develop after defervescence, with macules and papules on the face and trunk. The Boston exanthem, caused by echovirus 16, is a roseola-like rash that often affects multiple members of a family. A variety of other rashes have been associated with enteroviruses, including erythema multiforme and vesicular, urticarial, petechial, or purpuric lesions. Enanthems also occur, including lesions that resemble the Koplik's spots seen with measles.

Hand-Foot-and-Mouth Disease (Fig. 193-CD1) After an incubation period of 4 to 6 days, patients with hand-foot-and-mouth disease present with fever, anorexia, and malaise; these manifestations are followed by the development of sore throat and vesicles (Plate IID-39) on the buccal mucosa and often on the tongue and then by the appearance of tender vesicular lesions on the dorsum of the hands, sometimes with involvement of the palms. The vesicles may form bullae and quickly ulcerate. About one-third of patients also have lesions on the palate, uvula, or tonsillar pillars, and one-third have a rash on the feet (including the soles) or on the buttocks. The disease is highly infectious, with attack rates of close to 100% among young children. The lesions usually resolve in 1 week. Most cases are due to coxsackievirus A16 or enterovirus 71.

An epidemic of enterovirus 71 infection in Taiwan in 1998 resulted in thousands of cases of hand-foot-and-mouth disease or herpangina. Severe complications included CNS disease, myocarditis, and pulmonary hemorrhage. About 90% of those who died were children£5 years old, and these deaths were associated with pulmonary edema or pulmonary hemorrhage. CNS disease included aseptic meningitis, flaccid paralysis (similar to poliomyelitis), or rhombencephalitis with myoclonus and tremor or ataxia. The mean age of patients with CNS complications was 2.5 years, and magnetic resonance imaging in cases with encephalitis usually showed brain-stem lesions.

Herpangina Herpangina (Fig. 193-CD2) is usually caused by coxsackievirus A and presents as acute-onset fever, sore throat, dysphagia, and grayish-white papulovesicular lesions on an erythematous base that ulcerate. The lesions can persist for weeks; are present on the soft palate, anterior pillars of the tonsils, and uvula; and are concentrated in the posterior portion of the mouth. In contrast to herpes stomatitis, enteroviral herpangina is not associated with gingivitis. Acute lymphonodular pharyngitis associated with coxsackievirus A10 presents as white or yellow nodules surrounded by erythema in the posterior oropharynx. The lesions do not ulcerate.

Acute Hemorrhagic Conjunctivitis Patients with acute hemorrhagic conjunctivitis present with an acute onset of severe eye pain, blurred vision, photophobia, and watery discharge from the eye. Examination reveals edema, chemosis, and subconjunctival hemorrhage and often shows punctate keratitis and conjunctival follicles as well. Preauricular adenopathy is often found. Epidemics and nosocomial spread have been associated with enterovirus 70 and coxsackievirus A24. Systemic symptoms, including headache and fever, develop in 20% of cases, and recovery is usually complete in 10 days. The sudden onset and short duration of the illness help to distinguish acute hemorrhagic conjunctivitis from other ocular infections such as those due to adenovirus and *Chlamydia*. Paralysis has been associated with some cases of acute hemorrhagic conjunctivitis due to enterovirus 70 during epidemics.

Other Manifestations Enteroviruses are an infrequent cause of childhood pneumonia

and the common cold. Coxsackievirus B has been isolated at autopsy from the pancreas of a few children presenting with insulin-dependent diabetes mellitus; however, most attempts to isolate the virus have been unsuccessful. Other diseases that have been associated with enterovirus infection include bronchitis, bronchiolitis, croup, infectious lymphocytosis, polymyositis, acute arthritis, and acute nephritis.

REOVIRUSES

Reoviruses are double-stranded RNA viruses encompassing three serotypes. Serologic studies indicate that most humans are infected with reoviruses during childhood; however, it has been difficult to establish a definite link of reovirus infection with a particular disease. It is likely that most infections either are asymptomatic or cause very mild disease. One outbreak of reovirus infection in children resulted in minor upper respiratory tract symptoms. Reovirus is considered a rare cause of mild gastroenteritis in infants and children. Speculation regarding an association of reovirus type 3 with idiopathic neonatal hepatitis and extrahepatic biliary atresia is based on an elevated prevalence of antibody to reovirus among some of these patients, detection of viral RNA by PCR in hepatobiliary tissues in some studies, and detection of virus in the porta hepatis in one case.

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194. MEASLES (RUBEOLA) - *Anne Gershon*

DEFINITION

Measles (rubeola) is a highly contagious, acute, exanthematous respiratory disease with a characteristic clinical picture and pathognomonic enanthem. A successful live attenuated measles vaccine became available in 1963 in the United States and elsewhere, and measles is now an unusual disease in most developed countries where this vaccine is widely used. However, measles continues to occur sporadically in mini-epidemics in the United States, and major epidemics in developing nations make this disease a persistent cause of childhood morbidity and mortality.

ETIOLOGIC AGENT

Measles virus is a member of the genus *Morbillivirus* and the family Paramyxoviridae. It is closely related to the viruses causing canine and porcine distemper, rinderpest of cattle, and *peste des petits ruminants* of goats and sheep. There is only one antigenic type. Measles virions are pleomorphic spherical structures having a diameter of 100 to 250 nm and consisting of six proteins. The inner capsid is composed of a coiled helix of RNA and three proteins, and the outer envelope consists of a matrix protein bearing two types of short surface-glycoprotein projections or peplomers. One peplomer is a conical hemagglutinin (H) and the other a dumbbell-shaped fusion (F) protein. The genome has been sequenced, and it is thereby possible to distinguish vaccine-type measles virus from the wild type. In addition, genetic variability of wild-type measles virus occurs; eight genotypes have been identified.

EPIDEMIOLOGY

Measles has a worldwide distribution; humans are the only natural hosts, although other primates can be experimentally infected. During the prevaccination era in the United States, measles epidemics occurred every 2 to 5 years in the winter and spring. In an epidemic year, roughly half a million measles cases were reported; 99% of adults had serologic evidence of previous measles infection. After the live attenuated vaccine became available, the number of cases reported to the Centers for Disease Control and Prevention (CDC) fell, with a nadir of 1497 cases in 1983. After an upsurge to more than 27,000 cases (with 89 deaths) in 1990, the disease was once more brought under control (with only 312 cases reported to the CDC in 1993), in part through the routine administration of two doses of vaccine. The foremost reason for the resurgence of measles was failure to immunize infants and young children, especially in inner-city areas. Primary vaccine failure (documented in about 5% of individuals) and secondary vaccine failure or waning immunity accounted for some cases.

In recent years the majority of cases of measles have involved preschool children. Between 1993 and 1996, fewer than 1000 cases were reported annually in the United States; in 1995 there were 309 reported cases, and in 1996 there were 508. Molecular studies indicated interruption of transmission of indigenous measles in 1993. Most cases have since resulted from international importations of the virus. Mortality is highest among children under 2 years of age and among adults. Patients with impaired cell-mediated immunity are at especially high risk for severe or even fatal measles. The

measles-associated mortality rate in the United States is about 0.3%; in developing countries, mortality frequently exceeds 1% and sometimes approaches 10%.

Measles virus is transmitted by respiratory secretions, predominantly through exposure to aerosols but also through direct contact with larger droplets. Patients are contagious from 1 or 2 days before the onset of symptoms until 4 days after the appearance of the rash. Infectivity peaks during the prodromal phase. The mean intervals from infection to onset of symptoms and to appearance of rash are 10 and 14 days, respectively.

PATHOGENESIS AND PATHOLOGY

Measles virus invades the respiratory epithelium and spreads via the bloodstream to the reticuloendothelial system, from which it infects all types of white blood cells, thereby establishing infection of the skin, respiratory tract, and other organs. Both viremia and viruria develop. Multinucleated giant cells with inclusion bodies in the nucleus and cytoplasm (Warthin-Finkeldey cells) are found in respiratory and lymphoid tissues and are pathognomonic for measles. Direct invasion of T lymphocytes and increased levels of suppressive cytokines, such as interleukin 4, may play a role in the temporary depression of cellular immunity that accompanies and transiently follows measles. The major infected cell in the blood is the monocyte. Infection of the entire respiratory tract accounts for the characteristic cough and coryza of measles and for the less frequent manifestations of croup, bronchiolitis, and pneumonia. Generalized damage to the respiratory tract, with resultant loss of cilia, predisposes to secondary bacterial infections such as pneumonia and otitis media.

Specific antibodies are not detectable before the onset of rash. Cellular immunity (consisting of cytotoxic T cells and possibly natural killer cells) plays a prominent role in host defense, and patients who are deficient in cellular immunity are at high risk for severe measles. Children with isolated agammaglobulinemia are not at increased risk. Immune reactions to the virus in the endothelial cells of dermal capillaries play a substantial role in the development of Koplik's spots (the pathognomonic enanthem) as well as in that of rash; in immunodeficient hosts, measles may be severe despite the absence of these manifestations. Measles antigens have been demonstrated in involved skin during early stages of the illness.

Pathologic changes in measles encephalitis include focal hemorrhage, congestion, and perivascular demyelination. Measles virus is rarely isolated from cerebrospinal fluid (CSF) in cases of encephalitis, which are thought to be due to the interaction of virus-infected cells with local cellular immune factors.

CLINICAL MANIFESTATIONS

Measles begins with a 2- to 4-day respiratory prodrome of malaise, cough, coryza, conjunctivitis with lacrimation, nasal discharge, and increasing fever [with temperatures as high as 40.6°C (105°F), probably reflecting secondary viremia]. At this stage of the illness, in which the rash has not yet developed, influenza may be suspected. Just before the onset of the rash, Koplik's spots appear as 1- to 2-mm blue-white spots on a bright red background. Without adequate illumination for examination, they may be overlooked. Koplik's spots are typically located on the buccal mucosa alongside the

second molars and may be extensive; they are not associated with any other infectious disease. The spots wane after the onset of rash and soon disappear. The entire buccal and inner labial mucosa may be inflamed, and the lips may be reddened.

The characteristic erythematous, nonpruritic, maculopapular rash of measles (Fig. 194-CD1) begins at the hairline and behind the ears, spreads down the trunk and limbs to include the palms and soles, and often becomes confluent. At this time, the patient is at the most severe point of the illness. By the fourth day, the rash begins to fade in the order in which it appeared. Brownish discoloration of the skin and desquamation may occur later. Fever usually resolves by the fourth or fifth day after the onset of rash; prolonged fever suggests a complication of measles. Lymphadenopathy, diarrhea, vomiting, and splenomegaly are common features. The chest x-ray may be abnormal, even in uncomplicated measles, because of the propensity of this virus to invade the respiratory tract. The entire illness usually lasts about 10 days. The disease tends to be more severe in adults than in children, with higher fever, more prominent rash, and a higher incidence of complications.

Milder forms of the illness with less intense symptoms and a milder rash, termed *modified measles*, may occur in individuals with preexisting partial immunity induced by active or passive vaccination. These patients include infants under 1 year of age who retain some proportion of passively acquired maternal antibodies. On occasion, individuals with a history of immunization may develop modified measles.

COMPLICATIONS

The complications of measles can conveniently be divided into three groups, according to the site involved: the respiratory tract, the central nervous system (CNS), and the gastrointestinal tract. Respiratory tract involvement, manifested as laryngitis, croup, or bronchitis, occurs in the majority of cases of uncomplicated measles. In young children, otitis media is the most common complication. Pneumonia is a frequent reason for hospitalization, especially of adults. The pneumonia is of viral origin in the majority of cases, but secondary bacterial infection (most commonly caused by streptococci, pneumococci, or staphylococci) also takes place with some frequency. Primary giant cell (Hecht's) pneumonia is most often documented in immunocompromised and/or malnourished patients.

Encephalographic abnormalities in the absence of symptoms ofCNSdisease are extremely frequent in measles. Symptomatic CNS disease, with fever, headache, drowsiness, coma, and/or seizures, occurs in about 1 case in 1000. Symptoms usually begin within days after the onset of rash but occasionally appear for the first time several weeks later. About 10% of patients do not survive acute measles encephalitis; a significant percentage of surviving patients develop permanent sequelae, such as mental retardation or epilepsy. Most cases appear to result from an immune-mediated response to myelin proteins (postinfectious encephalomyelitis) and not directly from viral infection of the CNS (Chap. 371). Rarely, transverse myelitis follows measles. Immunocompromised patients are at risk for progressive fatal encephalitis 1 to 6 months after measles; in some cases, even though prior measles has not been recognized, the virus is identified at autopsy. Subacute sclerosing panencephalitis (SSPE) -- a protracted, chronic, extremely rare form of measles encephalitis -- sometimes follows

measles and is particularly common among children who have measles before the age of 2 years (Chap. 373). SSPE has virtually disappeared in the United States as a result of widespread vaccination. Typically, progressive dementia evolves over several months. SSPE is thought to be due to a complex interaction of the host with defective measles virus. It is associated with extremely high levels of antibodies to measles virus in the blood andCSF.

Gastrointestinal complications of measles include gastroenteritis, hepatitis, appendicitis, ileocolitis, and mesenteric adenitis. It is not uncommon to detect high levels of alanine and aspartate aminotransferases in the absence of gastrointestinal signs such as jaundice.

Other, rare complications include myocarditis, glomerulonephritis, and postinfectious thrombocytopenic purpura. Measles can exacerbate preexisting tuberculosis, presumably through depression of cellular immunity induced by the virus. Natural measles and immunization against measles can result in tuberculin skin-test anergy lasting for about 1 month.

ATYPICAL MEASLES

An atypical form of measles has been reported in individuals who received formalin-inactivated measles vaccine (used in the United States from 1963 through 1967 and in Canada until 1970) and subsequently were exposed to measles virus. After a several-day prodrome of fever, myalgia, and headache, the rash appears. Unlike the rash of typical measles, that of atypical measles begins peripherally and moves centrally; it can be urticarial, maculopapular, hemorrhagic, and/or vesicular. Fever is usually high and is accompanied by edema of the extremities, interstitial pulmonary infiltrates, hepatitis, and (on occasion) pleural effusion. The differential diagnosis often includes Rocky Mountain spotted fever, Henoch-Schonlein purpura, meningococcemia, drug allergy, toxic shock syndrome, and varicella. Despite the severity of atypical measles, patients invariably recover after a convalescence that may be prolonged. Measles virus is not isolated from these patients, and they do not spread the virus to others. This disease is believed to be due to hypersensitivity to measles virus induced by the inactivated vaccine. Formalin inactivation destroys the antigenicity of the F protein, antibodies to which are important in preventing spread of the virus from one cell to another. The role of cellular immunity in this process is unknown. Extremely high convalescent titers of antibody to measles virus (e.g., 1:1,000,000) are diagnostic of atypical measles. To prevent this syndrome, adults who received formalin-inactivated measles vaccine should be reimmunized with at least one dose of live attenuated measles vaccine. Since inactivated measles vaccine has not been available for more than 25 years, atypical measles has now virtually disappeared.

MEASLES IN THE IMMUNOCOMPROMISED HOST

Patients with defects in cell-mediated immunity are at risk for severe protracted and fatal measles. Included in this category are patients with congenital cellular immune defects or malignancy, recipients of immunosuppressive therapy, or persons infected with HIV. In these patients, measles may not be accompanied by a rash. Complications are primary measles (giant cell) pneumonia, progressive encephalitis beginning weeks to

months after initial infection, and (in HIV-infected patients) progression to AIDS.

MEASLES IN ADULTS

Measles is naturally a disease of childhood and, like many other viral infections, is more severe in adults than in children. About 3% of young adults with measles develop primary viral pneumonia and require hospitalization. Hepatitis and bronchospasm are more common among adults with measles than among children, and the rash is more severe and more confluent in adults. Bacterial superinfection is more common among adults, more than one-third of whom develop respiratory complications such as otitis media, sinusitis, and pneumonia. Adults may develop measles because they were never immunized or (more rarely) because their vaccine-induced immunity has waned. Very low titers of antibody to measles virus have been associated with lack of protection.

LABORATORY FINDINGS

Lymphopenia and neutropenia are common in measles and may be due to invasion of leukocytes by the virus, with subsequent cell death. Leukocytosis may herald a bacterial superinfection. Patients with measles encephalitis usually have an elevated protein concentration inCSF as well as lymphocytosis. A specific diagnosis of measles can be made quickly by immunofluorescent staining of a smear of respiratory secretions for measles antigen; monoclonal antibodies conjugated to fluorescein are commercially available for this purpose. Secretions can also be examined microscopically for multinucleated giant cells. Measles virus can be isolated from respiratory secretions or urine and rapidly identified in tissue culture with fluorescein-labeled monoclonal antibodies. Measles virus RNA has been demonstrated by diagnostic reverse-transcription polymerase chain reaction. A number of serologic tests are available for the diagnosis of measles; however, a serologic diagnosis cannot necessarily be made quickly since both acute- and convalescent-phase sera are usually tested, ideally at the same time. The older hemagglutination inhibition test has been replaced by enzyme immunoassay (EIA), which is more sensitive and simpler to perform. EIA can be used to measure specific IgM and thus to diagnose measles on the basis of an acute-phase serum sample alone. Specific IgM antibodies are detectable within 1 to 2 days after the appearance of rash, and the IgG titer rises significantly after 10 days. As already mentioned, atypical measles andSSPE are associated with extremely high titers of antibody.

DIFFERENTIAL DIAGNOSIS

Classic measles -- with Koplik's spots, cough, coryza, conjunctivitis, and a rash beginning on the head -- is easily diagnosed on clinical grounds. Modified measles is more difficult to diagnose clinically since one or more characteristic signs may be lacking. The differential diagnosis of measles includes Kawasaki's syndrome, scarlet fever, infectious mononucleosis, toxoplasmosis, drug eruption, and *Mycoplasma pneumoniae* infection. Most of these conditions can be identified by either culture or serologic assay. In the differential diagnosis of measles, attention should be paid to the current epidemiology of the disease in the community and to the patient's history of measles vaccination and foreign travel.

PREVENTION

The development of live attenuated measles vaccine by Enders and his colleagues was a milestone in American medicine. This vaccine, used in the United States for the routine immunization of children since 1963, induces seroconversion in about 95% of recipients and probably confers lifelong protection. Waning immunity to measles after immunization has been documented only on rare occasions. For the past 25 years, measles vaccine has been available as the combination vaccine measles-mumps-rubella (MMR); MMR vaccine should be administered to children between the ages of 12 and 15 months. (Vaccination at 12 months is preferred for infants whose mothers were immunized against measles in childhood. These mothers have lower antibody titers than women who have had natural measles, and their infants correspondingly have transplacental antibodies of lower titer and shorter duration.) A second dose of MMR vaccine is recommended for school-aged children at 4 to 12 years of age. This two-dose policy was developed in the late 1980s in response to measles outbreaks in the United States. Since the institution of the two-dose regimen and the increased effort to immunize all children, measles has again become an unusual disease in the United States. Regional guidelines that reflect the current local epidemiology of measles should be followed.

Older susceptible persons should also be immunized. Individuals should be considered susceptible to measles unless they have documentation of physician-diagnosed measles or of the receipt of two doses of vaccine, have laboratory evidence of measles immunity, or were born before 1957. Rarely, individuals born before 1957 develop measles, and those who are at risk of exposure to measles (e.g., health workers, teachers, and international travelers) should be tested for measles antibody and immunized if necessary. Approximately 10% of healthy vaccinees develop a fever, with temperatures up to 39.4°C (103°F), 5 to 7 days after vaccination; this fever lasts 1 to 5 days and is accompanied by a transient rash. Individuals previously immunized only with killed vaccine are considered susceptible and should receive at least one dose -- and preferably two doses -- ofMMRvaccine. Transient adverse reactions in these individuals include fever, malaise, and redness and swelling at the injection site.

Because of the severity of measles in this group and the lack of reported problems following vaccination, children with asymptomatic HIV infection should receiveMMRvaccine; those with severe immunosuppression (<15% CD4 lymphocytes) should not. A case of fatal measles due to vaccine-type virus was reported in a college student with AIDS. Measles vaccine is contraindicated for persons with impaired cell-mediated immunity, for pregnant women, and for persons with a history of anaphylaxis due to egg protein or neomycin. Minor illnesses, with or without fever and a history of convulsions, are not contraindications to vaccination. Vaccination should be deferred for 6 to 11 months after the receipt of immune globulin or of blood products containing antibodies and for at least 3 months after the discontinuation of immunosuppressive treatment. Vaccine failures have been ascribed to faulty storage of the preparation used, immunization of infants with preexisting (maternally derived) antibodies, and simultaneous administration of measles vaccine and immune globulin.

Children and adults who are susceptible to measles and are exposed to the disease should receive postexposure prophylaxis. Standard immune globulin, given

intramuscularly within 6 days of exposure, can exert a protective or modifying effect; the earlier it is given, the better the outcome. The dose is 0.25 mL/kg for healthy persons and 0.5 mL/kg for immunocompromised persons, with a maximum dose of 15 mL. Immune globulin is particularly strongly indicated for susceptible household contacts, especially those less than 1 year of age, and for immunocompromised persons. HIV-infected persons, particularly those with severe immunosuppression, should be given immune globulin after exposure, regardless of their measles immune status and whether or not they are receiving intravenous immunoglobulin. Vaccination within 72 h of exposure may also provide protection against clinical measles, but this strategy is contraindicated as postexposure prophylaxis for immunocompromised individuals. Vaccine and immune globulin should not be given concurrently.

TREATMENT

Therapy for measles is largely supportive and symptom-based. Patients with otitis media and pneumonia should be given standard antibiotics. Patients with encephalitis need supportive care, including observation for increased intracranial pressure. Controlled trials suggest clinical benefit from high doses of vitamin A in severe or potentially severe measles, especially in children under the age of 2 years. A dose of 50,000 IU is used for infants age 1 to 6 months, 100,000 IU for infants age 7 to 12 months, and 200,000 IU for children over 1 year. A single dose is administered on two consecutive days. Transient vomiting and headache may be associated with the administration of vitamin A. Ribavirin is effective against measles virus in vitro and may be considered for use in immunocompromised individuals.

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195. RUBELLA (GERMAN MEASLES) - *Anne Gershon*

DEFINITION

Rubella is an acute viral infection of children and adults that characteristically includes rash, fever, and lymphadenopathy and has a broad spectrum of other possible manifestations. However, a high percentage of rubella infections in both children and adults are subclinical. In addition, the illness can resemble a mild attack of measles (rubeola) and can cause arthritis, especially in adults. Rubella during pregnancy can lead to fetal infection, with the production of a significant constellation of malformations (*congenital rubella syndrome*) in a high proportion of infected fetuses.

ETIOLOGIC AGENT

Rubella virus, a togavirus, is the only member of the *Rubivirus* genus and is closely related to the alphaviruses. Unlike these agents, however, it does not require a vector for transmission. Moreover, there is no RNA sequence homology between rubella virus and the alphaviruses.

The rubella virion is composed of an inner icosahedral capsid of RNA and protein that is surrounded by a lipid-containing envelope with a diameter of about 60 nm. The structural proteins associated with rubella virus are E1 and E2 (transmembrane envelope glycoproteins) and C (the capsid protein that surrounds the viral RNA). Only one serotype has been identified.

EPIDEMIOLOGY

In the United States during the prevaccine era, rubella was most common in the spring and most often affected school-age children; only 80 to 90% of adults were immune; and major epidemics occurred every 6 to 9 years. The most recent epidemic in the United States occurred in 1964 to 1965, when there were more than 12 million reported cases of postnatal rubella and more than 20,000 cases of the congenital rubella syndrome. Since the introduction of live attenuated rubella vaccine in 1969, there have been no epidemics; limited outbreaks have been reported in settings where susceptible individuals come into close contact with one another (e.g., schools and workplaces). In 1996, only 213 cases of postnatally acquired rubella -- most of them in young adults -- and 2 confirmed cases of congenital rubella syndrome were reported to the Centers for Disease Control and Prevention (CDC).

Whether symptomatic or subclinical, rubella is contagious, albeit less so than measles. Its incubation period is 18 days on average, with a range of 12 to 23 days. The virus, which is spread in droplets shed in respiratory secretions, infects the respiratory tract and then the bloodstream. In postnatally acquired infections, rubella virus is shed during the prodromal phase of the illness, and shedding from the pharynx can continue for about a week after onset. Despite high titers of specific neutralizing antibodies, infants with congenital rubella may excrete rubella virus from the respiratory tract and in the urine until the age of 2 years. This excretion raises important issues related to infection control in hospital and day-care settings. Persons recently immunized with live attenuated rubella vaccine do not transmit the vaccine virus to others, although low

titers of rubella virus may be detected transiently in the pharynx.

After an attack of rubella, specific antibodies and cell-mediated immunity develop and probably play a significant role in protection against future disease. Asymptomatic reinfection at the level of the respiratory tract is common upon reexposure to the virus but is rarely if ever associated with viremia.

Rubella virus has been cultured from respiratory secretions during reinfection. Fetal infection may occur during maternal reinfection but is acknowledged to be extremely rare because of the absence of maternal viremia under these circumstances. Viremia following reinfection of individuals immunized against rubella is also rare. Thus the current level of congenital rubella in the United States is exceedingly low.

PATHOGENESIS AND PATHOLOGY

Little is known about the microscopic pathology of postnatally acquired rubella since the disease is invariably self-limited. Like that of measles, the rash of rubella is immunologically mediated; its onset coincides with the development of specific antibodies. Viremia can be demonstrated for about a week before and ends within a few days after the onset of rash.

The cause of the damage to cells and organs in congenital rubella is not well understood. Proposed mechanisms of fetal damage include mitotic arrest of cells, tissue necrosis without inflammation, and chromosomal damage. The growth of the fetus may be retarded. Other findings may include decreased numbers of megakaryocytes in the bone marrow, extramedullary hematopoiesis, and interstitial pneumonia.

CLINICAL MANIFESTATIONS

Postnatally Acquired Rubella Infection acquired after birth usually results in an extremely mild or subclinical illness. A prodromal phase is uncommon in children; adults may have more severe disease, with a brief prodrome of malaise, fever, and anorexia. The foremost symptoms of postnatally acquired rubella include posterior auricular, cervical, and suboccipital lymphadenopathy; fever; and rash. The rash often begins on the face and spreads down the body (Fig. 195-CD1). It is maculopapular but not confluent, is sometimes accompanied by mild coryza and conjunctivitis, and generally lasts for 3 to 5 days. A petechial enanthem on the soft palate, designated *Forschheimer spots*, may occur but is not specific for rubella. Fever may be absent entirely or may be present for only several days in the early phase of the illness.

Complications of postnatally acquired rubella are uncommon; bacterial superinfection is rare. One particularly troublesome complication is seen almost exclusively in women: arthritis, most frequently involving the fingers, wrists, and/or knees, develops as the rash is appearing and may take several weeks to resolve. Chronic arthritis resulting from rubella is extremely rare. Rubella virus has been isolated from joint fluid during acute rubella arthritis and from peripheral blood in chronic rubella arthritis.

Another complication of postnatally acquired rubella is hemorrhage due to both thrombocytopenia and vascular damage, which occurs in 1 of every 3000 patients.

Thrombocytopenia may last for weeks or months; it can have long-term consequences if there is bleeding into organs such as the eye or the brain.

Both children and adults may develop encephalitis after rubella; the incidence is about five times lower than that of encephalitis following measles. Adults are more likely than children to develop encephalitis; the mortality rate from this complication is 20 to 50%. Mild hepatitis is an unusual complication. Immunosuppressed patients are not at increased risk for rubella as they are for measles.

Congenital Rubella Maternal infection in early pregnancy can lead to fetal infection, with resultant congenital rubella. The classic signs of congenital rubella are cataract, heart disease, and deafness, but a myriad of other defects have been reported. These abnormalities include signs and symptoms that are transient, such as low birth weight, thrombocytopenia, hepatosplenomegaly, jaundice, and pneumonia; those that are permanent, such as deafness, pulmonic stenosis, patent ductus arteriosus, glaucoma, and cataract; and those that are developmental, such as mental retardation, diabetes mellitus, and behavioral disorders.

The most important factor in the pathogenicity of rubella virus for the fetus is gestational age at the time of infection. Maternal infection during the first trimester leads to fetal infection in about 50% of cases; maternal infection early in the second trimester leads to fetal infection in about one-third of cases. Fetal malformations not only are more common after maternal infection in the first trimester but also tend to be more severe and to involve more organ systems. While a fetus infected in the fourth week of gestation may develop many problems, one infected later (e.g., in the 20th week) may have isolated deafness as the only symptom.

DIAGNOSIS

Since postnatally acquired rubella is such a mild disease and since many cases are subclinical, diagnosis on clinical grounds can be difficult. Other diseases that may mimic rubella include toxoplasmosis, scarlet fever, modified measles, roseola, fifth disease (erythema infectiosum due to parvovirus B19), and enteroviral infection. Routine laboratory tests usually reveal leukopenia and atypical lymphocytes.

The isolation of rubella virus in cell cultures of throat samples, urine, or other secretions is difficult and expensive but is sometimes undertaken. This technique is most useful when congenital rubella is suspected. A laboratory diagnosis is more often made serologically. The most commonly used test is an enzyme-linked immunosorbent assay (ELISA) for IgG and IgM antibodies. Acute rubella is diagnosed by the documentation of a fourfold or greater rise in the titer of IgG antibodies in paired acute- and convalescent-phase serum specimens or by the detection of rubella-specific IgM antibodies in one serum specimen. However, false-negative and -positive IgM reactions are sometimes obtained. Moreover, true-positive IgM reactions can be obtained in both primary infection and reinfection. Congenital rubella is diagnosed by the isolation of rubella virus, the detection of IgM antibodies in a single serum sample, and/or the documentation of either the persistence of rubella antibodies in serum beyond 1 year of age or a rising antibody titer anytime during infancy in an unvaccinated child. Biopsied tissues and/or blood and cerebrospinal fluid have also been used for the demonstration

of rubella antigens with monoclonal antibodies and for the detection of rubella RNA by in situ hybridization and polymerase chain reaction.

PREVENTION

Live attenuated rubella vaccine was licensed in 1969, 7 years after the virus was first isolated in culture. This vaccine was developed as a strategy to prevent congenital rubella by ensuring that very few pregnant women would be susceptible and that there would be little circulating wild-type virus. Rubella vaccine induces seroconversion in more than 95% of recipients. Since its licensure, there have been no major epidemics in the United States, and the number of cases has declined by 98%. The vaccine currently licensed in the United States, RA 27/3, is propagated in human diploid cells and is more immunogenic (particularly with regard to the stimulation of secretory immunity) than previously licensed vaccines. The present vaccination strategy, developed in part when measles was not being adequately controlled, is to immunize all infants at 12 to 15 months of age with measles-mumps-rubella (MMR) vaccine and to administer a second dose at 4 to 12 years of age. Rubella vaccine may also be administered to anyone who is thought to be susceptible to the infection and is not pregnant; it is particularly important that hospital workers of either sex be immune to rubella so that nosocomial transmission is avoided. While there has been little change in the prevalence of immunity to rubella among women of childbearing age (about 80%), the incidence of congenital rubella is extremely low -- about 10 cases annually. It is likely that, although antibody may be undetectable years after immunization, protection against infection -- possibly due to cell-mediated immunity -- is the rule. At present, there is little if any evidence of significant waning of clinically important immunity to rubella with time.

On occasion, rubella vaccine may cause arthralgia or arthritis, especially in young women. Very rarely, rubella vaccination results in chronic arthritis; however, even cases of frank arthritis in vaccinees are self-limited, lasting only about 1 week.

After investigation of a series of more than 400 women who were inadvertently immunized during pregnancy and who carried their infants to term, theCDC has concluded that vaccine-type rubella virus either does not cause the congenital rubella syndrome at all or does so at an incidence too low to be detected. Nonetheless, rubella vaccine is contraindicated for use in pregnant women, and it is recommended that pregnancy be avoided for at least 3 months after rubella vaccination. It is acceptable for rubella-susceptible children whose mothers are also susceptible to be immunized, since vaccinated individuals do not shed rubella virus or transmit it to susceptible individuals. Although it is recommended that rubella vaccine not be given to immunosuppressed persons, the vaccine is given to children infected with HIV. No adverse effects of rubella vaccine have been reported in immunocompromised patients.

TREATMENT

There is no specific therapy for rubella. At one time, immune globulin was used in an effort to prevent congenital rubella when pregnant women became infected. However, since administration of immune globulin did not prevent maternal viremia, this approach was discarded. Treatment is given for symptoms such as fever, arthralgia, and arthritis.

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196. MUMPS - *Anne Gershon*

DEFINITION

Mumps is an acute, systemic, communicable viral infection whose most distinctive feature is swelling of one or both parotid glands. Involvement of other salivary glands, the meninges, the pancreas, and the gonads is also common.

ETIOLOGIC AGENT

Mumps virus, a paramyxovirus, is pleomorphic and has a diameter ranging from 100 to 600 nm. The virion is composed of RNA and five proteins. The RNA is surrounded by an envelope with glycoprotein projections. There are two envelope glycoproteins -- a hemagglutinin-neuraminidase (HN) and a hemolysis cell fusion antigen (F) -- as well as a matrix envelope protein (M). There are two internal components: a nucleocapsid protein (NP) and an RNA polymerase protein. There is only one antigenic type of mumps virus.

EPIDEMIOLOGY

After the introduction of mumps vaccine in 1967, the incidence of clinical mumps declined significantly in the United States. In 1968 (before widespread immunization), 185,691 cases of mumps were reported in this country. The 906 cases reported in 1995 represent a reduction in the number of cases by>99% from prevaccine levels; this is the lowest number of cases ever reported in a year. Before widespread vaccination, the incidence of mumps was highest in the winter and spring, with epidemics every 2 to 5 years. At that time, mumps was principally a disease of childhood, although today more than 50% of cases occur in young adults. Epidemics tended to occur in confined populations, such as those in schools and the military services.

The incubation period of mumps generally ranges from 14 to 18 days, with extremes of 7 and 23 days. However, because a contact may be shedding virus before the onset of clinical disease or (like one-third of patients) may have subclinical infection, the incubation period in individual cases is often uncertain. One attack of mumps usually confers lifelong immunity. Long-term immunity is also associated with immunization.

PATHOGENESIS

Mumps virus is transmitted by droplet nuclei, saliva, and fomites. Replication of the virus in the epithelium of the upper respiratory tract leads to viremia, which is followed by infection of glandular tissues and/or the central nervous system (CNS).

Little is known of the pathology of mumps since the disease is rarely fatal. The affected glands contain perivascular and interstitial mononuclear cell infiltrates with prominent edema. Necrosis of acinar and epithelial duct cells is evident in the salivary glands and in the germinal epithelium of the seminiferous tubules.

CLINICAL MANIFESTATIONS

The prodrome of mumps consists of fever, malaise, myalgia, and anorexia. Parotitis, if it develops, usually does so within the next 24 h but may be delayed for as long as a week; it is generally bilateral, although the onset on the two sides may not be synchronous and at times only one side is affected. The submaxillary and sublingual glands are involved less often than the parotid and are almost never involved alone. Swelling of the parotid is accompanied by tenderness and obliteration of the space between the ear lobe and the angle of the mandible. The patient frequently reports an earache and finds it difficult to eat, swallow, or talk. Glandular swelling increases for a few days and then gradually subsides, disappearing within a week. The orifice of Stensen's duct is commonly red and swollen. Presternal pitting edema has been described in about 5% of mumps cases, often in association with submandibular adenitis.

Other than parotitis, orchitis is the most common manifestation of mumps among postpubertal males, developing in about 20% of cases. The testis is painful and tender and is enlarged to several times its normal size; accompanying fever is common. Later, testicular atrophy develops in half of the affected men. Since orchitis is bilateral in fewer than 15% of cases, sterility after mumps is rare. Oophoritis in women -- far less common than orchitis in men -- may cause lower abdominal pain but does not lead to sterility.

Aseptic meningitis, which may develop before, during, after, or in the absence of parotitis, is a common manifestation of mumps in both children and adults. Symptoms include stiff neck, headache, and drowsiness. Pleocytosis of the cerebrospinal fluid (CSF), with up to 1000 cells/uL, may develop in up to 50% of cases of clinical mumps, but clinical signs of meningeal irritation are documented in only 5 to 25% of cases. Within the first 24 h, polymorphonuclear leukocytes may predominate in CSF, but by the second day nearly all the cells are lymphocytes. The glucose level in CSF may be abnormally low, and this finding may arouse suspicion of bacterial meningitis. Aseptic meningitis due to mumps without parotitis is indistinguishable clinically from that caused by other viruses. Mumps meningitis is almost invariably self-limited, although cranial nerve palsies have occasionally led to permanent sequelae, particularly deafness. More rarely, mumps virus may cause encephalitis, which presents as high fever with marked changes in the level of consciousness and frequently results in permanent sequelae in survivors. OtherCNSproblems occasionally associated with mumps include cerebellar ataxia, facial palsy, transverse myelitis, Guillain-Barre syndrome, and aqueductal stenosis leading to hydrocephalus.

Mumps pancreatitis, which may present as abdominal pain, is difficult to diagnose because an elevated serum amylase level can be associated with either parotitis or pancreatitis. Other unusual complications of mumps include myocarditis, mastitis, thyroiditis, nephritis, arthritis, and thrombocytopenic purpura. An excessive number of spontaneous abortions are associated with gestational mumps when the disease occurs during the first trimester. Mumps in pregnancy does not lead to premature birth or fetal malformations.

DIFFERENTIAL DIAGNOSIS

The diagnosis of mumps is made easily in patients with acute bilateral parotitis and a

history of recent exposure. When parotitis is unilateral or absent or when sites other than the parotid gland are involved, laboratory diagnosis is required (see below).

The myriad causes of bilateral parotid swelling other than mumps virus include infection with other viruses, such as parainfluenza virus type 3, coxsackieviruses, and influenza A virus; metabolic diseases, such as diabetes mellitus and uremia; and drugs, such as phenylbutazone and thiouracil. Unilateral parotid swelling can result from a tumor, a cyst, or a ductal obstruction due to stones or strictures. Other conditions associated with chronic parotid swelling include sarcoidosis, Sjogren's syndrome, and infection with HIV. Suppurative parotitis, usually caused by *Staphylococcus aureus*, is most often unilateral.

Other entities should be considered when manifestations consistent with mumps appear in organs other than the parotid. Testicular torsion may produce a painful scrotal mass resembling that seen in mumps orchitis. Other viruses (e.g., enteroviruses) may cause aseptic meningitis that is clinically indistinguishable from that due to mumps virus.

LABORATORY DIAGNOSIS

Mumps virus is readily isolated after inoculation of appropriate clinical specimens into a variety of host systems, such as rhesus monkey kidney cells and human embryonic lung fibroblasts. The virus can be rapidly identified by the use of cells grown in shell vials and of fluorescein-labeled monoclonal antibodies. Mumps virus may be recovered from saliva, throat, and urine during the first few days of illness and from the CSF of patients with mumps meningitis. Shedding of virus in the urine may persist for as long as 2 weeks. No particular peripheral blood cell count is characteristic of mumps.

Highly sensitive enzyme-linked immunosorbent assays are useful for diagnosis of mumps and for determination of susceptibility to the disease. Acute mumps can be diagnosed either by the examination of acute- and convalescent-phase sera for a significant increase in IgG antibody titer or by the demonstration of specific IgM in one serum specimen. Use of a skin-test antigen to assess immunity to mumps has been replaced by serologic testing.

PREVENTION

Live attenuated mumps vaccine (Jeryl Lynn strain) induces antibodies that protect against infection in more than 95% of cases. The subcutaneously administered vaccine may be given to children older than 1 year but is not recommended for younger infants because of the potential for interference by passive maternal antibodies. Mumps vaccine is usually administered as part of the measles-mumps-rubella (MMR) vaccine at the age of 12 to 15 months and again at 4 to 12 years of age. This MMR vaccine is also recommended for susceptible older children, adolescents, and adults, particularly adolescent males who have not had mumps. For these patients, either MMR or monovalent mumps vaccine may be given; two doses are preferred. Inadvertent immunization of individuals who are already immune is not associated with significant adverse reactions. Mumps vaccine is not recommended for pregnant women, for patients receiving glucocorticoids, or for other immunocompromised hosts. However, children with HIV infection who are not severely immunocompromised can safely be

immunized against mumps; MMR vaccine is usually used for this purpose (Chap. 194).

TREATMENT

Therapy for parotitis and other manifestations of mumps is symptom-based. The administration of analgesics and the application of warm or cold compresses to the parotid area may be helpful. Mumps immune globulin is of no value in the prophylaxis or treatment of established disease. Testicular pain may be minimized by the local application of cold compresses and gentle support for the scrotum. Anesthetic blocks may also be used. Neither the administration of glucocorticoids nor incision of the tunica albuginea is of proven value for the treatment of severe orchitis. Anecdotal information on a small number of patients with orchitis suggests that administration of interferona may be helpful.

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197. RABIES VIRUS AND OTHER RHABDOVIRUSES - *Lawrence Corey*

RABIES VIRUS

DEFINITION

Rabies is an acute viral disease of the central nervous system (CNS) that affects all mammals and that is transmitted by infected secretions, usually saliva. Most exposures to rabies are through the bite of an infected animal, but on occasion contact with a virus-containing aerosol or the ingestion or transplantation of infected tissues may initiate the disease process.

ETIOLOGY

The rabies virus is a bullet-shaped, enveloped, single-stranded RNA virus that is 75 to 80 nm in diameter and belongs to the genus *Lyssavirus* within the rhabdovirus family. The envelope glycoproteins of rabies viruses are arranged in knoblike structures that cover the surface of the virion. Genetic and phenotypic analyses of the envelope have been used to detail the molecular epidemiology and spread of unique variants within animal species. The viral glycoproteins bind to acetylcholine receptors, contribute to the neurovirulence of rabies virus, elicit neutralizing and hemagglutination-inhibiting antibodies, and stimulate cytotoxic T cell immunity. The nucleocapsid antigen induces a complement-fixing antibody as well as T helper cell reactivity. Neutralizing antibodies to the surface glycoproteins appear to be protective and are directed at conformational epitopes of the viral envelope glycoprotein. The antibodies to rabies virus used in diagnostic immunofluorescence assays are generally directed against the nucleocapsid antigens. Isolates of rabies virus from different animal species and locales differ in their antigenic and biologic properties. These variations may account for differences in virulence between isolates. Interferon is induced by rabies virus, particularly in those tissues with high virus concentrations, and may play some role in retarding progressive infection.

EPIDEMIOLOGY

Rabies is found in animals in all regions of the world except Australasia and Antarctica. Rabies exists in two epidemiologic forms: *urban rabies*, propagated chiefly by unimmunized domestic dogs and cats, and *sylvatic rabies*, propagated by skunks, foxes, raccoons, mongooses, wolves, and bats. Infection in domestic animals usually represents a "spillover" from sylvatic reservoirs of infection. Human infection occurs through contact with unimmunized domestic animals or from exposure to wild animals in locales where rabies is enzootic or epizootic. The worldwide incidence of rabies is estimated at more than 30,000 cases per year. Southeast Asia, the Philippines, Africa, the Indian subcontinent, and tropical South America are areas where the disease is especially common. In some endemic areas, 1 to 2% of autopsies yield evidence of rabies. Increased spread of terrestrial rabies (i.e., rabies in animals that walk on the ground rather than rabies in animals that fly) and increased travel to countries where urban rabies exists have made the recognition of clinical rabies and its prevention of increasing importance. While focal epidemics of terrestrial rabies have occurred in the United States and Europe, human rabies is uncommon, largely because of successful

domestic-animal vaccination programs. Since 1980, 36 human cases of rabies have been diagnosed in the United States; 58% of these cases were associated with exposure to bats, while one-third were acquired through dog bites sustained outside the United States. Most persons with proven clinical rabies in this country report no history of an animal bite. More than one-third of recent cases have been diagnosed post-mortem.

In most areas of the world, the dog is the most important vector of rabies virus for humans. However, the wolf (in eastern Europe and Arctic regions), the mongoose (in South Africa and the Caribbean), the fox (in western Europe), and the vampire bat (in Latin America) may also be prominent vectors. Although rabies in wildlife is common throughout both the developed and the undeveloped world, most cases of postexposure prophylaxis are associated with domesticated animals such as dogs and cats. In the United States, local governments are charged with initiating and maintaining programs for rabies vaccination of all dogs, cats, and ferrets. Rodents and lagomorphs are rarely infected with rabies virus. Several cases of human-to-human transmission of rabies through corneal transplantation have also been documented. Bite and nonbite exposures to infected humans could theoretically transmit rabies. Because of delayed diagnosis, postexposure prophylaxis of health care workers and close contacts of cases is common.

PATHOGENESIS

The first event in rabies is the introduction of live virus through the epidermis or onto a mucous membrane. Initial viral replication appears to occur within striated muscle cells at the site of inoculation. The peripheral nervous system is exposed at the neuromuscular and/or neurotendinous spindles of unmyelinated sensory nerve cell endings. The virus then spreads centripetally up the nerve to the CNS, probably via peripheral nerve axoplasm, at a rate of ~3 mm/h. Viremia has been documented in experimental conditions but is thought not to play a role in naturally acquired disease. Once the virus reaches the CNS, it replicates almost exclusively within the gray matter and then passes centrifugally along autonomic nerves to other tissues -- the salivary glands, adrenal medulla, kidneys, lungs, liver, skeletal muscles, skin, and heart. Passage of the virus into the salivary glands and viral replication in mucinogenic acinar cells facilitate further transmission via infected saliva. The incubation period of rabies is exceedingly variable, ranging from 7 days to>1 year (mean, 1 to 2 months) and apparently depending on the amount of virus introduced, the amount of tissue involved, host defense mechanisms, and the actual distance that the virus has to travel from the site of inoculation to the CNS. Rates of infection and mortality are highest from bites on the face, intermediate from bites on the hands and arms, and lowest from bites on the legs. Cases of human rabies with an extended incubation period (2 to 7 years) have been reported, but they are rare. Host immune responses and viral strains also influence disease expression.

The neuropathology of rabies resembles that of other viral diseases of theCNS: hyperemia, varying degrees of chromatolysis, nuclear pyknosis, and neuronophagia of the nerve cells; infiltration by lymphocytes and plasma cells of the Virchow-Robin space; microglial infiltration; and parenchymal areas of nerve cell destruction. In experimental animal models, adenohypophyseal infection with rabies virus, with reduction in growth

hormone and vasopressin release, is common. The most characteristic pathologic finding of rabies in the CNS is the formation of cytoplasmic inclusions called *Negri bodies* within neurons. Each eosinophilic mass measures ~10 nm and is made up of a finely fibrillar matrix and rabies virus particles. Negri bodies are distributed throughout the brain, particularly in Ammon's horn, the cerebral cortex, the brainstem, the hypothalamus, the Purkinje cells of the cerebellum, and the dorsal spinal ganglia. Negri bodies are not demonstrated in at least 20% of cases of rabies, and their absence from brain material does not rule out the diagnosis.

CLINICAL MANIFESTATIONS

The clinical manifestations of rabies can be divided into four stages: (1) a nonspecific prodrome, (2) an acute encephalitis similar to other viral encephalitides, (3) a profound dysfunction of brainstem centers that produces the classic features of rabies encephalitis, and (4) death or, in rare cases, recovery.

The prodromal period usually lasts 1 to 4 days and is marked by fever, headache, malaise, myalgias, increased fatigability, anorexia, nausea and vomiting, sore throat, and a nonproductive cough. The prodromal symptom suggestive of rabies is the complaint of paresthesia and/or fasciculations at or around the site of inoculation of virus. These sensations, which may be related to the multiplication of virus in the dorsal root ganglion of the sensory nerve supplying the area of the bite, are reported by 50 to 80% of patients.

The encephalitic phase is usually ushered in by periods of excessive motor activity, excitation, and agitation. Confusion, hallucinations, combativeness, bizarre aberrations of thought, muscle spasms, meningismus, opisthotonic posturing, seizures, and focal paralysis soon appear. Characteristically, the periods of mental aberration are interspersed with completely lucid periods, but as the disease progresses the lucid periods get shorter until the patient lapses into coma. Hyperesthesia, with excessive sensitivity to bright light, loud noise, touch, and even gentle breezes, is very common. On physical examination, the temperature may be found to be as high as 40.6°C (105°F). Abnormalities of the autonomic nervous system include dilated irregular pupils; increased lacrimation, salivation, and perspiration; and postural hypotension. Evidence of upper motor neuron paralysis, with weakness, increased deep tendon reflexes, and extensor plantar responses, is the rule. Paralysis of the vocal cords is common. Unfortunately, the presenting signs and symptoms of rabies are indistinguishable from those of other viral and neurologic diseases. Thus delays in diagnosis are frequent. The presence of hydrophobia or aerophobia (seen in about two-thirds of recent cases) increases the likelihood of antemortem diagnosis.

The manifestations of brainstem dysfunction begin shortly after the onset of the encephalitic phase. Cranial nerve involvement causes diplopia, facial palsies, optic neuritis, and the characteristic difficulty with deglutition. The combination of excessive salivation and difficulty in swallowing produces the traditional picture of "foaming at the mouth." Hydrophobia, the painful, violent, involuntary contraction of the diaphragmatic, accessory respiratory, pharyngeal, and laryngeal muscles initiated by swallowing liquids, is seen in ~50% of cases. Involvement of the amygdaloid nucleus may result in priapism and spontaneous ejaculation. The patient lapses into coma, and involvement

of the respiratory center produces an apneic death. The prominence of early brainstem dysfunction distinguishes rabies from other viral encephalitides and accounts for the rapid downhill course. The median period of survival after the onset of symptoms is 4 days, with a maximum of 20 days, unless artificial supportive measures are instituted.

If intensive respiratory support is used, a number of late complications may appear. These include inappropriate secretion of antidiuretic hormone, diabetes insipidus, cardiac arrhythmias, vascular instability, adult respiratory distress syndrome, gastrointestinal bleeding, thrombocytopenia, and paralytic ileus. Recovery is very rare and, when it occurs, gradual.

Rabies may also present as an ascending paralysis resembling the Landry/Guillain-Barre syndrome (dumb rabies, *rage tranquille*). Initially, this clinical pattern was reported most frequently among persons given postexposure rabies prophylaxis after being bitten by vampire bats. Paralytic rabies also occurs in Southeast Asia among persons with canine exposures.

The difficulty of diagnosing rabies associated with ascending paralysis is illustrated by cases of person-to-person transmission of the virus by tissue transplantation. Corneal transplants from donors who died of presumed Landry/Guillain-Barre syndrome produced clinical rabies in and caused the deaths of the recipients. Retrospective pathologic examinations of the brains of recipients demonstrated Negri bodies, and rabies virus was subsequently isolated from each donor's frozen eye.

LABORATORY FINDINGS

Early in the disease, hemoglobin values and routine blood chemistry results are normal; abnormalities develop as hypothalamic dysfunction, gastrointestinal bleeding, and other complications ensue. The peripheral white blood cell count is usually slightly elevated (12,000 to 17,000/uL) but may be normal or as high as 30,000/uL.

The specific diagnosis of rabies depends on (1) the isolation of virus from infected secretions [saliva or, rarely, cerebrospinal fluid (CSF)] or tissue (brain), (2) the serologic demonstration of acute infection, (3) the detection of viral antigen in infected tissue (e.g., corneal impression smears, skin biopsies, or brain), or (4) the detection of viral nucleic acid (RNA) by polymerase chain reaction (PCR). A reference laboratory evaluating antemortem samples can confirm rabies with high sensitivity and specificity. Isolation of virus from saliva, demonstration of viral nucleic acid in saliva, or detection of viral antigen in a nuchal skin biopsy specimen is most sensitive. Examination of corneal epithelium specimens appears less sensitive. In the unvaccinated person, demonstration of rabies antibodies in serum or CSF may be useful, although such antibodies may not appear until late in the course of disease. Samples of brain obtained at postmortem examination or brain biopsy should be subjected to (1) mouse inoculation studies for virus isolation, (2) fluorescent antibody (FA) staining for viral antigen, and (3) histologic and/or electron microscopic examination for Negri bodies or reverse transcription PCR for rabies virus RNA.

Postexposure rabies prophylaxis rarely elicitsCSFneutralizing antibody to rabies virus. If present after prophylaxis, such antibody is usually found at a low titer (<1:64), whereas

CSF titers in human rabies may vary from 1:200 to 1:160,000.

DIFFERENTIAL DIAGNOSIS

There is little to distinguish rabies from other viral encephalitides. The most helpful clue to the diagnosis is a history of a bite or other salivary exposure to a potentially infected animal. As bite exposures are infrequent among U.S. cases, a history of relatively recent travel to a rabies-endemic area should be sought. Other problems to be considered in the differential diagnosis include hysterical reactions to animal bites (pseudohydrophobia), Landry/Guillain-Barre syndrome, poliomyelitis, and allergic encephalomyelitis developing in response to rabies vaccine; this last problem is usually associated with receipt of nerve tissue-derived vaccine and usually begins 1 to 4 weeks after vaccination.

TREATMENT

Postexposure Prophylaxis (See Fig. 197-1) Although rabies among humans is rare in the United States, each year ~35,000 persons receive postexposure prophylaxis. The decision to initiate postexposure prophylaxis should include the following considerations: (1) whether the individual came into physical contact with saliva or another substance likely to contain rabies virus, (2) whether rabies is known or suspected in the species and area associated with the exposure (e.g., all persons within the continental United States bitten by a bat that escapes should receive postexposure prophylaxis), and (3) the circumstances surrounding the exposure (e.g., whether the bite was provoked or unprovoked). Bites associated with the feeding of an animal are considered to have been provoked.

If rabies is known or suspected to be present in the animal species involved in a human exposure, the implicated animal should be captured if possible. Any wild animal involved in a rabies exposure; any ill, unvaccinated, or stray domestic animal involved in a rabies exposure; and any animal inflicting an unprovoked bite, exhibiting abnormal behavior, or suspected of being rabid should be humanely killed. The animal's head should be sent immediately to an appropriate laboratory for rabiesFAexamination. If examination of the brain by the FA technique gives negative results, it can be assumed that the saliva contains no virus, and the exposed person need not be treated. Persons exposed to wild animals that subsequently escape, that are capable of carrying rabies (bats, skunks, coyotes, foxes, raccoons, etc.), and that inhabit an area where rabies is known or suspected to be present should undergo both passive and active immunization against rabies (see below) as soon as possible after exposure.

In an area in which feline or canine rabies is not prevalent, a healthy biting dog, cat, or ferret can be confined and observed for 10 days. Persons in such an area should not begin a course of prophylaxis unless the animal develops clinical signs of rabies. If the animal becomes ill or behaves abnormally during the observation period, it should be killed forFAexamination. Experimental and epidemiologic evidence suggests that animals that remain healthy for 10 days after a bite will not have transmitted rabies virus at the time of the bite. In areas of high endemicity for canine rabies, immediate examination of the animal's brain, especially in the case of a severe bite, may be warranted. Bites of rodents, rabbits, and hares almost never require antirabies

postexposure prophylaxis. Unless the exposed person can rule out a bite, scratch, or mucous membrane exposure, postexposure prophylaxis should be considered after direct contact between a human and a bat.

Postexposure prophylaxis of rabies includes rigorous cleansing and treatment of the wound and the administration of rabies vaccine together with antirabies immunoglobulin. Postexposure prophylaxis should be initiated as soon as possible after exposure. As the incubation period of rabies is quite variable, postexposure prophylaxis should be begun as long as clinical signs of rabies are not present.

1. *Wound cleansing and treatment*. Thorough cleansing and treatment of the bite wound constitute an important component of rabies prevention. The wound should be scrubbed with soap and then flushed with water. Both mechanical cleansing and chemical cleansing are important. Quaternary ammonium compounds such as 1 to 4% benzalkonium chloride, 1% cetrimonium bromide, or povidone-iodine solutions should be utilized. Tetanus toxoid and antibiotic prophylaxis should be administered as needed.

2. *Passive immunization with antirabies antiserum of either equine or human origin*. Postexposure antirabies vaccination should include the administration of both passive antibody and vaccine, except when the individual has previously received preexposure prophylaxis. Human rabies immune globulin (RIG) is preferred because equine antiserum may cause serum sickness. RIG is administered only once, at the beginning of the postexposure prophylaxis regimen. The recommended dose of RIG is 20 IU/kg. The dose of equine antiserum is 40 units/kg. The full dose should be thoroughly infiltrated into the area around the wound and into the wound itself. Any remaining portion of the dose is injected intramuscularly at a site distant from the vaccine.

3. *Active immunization with antirabies vaccine*. Three rabies vaccines are available in the United States: (1) human diploid cell vaccine (HDCV), which can be given either intramuscularly or intradermally; (2) rabies vaccine absorbed (RVA); and (3) purified chick embryo cell vaccine. The latter two vaccines are administered intramuscularly. Each vaccine is derived from a different strain of rabies virus and prepared in a slightly different formulation. The three vaccines are considered equally efficacious and safe, and any of the three can be administered in conjunction withRIG. Five 1-mL doses of HDCV are given intramuscularly, preferably in the deltoid or anterolateral thigh area: the gluteal area should not be utilized. The five doses of HDCV should be administered within 28 days on the following schedule: days 0, 3, 7, 14, and 28. The World Health Organization also recommends 21- and 90-day injections. Severe reactions to these vaccines are uncommon. Immediate hypersensitivity responses, such as urticaria, have been reported in ~1 of every 650 recipients. Systemic reactions, such as fever, headache, and nausea, are generally mild and are reported in 1 to 4% of recipients. Local reactions, such as swelling, erythema, and induration at the injection site, occur in 15 to 20% of vaccinees. Guillain-Barre syndrome has been reported but appears to be quite rare.

In the developing world, several other effective rabies vaccines have been licensed and used extensively. They include vaccines made in chick embryonic cells, primary hamster cells, Vero cells, and duck embryonic cells. As some of these preparations are somewhat less immunogenic than the vaccines approved by the U.S. Food and Drug

Administration (FDA), evaluation of serum antibodies after immunization is suggested by some authorities.

The combination ofRIG andHDCVelicits high titers of neutralizing antibodies in almost all recipients. Only rarely has this regimen proved unsuccessful in preventing the development of rabies. None of the patients in whom rabies was diagnosed in the United States between 1980 and 1996 had received postexposure prophylaxis. Administration of vaccine alone appears to be associated with a higher failure rate than use of the combination, especially in severe bite exposures. Because of cost, postexposure prophylaxis consisting of intradermal injections of rabies vaccine is being used increasingly in the developing world. The combination of RIG plus 0.1-mL intradermal doses of HDCV at eight sites on day 0, four sites on day 7, and one site on days 28 and 91 produces good antibody responses and has had excellent clinical results. Alternatively, the World Health Organization has approved a regimen of two 0.1-mL doses at two intradermal sites on days 0, 3, and 7 and a 0.1-mL intradermal injection at a single site on days 21 and 90. TheFDA has not approved the intradermal route for postexposure prophylaxis.

Preexposure Prophylaxis Individuals at high risk of contact with rabies virus, including veterinarians, cave explorers, laboratory workers, and animal handlers, should receive preexposure prophylaxis with rabies vaccine. Three 1-mL intramuscular or three 0.1-mL intradermal injections ofHDCV on days 0, 7, and 21 or 28 should be administered. Concomitant chloroquine administration interferes with the antibody response to rabies vaccine. Depending on the level of risk, serologic testing should be done at 6-month to 2-year intervals.

An immune complex reaction consisting of urticaria, arthralgia, arthritis, angioedema, and systemic symptoms has been reported in up to 6% of persons receiving intramuscular booster doses ofHDCV. This reaction is self-limited and appears to be associated with the presence ofb-propiolactone-altered human serum albumin in the vaccine and the development of IgE antibodies to this antigen.

Persons who work in high-risk areas should undergo periodic measurement of antibodies. When neutralizing titers fall below 1:5, booster doses should be given. Booster doses may be administered as a single 1-mL intramuscular or 0.1-mL intradermal injection. Postexposure prophylaxis in individuals previously given preexposure prophylaxis consists of two intramuscular doses ofHDCV on days 0 and 3.RIG is not given in these situations.

MOKOLA VIRUS

Mokola virus was first isolated from wild shrews captured in Nigeria and was shown to be related morphologically and serologically to rabies virus. The subsequent isolation of the virus from cats in South Africa suggested a wider prevalence of the agent than had previously been expected. Only two cases of clinical infection have been reported; both were in children. One patient had a nonfatal illness characterized by fever, pharyngitis, and convulsions; Mokola virus was recovered fromCSF. In the second patient, fever with cough and vomiting was followed within several days by drowsiness, confusion, and generalized flaccid weakness. The CSF was normal. The patient progressed to

deep coma and died within 10 days of onset. Mokola virus was isolated from the brain, and examination of histopathologic sections revealed finely granular cytoplasmic inclusions that were distinguishable from Negri bodies in many neurons.

VESICULAR STOMATITIS VIRUS

Vesicular stomatitis is a viral illness of animals that occasionally affects humans. It presents as an acute, self-limited, influenza-like disease. The disease in animals is found in the United States and South America and affects chiefly domestic cattle, horses, swine, wild deer, raccoons, skunks, and bobcats.

In animals, vesicular stomatitis is characterized by the development of vesicles on the oral mucosa, particularly the tongue; the udders; and the heels. The mode of spread is probably by direct contact; however, epidemics tend to occur in warm weather, and isolation of the virus from *Phlebotomus* sandflies in Panama and *Aedes* species in New Mexico suggests that these insects may be vectors. Two distinct serotypes, New Jersey and Indiana, have been recognized, and most outbreaks in North America have been attributed to the New Jersey strain.

In humans, vesicular stomatitis is most common among laboratory workers. In one report, three-fourths of laboratory personnel handling experimentally infected animals or manipulating the virus developed neutralizing antibodies. The disease is also transmissible, however, under natural conditions among workers having direct contact with infected animals, especially cattle. An incubation period ranging from 1 to 6 days is followed by the sudden onset of fever [with temperatures of up to 40°C (104°F)], chills, profuse sweating, myalgias, malaise, headache, and pain on ocular movement. One-third to one-half of patients have a sore throat and cervical and/or submandibular adenopathy. Small raised vesicular lesions may appear on the buccal mucosa. Conjunctivitis and coryza are evident in ~20% of cases. Occasionally, small subcorneal, intraepithelial vesicles appear on the fingers, usually in association with direct inoculation of the virus. Symptoms generally last 3 to 4 days, but occasionally the course is diphasic. Inapparent infection is common: among laboratory workers with serologic evidence of infection, only about one-half report symptoms. In some areas of Panama, 17 to 35% of the population have neutralizing antibodies to vesicular stomatitis virus.

The differential diagnosis includes hand-foot-and-mouth disease, herpangina, primary herpetic pharyngitis and other mucocutaneous syndromes, and influenza. The virus is not commonly isolated from patients. However, a rise in titer of complement-fixation and/or neutralizing antibody to vesicular stomatitis virus between acute- and convalescent-phase sera helps to confirm the diagnosis. Treatment is nonspecific.

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198. INFECTIONS CAUSED BY ARTHROPOD- AND RODENT-BORNE VIRUSES - *C. J. Peters*

Most viral infections that come to medical attention in office or hospital practice in the developed countries are caused by viruses that can be latent in the human host, such as the herpesviruses, or by viruses that are continuously transmitted among humans, such as measles virus, influenza virus, and HIV. However, some other viruses are transmitted in nature without regard to humans and only incidentally infect and produce disease in humans; in addition, a few agents are regularly spread among humans by arthropods. Most of these viruses either are maintained by arthropods or chronically infect rodents. Obviously, the mode of transmission is not a rational basis for taxonomic classification. Indeed, zoonotic viruses from at least seven virus families act as significant human pathogens (Table 198-1). The virus families differ fundamentally from one another in terms of morphology, replication mechanisms, and genetics. Information on a virus's membership in a family or genus is enlightening with regard to maintenance strategies, sensitivity to antivirals, and some aspects of pathogenesis but does not necessarily predict which clinical syndromes -- if any -- the virus will cause in humans.

FAMILIES OF ARTHROPOD- AND RODENT-BORNE VIRUSES

The Arenaviridae The Arenaviridae are spherical, 110- to 130-nm particles that bud from the cell's plasma membrane and utilize ambisense RNA genomes with two segments for replication. There are two main phylogenetic branches of Arenaviridae: the Old World viruses, such as Lassa fever and lymphocytic choriomeningitis (LCM) viruses, and the New World viruses, including those causing the South American hemorrhagic fevers (HFs). Arenaviruses persist in nature by chronically infecting rodents with a striking one-virus-one-rodent species relationship. These rodent infections result in long-term virus excretion and perhaps in lifelong viremia; vertical infection is common with some arenaviruses. Humans become infected through the inhalation of aerosols containing arenaviruses, which are then deposited in the terminal air passages, and probably also through close contact with rodents and their excreta, which results in the contamination of mucous membranes or breaks in the skin.

The Bunyaviridae The family Bunyaviridae includes four medically significant genera. All of these spherical viruses have three negative-sense RNA segments maturing into 90- to 120-nm particles in the Golgi complex and exiting the cell by exocytosis. Viruses of the genus *Bunyavirus* are largely mosquito-borne and have a viremic vertebrate intermediate host; many are also transovarially transmitted in their specific mosquito host. One serologic group also uses biting midges as vectors. Sandflies or mosquitoes are the vectors for the genus *Phlebovirus* (named after phlebotomus fever or sandfly fever, the best-known disease associated with the genus), while ticks serve as vectors for the genus *Nairovirus*. Viruses of both of these genera are also associated with vertical transmission in the arthropod host and with horizontal spread through viremic vertebrate hosts. The genus *Hantavirus* is unique among the Bunyaviridae in that it is not transmitted by arthropods but is maintained in nature by rodent hosts that chronically shed virus. Like the arenaviruses, the hantaviruses usually display striking virus-rodent species specificity. Hantaviruses do not cause chronic viremia in their rodent host and are transmitted only horizontally from rodent to rodent.

Other Families The Flaviviridae are positive-sense, single-stranded RNA viruses that form particles of 40 to 50 nm in the endoplasmic reticulum. The flaviviruses discussed here are from the genus *Flavivirus* and make up two phylogenetically and antigenically distinct divisions transmitted among vertebrates by mosquitoes and ticks, respectively. The mosquito-borne viruses fall into phylogenetic groups that include yellow fever virus, the four dengue viruses, and encephalitis viruses, while the tick-borne group encompasses a geographically varied spectrum of species, some of which are responsible for encephalitis or for hemorrhagic disease with encephalitis. The Reoviridae are double-stranded RNA viruses with multisegmented genomes. These 80-nm particles are the only viruses discussed in this chapter that do not have a lipid envelope and thus are insensitive to detergents. The Togaviridae have a single positive strand RNA genome and bud particles of ~60 to 70 nm from the plasma membrane. The togaviruses discussed here are all members of the genus *Alphavirus* and are transmitted among vertebrates by mosquitoes in their natural cycle.**The Filoviridae and the Rhabdoviridae are discussed in Chaps. 199 and 197, respectively.*

PROMINENT FEATURES OF ARTHROPOD- AND RODENT-BORNE VIRUSES

Although this chapter discusses the major features of selected arthropod- and rodent-borne viruses, it does not deal with more than 500 other distinct recognized zoonotic viruses, about one-fourth of which infect humans. Zoonotic viruses are undergoing genetic evolution, "new" zoonotic viruses are being discovered, and the epidemiology of zoonotic viruses is continuing to evolve through environmental changes affecting vectors, reservoirs, and humans. These zoonotic viruses are most numerous in the tropics but are also found in temperate and frigid climates. Their distribution and seasonal activity may be variable and often depend largely on ecologic conditions such as rainfall and temperature, which in turn affect the density of vectors and reservoirs and the development of infection therein.

Maintenance and Transmission Arthropod-borne viruses infect their vectors after the ingestion of a blood meal from a viremic vertebrate. The vectors then develop chronic, systemic infection as the viruses penetrate the gut and spread throughout the body. The viruses eventually reach the salivary glands during a period that is referred to as *extrinsic incubation* and that typically lasts 1 to 3 weeks in mosquitoes. At this point an arthropod is competent to continue the chain of transmission by infecting another vertebrate when a subsequent blood meal is taken. The arthropod generally is unharmed by the infection, and the natural vertebrate partner usually has only transient viremia with no overt disease. An alternative mechanism for virus maintenance in its arthropod host is transovarial transmission, which is common among members of the family Bunyaviridae.

Rodent-borne viruses such as the hantaviruses and arenaviruses are maintained in nature by chronic infection transmitted between rodents. As in arthropod-borne virus cycles, there is usually a high degree of rodent-virus specificity, and there is no overt disease in the reservoir/vector.

Epidemiology The distribution of arthropod- and rodent-borne viruses is restricted by the areas inhabited by their reservoir/vectors and provides an important clue in the differential diagnosis. Table 198-2 shows the approximate geographic distribution of the

most important of these viruses. Members of each family, each genus, and even each serologically related group usually occur in each area but may not be pathogenic in all areas or may not be a commonly recognized cause of disease in all areas and so may not be included in the table. Although there is generally no overt disease in the vertebrate reservoirs, disease in nonhuman target species may be a useful diagnostic clue, and serologic testing of selected animals may be a useful way to monitor virus circulation.

Most of these diseases are acquired in a rural setting; a few have urban vectors. Seoul, sandfly fever, and Oropouche viruses are examples of urban viruses, but the most notable are yellow fever, dengue, and chikungunya viruses, which are transmitted between humans with the mosquito *Aedes aegypti* as a principal or alternate vector. A history of mosquito bite has little diagnostic significance in the individual; a history of tick bite is more diagnostically specific. Rodent exposure is often reported by persons infected with an arenavirus or a hantavirus but again has little specificity. Indeed, aerosols may infect persons who have no recollection of having even seen rodents.

Syndromes Human disease caused by arthropod- and rodent-borne viruses is often subclinical. The spectrum of possible responses to infection is wide, and our knowledge of the outcome of most of these infections is limited. The usual disease syndromes associated with these viruses have been grouped into four categories: fever and myalgia, arthritis and rash, encephalitis, and hemorrhagic fever. Although for the purposes of this discussion most viruses have been placed in a single group, the categories often overlap. For example, West Nile and Venezuelan equine encephalitis viruses are discussed as encephalitis viruses, but during epidemics they may cause many cases of milder febrile syndromes and relatively uncommon cases of encephalitis. Similarly, Rift Valley fever virus is best known as a cause ofHF, but the attack rates for febrile disease are far higher, and encephalitis is occasionally seen as well.LCMvirus is classified as a cause of fever and myalgia because this syndrome is its most common disease manifestation and, even when central nervous system (CNS) disease occurs, it is usually mild and is preceded by fever and myalgia. Dengue virus infection is considered as a cause of fever and myalgia (dengue fever) because this is by far the most common manifestation worldwide and is the syndrome most likely to be seen in the United States; however, dengue HF is also discussed in the HF section because of its complicated pathogenesis and importance in pediatric practice in certain areas of the world.

Diagnosis Laboratory diagnosis is required in any given case, although epidemics occasionally provide clinical and epidemiologic clues on which an educated guess as to etiology can be based. For most arthropod- and rodent-borne viruses, acute-phase serum samples (collected within 3 or 4 days of onset) have yielded isolates, and paired sera have been used to demonstrate rising antibody titers by a variety of tests. Intensive efforts to develop rapid tests forHF have resulted in an antigen-detection enzyme-linked immunosorbent assay (ELISA) and an IgM-capture ELISA that can provide a diagnosis based on a single serum sample within a few hours and are particularly useful in severe cases. More sensitive reverse transcription polymerase chain reaction (RT-PCR) tests may yield diagnoses based on samples without detectable antigen and may also provide useful genetic information about the virus. Preliminary data suggest that similar tests applied to some fever-myalgia syndromes would give positive results if developed

further. Hantavirus infections differ from others discussed here in that severe acute disease is immunopathologic; patients present with serum IgM that serves as the basis for a sensitive and specific test. Every ELISA must include a control incorporating a negative antigen with each serum sample tested; the frequent failure to include such a control has resulted in numerous false-positive results in diagnostic tests.

At the time of diagnosis, patients with encephalitis are generally no longer viremic or antigenemic and usually do not have virus in cerebrospinal fluid (CSF). In this situation, the value of serologic methods andRT-PCRis being validated. IgM capture is increasingly being used for the simultaneous testing of serum and CSF. IgGELISA or classic serology is useful in the evaluation of past exposure to the viruses, many of which circulate in areas with a minimal medical infrastructure and sometimes cause mild or subclinical infection.

The remainder of this chapter offers general descriptions of the broad syndromes caused by arthropod- and rodent-borne viruses and then addresses specific differences between diseases. It is important to remember that most of the diseases under consideration have not been studied in detail with modern medical approaches and thus available data may be incomplete or biased.

FEVER AND MYALGIA

Fever and myalgia constitute the syndrome most commonly associated with zoonotic virus infection. Many of the numerous viruses belonging to the families listed inTable 198-1 probably cause this syndrome, but several viruses have been selected for inclusion in the table because of their prominent associations with the syndrome and their biomedical importance.

The syndrome typically begins with the abrupt onset of fever, chills, intense myalgia, and malaise. Patients may also report joint pains, but no true arthritis is detectable. Anorexia is characteristic and may be accompanied by nausea or even vomiting. Headache is common and may be severe, with photophobia and retroorbital pain. Physical findings are minimal and are usually confined to conjunctival injection with pain on palpation of muscles or the epigastrium. The duration of symptoms is quite variable but generally is 2 to 5 days, with a biphasic course in some instances. The spectrum of disease varies from subclinical to temporarily incapacitating.

Less constant findings include a maculopapular rash. Epistaxis may occur but does not necessarily indicate a bleeding diathesis. A minority of the cases caused by some viruses are known or suspected to include aseptic meningitis, but this diagnosis is difficult in remote areas, given the patients' photophobia and myalgia as well as the lack of opportunity to examine theCSF. Although pharyngitis may be noted or radiographic evidence of pulmonary infiltrates found in some cases, these viruses are not primary respiratory pathogens. The differential diagnosis includes anicteric leptospirosis, rickettsial diseases, and the early stages of other syndromes discussed in this chapter. These diseases are often described as "flulike," but the usual absence of cough and coryza makes influenza an unlikely confounder except at the earliest stages.

Complete recovery is generally the outcome in this syndrome, although prolonged

asthenia and nonspecific symptoms have been described in some cases, particularly after infection withLCM or dengue virus. Treatment is supportive, with aspirin avoided because of the potential for exacerbated bleeding and Reye's syndrome. Efforts at prevention are best based on vector control, which, however, may be expensive or impossible. For mosquito control, destruction of breeding sites is generally the most economically and environmentally sound approach; spraying to kill adult mosquitoes and thus to reduce their numbers transiently may have a preventive role in selected settings but has not been notably effective in the past. Measures taken by the individual to avoid the vector can be valuable. Avoiding the vector's habitat and times of peak activity, preventing the vector from entering dwellings by using screens or other barriers, judiciously applying arthropod repellents such as diethyltoluamide (DEET) to the skin, and wearing permethrin-impregnated clothing are all possible approaches, depending on the vector and its habits.

LYMPHOCYTIC CHORIOMENINGITIS

LCMis transmitted from the common house mouse (*Mus musculus*) to humans by aerosols of excreta and secreta. LCM virus, an arenavirus, is maintained in the mouse mainly by vertical transmission from infected dams. The vertically infected mouse remains viremic for life, with high concentrations of virus in all tissues. Infected colonies of pet hamsters have also served as a link to humans. LCM virus is widely used in immunology laboratories as a model of T cell function and can silently infect cell cultures and passaged tumor lines, resulting in infections among scientists and animal caretakers. Patients with LCM may have a history of residence in rodent-infested housing or other exposure to rodents. An antibody prevalence of ~5 to 10% has been reported in adults from the United States, Argentina, and endemic areas of Germany.

LCMdiffers from the general syndrome of fever and myalgia in that its onset is gradual. Among the conditions occasionally associated with LCM are orchitis, transient alopecia, arthritis, pharyngitis, cough, and maculopapular rash. An estimated one-fourth of patients or fewer suffer a febrile phase of 3 to 6 days and then, after a brief remission, develop renewed fever accompanied by severe headache, nausea and vomiting, and meningeal signs lasting for about a week. These patients virtually always recover fully, as do the uncommon patients with clear-cut signs of encephalitis. Recovery may be delayed by transient hydrocephalus.

During the initial febrile phase, leukopenia and thrombocytopenia are common and virus can usually be isolated from blood. During theCNSphase of the illness, virus may be found in theCSF, but antibodies are present in blood. The pathogenesis ofLCM is thought to resemble that following direct intracranial inoculation of the virus into adult mice; the onset of the immune response leads to T cell-mediated immunopathologic meningitis. During the meningeal phase, CSF mononuclear-cell counts range from the hundreds to the low thousands per microliter, and hypoglycorrhachia is found in one-third of cases. The IgM-captureELISA of serum and CSF is usually positive;RT-PCRassays have been developed for application to CSF.

Infection withLCMvirus should be suspected in acutely ill febrile patients with marked leukopenia and thrombocytopenia. In cases of aseptic meningitis, any of the following should suggest LCM: well-marked febrile prodrome, adult age, autumn seasonality, low

CSFglucose levels, or CSF mononuclear cell counts>1000/uL.

In pregnant women,LCMvirus infection may lead to fetal invasion with consequent congenital hydrocephalus and chorioretinitis. Since the maternal infection may be mild, consisting of only a short febrile illness, antibodies to the virus should be sought in both the mother and the fetus in suspicious circumstances, particularly TORCH-negative neonatal hydrocephalus. [TORCH is a battery of tests encompassing *t*oxoplasmosis, *o*ther conditions (congenital syphilis and viruses), *r*ubella, *c*ytomegalovirus, and *h*erpes simplex virus.]

BUNYAMWERA VIRUS INFECTION

The mosquito-transmitted Bunyamwera serogroup viruses are found on every continent except Australia and Antarctica. Bunyamwera virus and its close relative Ilesha virus commonly cause febrile disease in Africa. Other related viruses are implicated in such disease in Southeast Asia (Batai virus), Europe (Calovo virus), and South America (Wyeomyia virus). In North America, Cache Valley virus has been implicated in febrile human disease and in rare instances of more serious systemic illness; the presence of serum antibodies to this virus may be associated with congenital malformations. In Central America, the closely related Fort Sherman virus causes the fever-myalgia syndrome.

GROUP C VIRUS INFECTION

The group C viruses include at least 11 agents transmitted by mosquitoes in neotropical forests. These agents are among the most common causes of arboviral infection in humans entering American jungles and cause acute febrile disease.

TAHYNA VIRUS INFECTION

This California serogroup virus (see discussion of California encephalitis, below) occurs in central and western Europe, and related viruses are emerging in Russia. The significance of Tahyna virus in human health has been well studied only in the Czech and Slovak Republics; there, the virus was found to be a prominent cause of febrile disease, in some cases causing pharyngitis, pulmonary syndromes, and aseptic meningitis. The potential for arboviruses to be unexpectedly involved in such cases in areas of high mosquito prevalence needs to be kept in mind.

OROPOUCHE FEVER

Oropouche virus is transmitted in Central and South America by a biting midge, *Culicoides paraensis*, which often breeds to high density in cacao husks and other vegetable detritus found in towns and cities. Explosive epidemics involving thousands of cases have been reported from several towns in Brazil and Peru. Rash and aseptic meningitis have been detected in a number of cases.

SANDFLY FEVER

The sandfly *Phlebotomus papatasi* transmits sandfly fever. Female sandflies may be

infected by the oral route as they take a blood meal and may transmit the virus to offspring when they lay their eggs after a second blood meal. This prominent transovarial pattern was the first to be recognized among dipterans and complicates virus control. A previous designation for sandfly fever, "3-day fever," instructively describes the brief, debilitating course associated with this essentially benign infection. There is neither a rash norCNSinvolvement, and complete recovery is the rule.

Sandfly fever is found in the circum-Mediterranean area, extending to the east through the Balkans into China as well as into the Middle East and southwestern Asia. The vector is found in both rural and urban settings and is known for its small size, which enables it to penetrate standard mosquito screens and netting, and for its short flight range. Epidemics have been described in the wake of natural disasters and wars. In parts of Europe, sandfly populations and virus transmission were greatly reduced by the extensive residual spraying conducted after World War II to control malaria, and the incidence continues to be low. A common pattern of disease in endemic areas consists of high attack rates among travelers and military personnel with little or no disease in the local population, who are protected after childhood infection. In addition to the two well-characterized, non-cross-protective Sicilian and Naples virus species, more than 30 related phleboviruses are transmitted by sandflies and mosquitoes, but most are of unknown significance in terms of human health.

TOSCANA VIRUS DISEASE

Toscana virus is a *Phlebovirus* (family Bunyaviridae) transmitted primarily by the circum-Mediterranean sandfly *P. perniciosus*. The vertebrate amplifying host, if one exists, is unknown. Toscana virus infection is common during the summer among rural residents and vacationers; a number of cases have been identified in travelers returning to Germany and Scandinavia. The disease may manifest as an uncomplicated febrile illness but is often associated with aseptic meningitis, with virus isolated from theCSF.

PUNTA TORO VIRUS DISEASE

Of the several phleboviruses that are associated with New World sandflies and infect humans, Punta Toro virus is the best known. The disease caused by this virus is clinically similar to but epidemiologically different from that caused by the Naples or Sicilian sandfly fever viruses. Punta Toro virus infections are sporadic and are acquired in the tropical forest, where the vectors rest on tree buttresses. Epidemics have not been reported, but antibody prevalences among inhabitants of villages in the endemic areas indicate a cumulative lifetime exposure rate of>50%.

DENGUE FEVER

All four distinct dengue viruses (dengue 1-4) have *A. aegypti* as their principal vector, and all cause a similar clinical syndrome. In rare cases, second infection with a serotype of dengue virus different from that involved in the primary infection leads to dengueHF with severe shock (see below). Sporadic cases are seen in the settings of endemic transmission and epidemic disease. Year-round transmission between latitudes 25°N and 25°S has been established, and seasonal forays of the viruses to points as far north as Philadelphia are thought to have taken place in the United States. With increasing

spread of the vector mosquito throughout the tropics and subtropics, large areas of the world have become vulnerable to the introduction of dengue viruses, particularly through air travel by infected humans, and both dengue fever and the related dengue HF are becoming increasingly common. Conditions favorable to dengue transmission exist in the southern United States, and bursts of dengue fever activity are to be expected in this region, particularly along the Mexican border, where water may be stored in containers and *A. aegypti* numbers may therefore be greatest: this mosquito, which is also an efficient vector of the yellow fever and chikungunya viruses, typically breeds near human habitation, using relatively fresh water from sources such as water jars, vases, discarded containers, coconut husks, and old tires. *A. aegypti* usually inhabits dwellings and bites during the day.

After an incubation period of 2 to 7 days, the typical patient experiences the sudden onset of fever, headache, retroorbital pain, and back pain along with the severe myalgia that gave rise to the colloquial designation "break-bone fever." There is often a macular rash on the first day as well as adenopathy, palatal vesicles, and scleral injection. The illness may last a week, with additional symptoms usually including anorexia, nausea or vomiting, marked cutaneous hypersensitivity, and -- near the time of defervescence -- a maculopapular rash beginning on the trunk and spreading to the extremities and the face. Epistaxis and scattered petechiae are often noted in uncomplicated dengue, and preexisting gastrointestinal lesions may bleed during the acute illness.

Laboratory findings include leukopenia, thrombocytopenia, and, in many cases, serum aminotransferase elevations. The diagnosis is made by IgMELISA or paired serology during recovery or by antigen-detection ELISA orRT-PCRduring the acute phase. Virus is readily isolated from blood in the acute phase if mosquito inoculation or mosquito cell culture is used.

COLORADO TICK FEVER

Several hundred cases of Colorado tick fever are reported annually in the United States. The infection is acquired between March and November through the bite of an infected *Dermacentor andersoni* tick in mountainous western regions at altitudes of 1200 to 3000 m (4000 to 10,000 ft). Small mammals serve as the amplifying host. The most common presentation consists of fever and myalgia; meningoencephalitis is not uncommon, and hemorrhagic disease, pericarditis, myocarditis, orchitis, and pulmonary presentations are also reported. Rash develops in a substantial minority of cases. The disease usually lasts 7 to 10 days and is often biphasic. The most important differential diagnostic considerations since the beginning of the twentieth century have been Rocky Mountain spotted fever and tularemia.

Infection of erythroblasts and other marrow cells by Colorado tick fever virus results in the appearance and persistence (for several weeks) of erythrocytes containing the virus. This feature, detected in smears stained by immunofluorescence, can be diagnostically helpful. The clinical laboratory detects leukopenia and thrombocytopenia.

ORBIVIRUS INFECTION

The orbiviruses encompass many human and veterinary pathogens. For example,

Orungo virus is widely transmitted by mosquitoes in tropical Africa and causes febrile disease in humans. The Kemerova complex includes the Kemerova, Lipovnik, and Tribec viruses of Russia and central Europe; these viruses are transmitted by ticks and are associated with febrile and neurologic disease.

VESICULAR STOMATITIS

SeeChap. 197.

ENCEPHALITIS

Arboviral encephalitis is a seasonal disease, commonly occurring in the warmer months. Its incidence varies markedly with time and place, depending on ecologic factors. The causative viruses differ substantially in terms of case-infection ratio (i.e., the ratio of clinical to subclinical infection), mortality, and residua (Table 198-3). Humans are not an important amplifier of these viruses.

All the viral encephalitides discussed in this section have a similar pathogenesis as far as is known. An infected arthropod ingests a blood meal from a human and infects the host. The initial period of viremia is thought to originate most commonly from the lymphoid system. Viremia leads toCNSinvasion, presumably through infection of olfactory neuroepithelium with passage through the cribiform plate or through infection of brain capillaries and multifocal entry into the CNS. During the viremic phase, there may be little or no recognized disease except in the case of tick-borne flaviviral encephalitis, in which there may be a clearly delineated phase of fever and systemic illness. The disease process in the CNS arises partly from direct neuronal infection and subsequent damage and partly from edema, inflammation, and other indirect effects. The usual pathologic picture is one of focal necrosis of neurons, inflammatory glial nodules, and perivascular lymphoid cuffing; the severity and distribution of these abnormalities vary with the infecting virus. Involved areas display the "luxury perfusion" phenomenon, with normal or increased total blood flow and low oxygen extraction.

The typical patient presents with a prodrome of nonspecific constitutional symptoms, including fever, abdominal pain, vertigo, sore throat, and respiratory symptoms. Headache, meningeal signs, photophobia, and vomiting follow quickly. Involvement of deeper structures may be signaled by lethargy, somnolence, and intellectual deficit (as disclosed by the mental status examination or failure at serial 7 subtraction); more severely affected patients will be obviously disoriented and may be comatose. Tremors, loss of abdominal reflexes, cranial nerve palsies, hemiparesis, monoparesis, difficulty in swallowing, and frontal lobe signs are all common. Convulsions and focal signs may be evident early or may appear during the course of the disease. Some patients present with an abrupt onset of fever, convulsions, and other signs ofCNSinvolvement. The results of human infection range from no significant symptoms through febrile headache to aseptic meningitis and finally to full-blown encephalitis; the proportions and severity of these manifestations vary with the infecting virus.

The acute encephalitis usually lasts from a few days to as long as 2 to 3 weeks, but recovery may be slow, with weeks or months required for the return of maximal recoupable function. Common complaints during recovery include difficulty

concentrating, fatigability, tremors, and personality changes. The acute illness requires management of a comatose patient who may have intracranial pressure elevations, inappropriate secretion of antidiuretic hormone, respiratory failure, and convulsions. There is no specific therapy for these viral encephalitides. The only practical preventive measures are vector management and personal protection against the arthropod transmitting the virus; for Japanese encephalitis or tick-borne encephalitis, vaccination should be considered in certain circumstances (see relevant sections below).

The diagnosis of arboviral encephalitis depends on the careful evaluation of a febrile patient with CNSdisease, with rapid identification of treatable herpes simplex encephalitis, ruling out of brain abscess, exclusion of bacterial meningitis by serialCSFexamination, and performance of laboratory studies to define the viral etiology. Leptospirosis, neurosyphilis, Lyme disease, cat-scratch fever, and newer viral encephalitides such as Nipah virus infection from Malaysia should be considered. The CSF examination usually shows a modest cell count -- in the tens or hundreds or perhaps a few thousand. Early in the process, a significant proportion of these cells may be polymorphonuclear leukocytes, but usually there is a mononuclear cell predominance. CSF glucose levels are usually normal. There are exceptions to this pattern of findings. In eastern equine encephalitis, for example, polymorphonuclear leukocytes may predominate during the first 72 h of disease and hypoglycorrhachia may be detected. InLCM, lymphocyte counts may be in the thousands, and the glucose concentration may be diminished. Experience with imaging studies is still evolving; clearly, however, both computed tomography (CT) and magnetic resonance imaging (MRI) may be normal except for evidence of preexisting conditions or sometimes may suggest diffuse edema. Several patients with eastern equine encephalitis have had focal abnormalities, and individuals with severe Japanese encephalitis have presented with bilateral thalamic lesions that have often been hemorrhagic. Electroencephalography usually shows diffuse abnormalities and is not directly helpful.

A humoral immune response is usually detectable at or near the onset of disease. Both serum andCSFshould be examined for IgM antibodies. Virus generally cannot be isolated from blood or CSF, although Japanese encephalitis virus has been recovered from CSF in severe cases. Virus can be obtained from and viral antigen is present in brain tissue, although its distribution may be focal.

CALIFORNIA, LA CROSSE, AND JAMESTOWN CANYON VIRUS ENCEPHALITIS

The isolation of California encephalitis virus established the California serogroup of viruses as a cause of encephalitis, and its use as a diagnostic antigen led to the description of many cases of "California encephalitis." In fact, however, this virus has been implicated in only a few cases of encephalitis, and the serologically related La Crosse virus is the major cause of encephalitis among viruses in the California serogroup. "California encephalitis" due to La Crosse virus infection is most commonly reported from the upper Midwest but is also found in other areas of the central and eastern United States, most often in West Virginia, Tennessee, North Carolina, and Georgia. The serogroup includes 13 other viruses, some of which may also be involved in human disease that is misattributed because of the complexity of the group's serology; these viruses include the Jamestown Canyon, snowshoe hare, Inkoo, and Trivittatus viruses, all of which have *Aedes* mosquitoes as their vector and all of which

have a strong element of transovarial transmission in their natural cycles.

The mosquito vector of La Crosse virus is *A. triseriatus*. In addition to a prominent transovarial component of transmission, a mosquito can also become infected through feeding on viremic chipmunks and other mammals as well as through venereal transmission from another mosquito. The mosquito breeds in sites such as tree holes and abandoned tires and bites during daylight hours; these findings correlate with the risk factors for cases: recreation in forested areas, residence at the forest's edge, and the presence of abandoned tires around the home. Intensive environmental modification based on these findings has reduced the incidence of disease in a highly endemic area in the Midwest. Most cases occur from July through September. The Asian tiger mosquito, *A. albopictus*, efficiently transmits the virus to mice and also transmits the agent transovarially in the laboratory; this aggressive anthropophilic mosquito has the capacity to urbanize, and its possible impact on transmission to humans is of concern.

An antibody prevalence of³20% in endemic areas indicates that infection is common, butCNSdisease has been recognized primarily in children<15 years of age. The illness varies from a picture of aseptic meningitis accompanied by confusion to severe and occasionally fatal encephalitis. Although there may be prodromal symptoms, the onset of CNS disease is sudden, with fever, headache, and lethargy often joined by nausea and vomiting, convulsions (in one-half of patients), and coma (in one-third of patients). Focal seizures, hemiparesis, tremor, aphasia, chorea, Babinski's sign, and other evidence of significant neurologic dysfunction are common, but residua are not. Perhaps 10% of patients have recurrent seizures in the succeeding months. Other serious sequelae are rare, although a decrease in scholastic standing has been reported and mild personality change has occasionally been suggested. Treatment is supportive over a 1- to 2-week acute phase during which status epilepticus, cerebral edema, and inappropriate secretion of antidiuretic hormone are important concerns. Ribavirin has been used in severe cases, and a clinical trial of this drug is under way.

The blood leukocyte count is commonly elevated, sometimes reaching levels of 20,000/uL, and there is usually a left shift.CSF cell counts are typically 30 to 500/uL with a mononuclear cell predominance (although 25 to 90% of cells are polymorphonuclear in some cases). The protein level is normal or slightly increased, and the glucose level is normal. Specific virologic diagnosis based on IgM-capture assays of serum and CSF is efficient. The only human anatomic site from which virus has been isolated is the brain.

Jamestown Canyon virus has been implicated in several cases of encephalitis in adults; in these cases the disease was usually associated with a significant respiratory illness at onset. Human infection with this virus has been documented in New York, Wisconsin, Ohio, Michigan, Ontario, and other areas of North America where the vector mosquito, *A. stimulans*, feeds on its main host, the white-tailed deer.

ST. LOUIS ENCEPHALITIS

St. Louis encephalitis virus is transmitted between *Culex* mosquitoes and birds. This virus causes low-level endemic infection among rural residents of the western and central United States, where *C. tarsalis* is the vector (see "Western Equine

Encephalitis," below), but the more urbanized mosquito species *C. pipiens* and *C. quinquefasciatus* have been responsible for epidemics resulting in hundreds or even thousands of cases in cities of the central and eastern United States. Most cases occur in June through October. The urban mosquitoes breed in accumulations of stagnant water and sewage with high organic content and readily bite humans in and around houses at dusk. The elimination of open sewers and trash-filled drainage systems is expensive and may not be possible, but screening of houses and implementation of personal protective measures may be an effective approach for individuals. The rural vector is most active at dusk and outdoors; its bites can be avoided by modification of activities and use of repellents.

Disease severity increases with age: infections that result in aseptic meningitis or mild encephalitis are concentrated in children and young adults, while severe and fatal cases primarily affect the elderly. Infection rates are similar in all age groups; thus the greater susceptibility of older persons to disease is a biologic consequence of aging. The disease has an abrupt onset, sometimes following a prodrome, and begins with fever, lethargy, confusion, and headache. In addition, nuchal rigidity, hypotonia, hyperreflexia, myoclonus, and tremor are common. Severe cases can include cranial nerve palsies, hemiparesis, and convulsions. Patients often complain of dysuria and may have viral antigen in urine as well as pyuria. The overall mortality is generally ~7% but may reach 20% among patients over the age of 60. Recovery is slow. Emotional lability, difficulties in concentration and memory, asthenia, and tremor are commonly prolonged in older patients.

TheCSF of patients with St. Louis encephalitis usually contains tens to hundreds of cells, with a lymphocytic predominance and a normal glucose level. Leukocytosis with a left shift is often documented.

JAPANESE ENCEPHALITIS

Japanese encephalitis virus is found throughout Asia, including far eastern Russia, Japan, China, India, Pakistan, and Southeast Asia, and causes occasional epidemics on western Pacific islands. The virus has been detected in the Torres Strait islands, and a human encephalitis case has been identified on the nearby Australian mainland. This flavivirus is particularly common in areas where irrigated rice fields attract the natural avian vertebrate hosts and provide abundant breeding sites for mosquitoes such as *C. tritaeniorhyncus*, which transmit the virus to humans. Additional amplification by pigs, which suffer abortion, and horses, which develop encephalitis, may be significant as well. Vaccination of these additional amplifying hosts may reduce the transmission of the virus. An effective, formalin-inactivated vaccine purified from mouse brain is produced in Japan and licensed for human use in the United States. It is given on days 0, 7, and 30 or -- with some sacrifice in serum neutralizing titer -- on days 0, 7, and 14. Vaccination is indicated for summer travelers to rural Asia, where the risk of clinical disease may be 0.05 to 2.1/10,000 per week. The severe and often fatal disease reported in expatriates must be balanced against the 0.1 to 1% chance of a late systemic or cutaneous allergic reaction. These reactions are rarely fatal but may be severe and have been known to begin 1 to 9 days after vaccination, with associated pruritus, urticaria, and angioedema. Live attenuated vaccines are being used in China but are not recommended in the United States at this time.

WEST NILE VIRUS INFECTION

West Nile virus is transmitted among wild birds by *Culex* mosquitoes in Africa, the Middle East, southern Europe, and Asia. It is a frequent cause of febrile disease withoutCNSinvolvement, but it occasionally causes aseptic meningitis and severe encephalitis; these serious infections are particularly common among children and the elderly. The febrile-myalgic syndrome caused by West Nile virus differs from many others by the frequent appearance of a maculopapular rash concentrated on the trunk and lymphadenopathy. Headache, ocular pain, sore throat, nausea and vomiting, and arthralgia (but not arthritis) are common accompaniments. In addition, the virus has been implicated in severe and fatal hepatic necrosis in Africa.

In 1996 West Nile virus caused more than 300 cases ofCNSdisease, with 10% mortality, in the Danube flood plain, including Bucharest. In 1999 the virus appeared in New York City and other areas of the northeastern United States, causing more than 60 cases of aseptic meningitis or encephalitis among humans as well as die-offs among crows, exotic zoo birds, and other avians. The encephalitis was most severe among the elderly and was often associated with notable muscle weakness and even with flaccid paralysis. The virus, thought to have been transmitted in New York City by the ubiquitous *C. pipiens* mosquito, returned to larger areas of the northeastern United States in the summer of 2000 and threatens to spread farther in the Americas via bird migration.

West Nile virus falls into the same phylogenetic group of flaviviruses as St. Louis and Japanese encephalitis viruses, as do Murray Valley and Rocio viruses. The latter two viruses are both maintained in mosquitoes and birds and produce a clinical picture resembling that of Japanese encephalitis. Murray Valley virus has caused occasional epidemics and sporadic cases in Australia. Rocio virus caused recurrent epidemics in a focal area of Brazil in 1975 to 1977 and then virtually disappeared.

CENTRAL EUROPEAN TICK-BORNE ENCEPHALITIS AND RUSSIAN SPRING-SUMMER ENCEPHALITIS

A spectrum of tick-borne flaviviruses has been identified across the Eurasian land mass. Many are known mainly as agricultural pathogens (e.g., louping ill virus in the United Kingdom). From Scandinavia to the Urals, central European tick-borne encephalitis is transmitted by *Ixodes ricinus.* Human cases occur between April and October, with a peak in June and July. A related and more virulent virus is that of Russian spring-summer encephalitis, which is associated with *I. persulcatus* and is distributed from Europe across the Urals to the Pacific Ocean. The ticks transmit the disease primarily in the spring and early summer, with a lower rate of transmission later in summer. Small mammals are the vertebrate amplifiers for both viruses. The risk varies by geographic area and can be highly localized within a given area; human cases usually follow outdoor activities or consumption of raw milk from infected goats or other infected animals.

After an incubation period of 7 to 14 days or perhaps longer, the central European viruses classically result in a febrile-myalgic phase that lasts for 2 to 4 days and is

thought to correlate with viremia. A subsequent remission for several days is followed by the recurrence of fever and the onset of meningeal signs. TheCNSphase varies from mild aseptic meningitis, which is more common among younger patients, to severe encephalitis with coma, convulsions, tremors, and motor signs lasting for 7 to 10 days before improvement begins. Spinal and medullary involvement can lead to typical limb-girdle paralysis and to respiratory paralysis. Most patients recover, only a minority with significant deficits. Infections with the far eastern viruses generally run a more abrupt course. The encephalitic syndrome caused by these viruses sometimes begins without a remission and has more severe manifestations than the European syndrome. Mortality is high, and major sequelae -- most notably, lower motor neuron paralyses of the proximal muscles of the extremities, trunk, and neck -- are common.

In the early stage of the illness, virus may be isolated from the blood. In theCNSphase, IgM antibodies are detectable in serum and/orCSF. Thrombocytopenia sometimes develops during the initial febrile illness, which resembles the early hemorrhagic phase of some other tick-borne flaviviral infections, such as Kyasanur Forest disease. Other tick-borne flaviviruses are less common causes of encephalitis, including louping ill virus in the United Kingdom and Powassan virus.

There is no specific therapy for infection with these viruses. However, effective alum-adjuvanted, formalin-inactivated vaccines are produced in Austria, Germany, and Russia. Two doses of the Austrian vaccine separated by an interval of 1 to 3 months appear to be effective in the field, and antibody responses are similar when vaccine is given on days 0 and 14. Other vaccines have elicited similar neutralizing antibody titers. Since rare cases of postvaccination Guillain-Barre syndrome have been reported, vaccination should be reserved for persons likely to experience rural exposure in an endemic area during the season of transmission. Cross-neutralization for the central European and far eastern strains has been established, but there are no published field studies on cross-protection of formalin-inactivated vaccines. Because 0.2 to 4% of ticks in endemic areas may be infected, tick bites raise the issue of immunoglobulin prophylaxis. Prompt administration of high-titered specific preparations should probably be undertaken, although no controlled data are available to prove the efficacy of this measure. Immunoglobulin should not be administered late because of the risk of antibody-mediated enhancement.

POWASSAN ENCEPHALITIS

Powassan virus is a member of the tick-borne encephalitis virus complex and is transmitted by *I. cookei* among small mammals in eastern Canada and the United States, where it has been responsible for 20 recognized cases of human disease. Other ticks may transmit the virus in a wider geographic area, and there is some concern that *I. scapularis* (also called *I. dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States. Patients with Powassan encephalitis -- often children -- present in May through December after outdoor exposure and an incubation period thought to be about 1 week. Powassan encephalitis is severe, and sequelae are common.

EASTERN EQUINE ENCEPHALITIS

Eastern equine encephalitis is found primarily within endemic swampy foci along the eastern coast of the United States, with a few inland foci as far removed as Michigan. Human cases present from June through October, when the bird-*Culiseta* mosquito cycle spills over into other mosquito species such as *A. sollicitans* or *A. vexans*, which are more likely to bite mammals. There is concern over the potential role of the introduced anthropophilic mosquito species *A. albopictus*, which has been found to be naturally infected and is an effective vector in the laboratory. Horses are a common target for the virus; if not vaccinated, they serve as a harbinger of human disease but probably do not play a significant role in amplification of the virus.

Eastern equine encephalitis is one of the most destructive of the arboviral conditions, with a brusque onset, rapid progression, high mortality, and frequent residua. This severity is reflected in the extensive necrotic lesions and polymorphonuclear infiltrates found at postmortem examination of the brain and the acute polymorphonuclearCSFpleocytosis often occurring during the first 1 to 3 days of disease. In addition, leukocytosis with a left shift is a common feature. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

WESTERN EQUINE ENCEPHALITIS

The primary maintenance cycle for western equine encephalitis virus in the United States is between *C. tarsalis* and birds, principally sparrows and finches. Equines and humans become infected, and both species suffer encephalitis without amplifying the virus in nature. St. Louis encephalitis is transmitted in a similar cycle in the same region but causes human disease about a month earlier than the period (July through October) in which western equine encephalitis virus is active. Large epidemics of western equine encephalitis took place in the western and central United States and Canada during the 1930s to 1950s, but in recent years the disease has been uncommon. There were 41 reported cases in the United States in 1987 but only 4 reported cases from 1988 to 1995. This decline in incidence may reflect in part the integrated approach to mosquito management that has been employed in irrigation projects and the increasing use of agricultural pesticides; it almost certainly reflects the increased tendency for humans to be indoors behind closed windows at dusk, the peak period of biting by the major vector.

Western equine encephalitis virus causes a typical diffuse viral encephalitis with an increased attack rate and increased morbidity in the young, particularly children<2 years old. In addition, mortality is high among the young and the very elderly. One-third of individuals who have convulsions during the acute illness have subsequent seizure activity. Infants<1 year old -- particularly those in the first months of life -- are at serious risk of motor and intellectual damage. Twice as many males as females develop clinical encephalitis after 5 to 9 years of age; this difference may be related to greater outdoor exposure of boys to the vector but is also likely due in part to biologic differences. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

VENEZUELAN EQUINE ENCEPHALITIS

There are six known types of virus in the Venezuelan equine encephalitis complex. An

important distinction is between the "epizootic" viruses (subtypes IAB and IC) and the "enzootic" viruses (subtypes ID to IF and types II to VI). The epizootic viruses have an unknown natural cycle but periodically cause extensive epidemics in equines and humans in the Americas. These epidemics rely on the high-level viremia in horses and mules that results in the infection of several species of mosquitoes, which in turn infect humans and perpetuate virus transmission. Humans also have high-level viremia but probably are not important in virus transmission. Enzootic viruses are found primarily in humid tropical forest habitats and are maintained between *Culex* mosquitoes and rodents; these viruses cause human disease but are not pathogenic for horses and do not cause epizootics.

Epizootics of Venezuelan equine encephalitis occurred repeatedly in Venezuela, Colombia, Ecuador, Peru, and other South American countries at intervals of£10 years from the 1930s until 1969, when a massive epizootic spread throughout Central America and Mexico, reaching southern Texas in 1972. Genetic sequencing of the virus from the 1969 to 1972 outbreak suggested that it originated from residual "un-inactivated" virus in veterinary vaccines. The outbreak was terminated in Texas with the use of a live attenuated vaccine (TC-83) originally developed for human use by the U.S. Army; this virus was then used for further production of inactivated veterinary vaccines. No further epizootic disease was identified until 1995 and subsequently, when additional epizootics took place in Colombia, Venezuela, and Mexico. The viruses involved in these epizootics as well as previously epizootic subtype IC viruses have been shown to be close phylogenetic relatives of known enzootic subtype ID viruses. This finding suggests that active evolution and selection of epizootic viruses are under way in northern South America.

During epizootics, extensive human infection is the rule, with clinical disease in 10 to 60% of infected individuals. Most infections result in notable acute febrile disease, while relatively few result in encephalitis. A low rate ofCNSinvasion is supported by the absence of encephalitis among the many infections resulting from exposure to aerosols in the laboratory or from vaccine accidents. The most recent large epizootic of Venezuelan equine encephalitis occurred in Colombia and Venezuela in 1995; of the more than 85,000 clinical cases, 4% (with a higher proportion among children than adults) included neurologic symptoms and 300 ended in death.

Enzootic strains of Venezuelan equine encephalitis virus are common causes of acute febrile disease, particularly in areas such as the Florida Everglades and the humid Atlantic coast of Central America. Encephalitis has been documented only in the Florida infections; the three cases were caused by type II enzootic virus, also called *Everglades virus*. All three patients had preexisting cerebral disease. Extrapolation from the rate of genetic change suggests that Everglades virus may have been introduced into Florida <200 years ago and that it is most closely related to the ID subtypes that appear to have given evolutionary rise to the epizootic strains active in South America.

The prevention of epizootic Venezuelan equine encephalitis depends on vaccination of horses with the attenuated TC-83 vaccine or with an inactivated vaccine prepared from that strain. Humans can be protected with similar vaccines, but the use of such products is restricted to laboratory personnel because of reactogenicity and limited availability. In addition, wild-type virus and perhaps TC-83 vaccine may have some degree of fetal

pathogenicity. Enzootic viruses are genetically and antigenically different from epizootic viruses, and protection against the former with vaccines prepared from the latter is relatively ineffective.

ARTHRITIS AND RASH

True arthritis is a common accompaniment of several viral diseases, such as rubella (caused by a non-alphavirus togavirus), parvovirus B19 infection, and hepatitis B; it is an occasional accompaniment of infection due to mumps virus, enteroviruses, herpesviruses, and adenoviruses. It is not generally appreciated that the alphaviruses are also common causes of arthritis. In fact, the alphaviruses discussed below all cause acute febrile diseases accompanied by the development of true arthritis and a maculopapular rash. Rheumatic involvement includes arthralgia alone, periarticular swelling, and (less commonly) joint effusions. Most of these diseases are less severe and have fewer articular manifestations in children than in adults. In temperate climates, these are summer diseases. No specific therapy or licensed vaccines exist.

SINDBIS VIRUS INFECTION

Sindbis virus is transmitted among birds by mosquitoes. Infections with the northern European strains of this virus (which cause, for example, Pogosta disease in Finland, Karelian fever in the independent states of the former Soviet Union, and Okelbo disease in Sweden) and with the genetically related southern African strains are particularly likely to result in the arthritis-rash syndrome. Exposure to a rural environment is commonly associated with this infection, which has an incubation period of<1 week.

The disease begins with rash and arthralgia. Constitutional symptoms are not marked, and fever is modest or lacking altogether. The rash, which lasts about a week, begins on the trunk, spreads to the extremities, and evolves from macules to papules that often vesiculate. The arthritis of this condition is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days. Wrists, ankles, phalangeal joints, knees, elbows, and -- to a much lesser extent -- proximal and axial joints are involved. Persistence of joint pains and occasionally of arthritis is a major problem and may go on for months or even years despite a lack of deformity.

CHIKUNGUNYA VIRUS INFECTION

It is likely that chikungunya virus ("that which bends up") is of African origin and is maintained among nonhuman primates on that continent by *Aedes* mosquitoes of the subgenus *Stegomyia* in a fashion similar to yellow fever virus. Like yellow fever virus, chikungunya virus is readily transmitted among humans in urban areas by *A. aegypti*. The *A. aegypti*-chikungunya virus transmission cycle has also been introduced into Asia, where it poses a prominent health problem. The disease is endemic in rural areas of Africa, and intermittent epidemics take place in towns and cities of Africa and Asia. Chikungunya is one more reason (in addition to dengue and yellow fever) that *A. aegypti* must be controlled.

Full-blown disease is most common among adults, in whom the clinical picture may be dramatic. The brusque onset follows an incubation period of 2 to 3 days. Fever and

severe arthralgia are accompanied by chills and constitutional symptoms such as headache, photophobia, conjunctival injection, anorexia, nausea, and abdominal pain. Migratory polyarthritis mainly affects the small joints of the hands, wrists, ankles, and feet, with lesser involvement of the larger joints. Rash may appear at the outset or several days into the illness; its development often coincides with defervescence, which takes place around day 2 or day 3 of disease. The rash is most intense on the trunk and limbs and may desquamate. Petechiae are occasionally seen, and epistaxis is not uncommon, but this virus is not a regular cause of theHFsyndrome, even in children. A few patients develop leukopenia. Elevated levels of aspartate aminotransferase (AST) and C-reactive protein have been described, as have mildly decreased platelet counts. Recovery may require weeks. Some older patients continue to suffer from stiffness, joint pain, and recurrent effusions for several years; this persistence may be especially common in HLA-B27 patients. An investigational live attenuated vaccine has been developed but requires further testing.

A related virus, O'nyong-nyong, caused a major epidemic of arthritis and rash involving at least 2 million people as it moved across eastern and central Africa in the 1960s. After its mysterious emergence, the virus virtually disappeared, leaving only occasional evidence of its persistence in Kenya until a transient resurgence of epidemic activity in 1997.

MAYARO FEVER

Mayaro virus is maintained in the forests of the Americas by *Haemagogus* mosquitoes and nonhuman primates. It causes a frequently endemic and sometimes epidemic infection of humans and appears to produce a syndrome resembling chikungunya.

EPIDEMIC POLYARTHRITIS (ROSS RIVER VIRUS INFECTION)

Ross River virus has caused epidemics of distinctive clinical disease in Australia since the beginning of the twentieth century and continues to be responsible for thousands of cases in rural and suburban areas annually. The virus is transmitted by *A. vigilax* and other mosquitoes, and its persistence is thought to involve transovarial transmission. No definitive vertebrate host has been identified, but several mammalian species, including wallabies, have been suggested. Endemic transmission has also been documented in New Guinea, and in 1979 the virus swept through the eastern Pacific Islands, causing hundreds of thousands of illnesses. The virus was carried from island to island by infected humans and was believed to have been transmitted among humans by *A. polynesiensis* and *A. aegypti*.

The incubation period is 7 to 11 days long, and the onset of illness is sudden, with joint pain usually ushering in the disease. The rash generally develops coincidentally or follows shortly but in some cases precedes joint pains by several days. Constitutional symptoms such as low-grade fever, asthenia, myalgia, headache, and nausea are not prominent and indeed are absent in many cases. Most patients are incapacitated for considerable periods by joint involvement, which interferes with sleeping, walking, and grasping. Wrist, ankle, metacarpophalangeal, interphalangeal, and knee joints are the most commonly involved, although toes, shoulders, and elbows may be affected with some frequency. Periarticular swelling and tenosynovitis are common, and one-third of

patients have true arthritis. Only half of all arthritis patients can resume normal activities within 4 weeks, and 10% still must limit their activity at 3 months. Occasional patients are symptomatic for 1 to 3 years but without progressive arthropathy. Aspirin and nonsteroidal anti-inflammatory drugs are effective for the treatment of symptoms.

Clinical laboratory values are normal or variable in Ross River virus infection. Tests for rheumatoid factor and antinuclear antibodies are negative, and the erythrocyte sedimentation rate is acutely elevated. Joint fluid contains 1000 to 60,000 mononuclear cells per microliter, and Ross River virus antigen is demonstrable in macrophages. IgM antibodies are valuable in the diagnosis of this infection, although they occasionally persist for years. The isolation of the virus from blood by mosquito inoculation or mosquito cell culture is possible early in the illness. Because of the great economic impact of annual epidemics in Australia, an inactivated vaccine is being developed and has been found to be protective in mice.

Perhaps because of the local interest in arboviruses in general and in Ross River virus in particular, other arthritogenic arboviruses have been identified in Australia, including Gan Gan virus, a member of the family Bunyaviridae; Kokobera virus, a flavivirus; and Barmah Forest virus, an alphavirus. The last virus is a common cause of infection and must be differentiated from Ross River virus by specific testing.

HEMORRHAGIC FEVERS

The viralHFsyndrome is a constellation of findings based on vascular instability and decreased vascular integrity. An assault, direct or indirect, on the microvasculature leads to increased permeability and (particularly when platelet function is decreased) to actual disruption and local hemorrhage. Blood pressure is decreased, and in severe cases shock supervenes. Cutaneous flushing and conjunctival suffusion are examples of common, observable abnormalities in the control of local circulation. The hemorrhage is inconstant and is in most cases an indication of widespread vascular damage rather than a life-threatening loss of blood volume. Disseminated intravascular coagulation is occasionally found in any severely ill patient with HF but is thought to occur regularly only in the early phases of HF with renal syndrome, Crimean Congo HF, and perhaps some cases of filovirus HF. In some viral HF syndromes, specific organs may be particularly impaired, such as the kidney in HF with renal syndrome, the lung in hantavirus pulmonary syndrome, or the liver in yellow fever, but in all these diseases the generalized circulatory disturbance is critically important.

The pathogenesis ofHF is poorly understood and varies among the viruses regularly implicated in the syndrome, which number more than a dozen. In some cases direct damage to the vascular system or even to parenchymal cells of target organs is important, whereas in others soluble mediators are thought to play the major role. The acute phase in most cases of HF is associated with ongoing virus replication and viremia. Exceptions are the hantavirus diseases and dengue HF/dengue shock syndrome (DHF/DSS), in which the immune response plays a major pathogenic role.

TheHFsyndromes all begin with fever and myalgia, usually of abrupt onset. Within a few days the patient presents for medical attention because of increasing prostration that is often accompanied by severe headache, dizziness, photophobia, hyperesthesia,

abdominal or chest pain, anorexia, nausea or vomiting, and other gastrointestinal disturbances. Initial examination often reveals only an acutely ill patient with conjunctival suffusion, tenderness to palpation of muscles or abdomen, and borderline hypotension or postural hypotension, perhaps with tachycardia. Petechiae (often best visualized in the axillae), flushing of the head and thorax, periorbital edema, and proteinuria are common. Levels ofAST are usually elevated at presentation or within a day or two thereafter. Hemoconcentration from vascular leakage, which is usually evident, is most marked in hantavirus diseases and inDHF/DSS. The seriously ill patient progresses to more severe symptoms and develops shock and other findings typical of the causative virus. Shock, multifocal bleeding, and CNSinvolvement (encephalopathy, coma, convulsions) are all poor prognostic signs.

One of the major diagnostic clues is travel to an endemic area within the incubation period for a given syndrome (Table 198-4). Except for Seoul, dengue, and yellow fever virus infections, which have urban vectors, travel to a rural setting is especially suggestive of a diagnosis ofHF.

Early recognition is important because of the need for virus-specific therapy and supportive measures, including prompt, atraumatic hospitalization; judicious fluid therapy that takes into account the patient's increased capillary permeability; administration of cardiotonic drugs; use of pressors to maintain blood pressure at levels that will support renal perfusion; treatment of the relatively common secondary bacterial infections; replacement of clotting factors and platelets as indicated; and the usual precautionary measures used in the treatment of patients with hemorrhagic diatheses. Disseminated intravascular coagulation should be treated only if clear laboratory evidence of its existence is found and if laboratory monitoring of therapy is feasible; there is no proven benefit of such therapy. The available evidence suggests thatHFpatients have a decreased cardiac output and will respond poorly to fluid loading as it is often practiced in the treatment of shock associated with bacterial sepsis. Specific therapy is available for several of the HF syndromes. In addition, several diseases considered in the differential diagnosis -- malaria, shigellosis, typhoid, leptospirosis, relapsing fever, and rickettsial disease -- are treatable and potentially lethal. Strict barrier nursing and other precautions against infection of medical staff and visitors are indicated in HF except that due to hantaviruses, yellow fever, Rift Valley fever, and dengue.

LASSA FEVER

Lassa virus is known to cause endemic and epidemic disease in Nigeria, Sierra Leone, Guinea, and Liberia, although it is probably more widely distributed in West Africa. This virus and its relatives exist elsewhere in Africa, but their health significance is unknown. Like other arenaviruses, Lassa virus is spread to humans by small-particle aerosols from chronically infected rodents and may also be acquired during the capture or eating of these animals. It can be transmitted by close person-to-person contact. The virus is often present in urine during convalescence and is suspected to be present in seminal fluid early in recovery. Nosocomial spread has occurred but is uncommon if proper sterile parenteral techniques are used. People of all ages and both sexes are affected; the incidence of disease is highest in the dry season, but transmission takes place year-round. In countries where Lassa virus is endemic, Lassa fever can be a prominent

cause of febrile disease. For example, in one hospital in Sierra Leone, laboratory-confirmed Lassa fever is consistently responsible for one-fifth of admissions to the medical wards. There are probably tens of thousands of Lassa fever cases annually in West Africa alone.

The average case has a gradual onset (among theHFagents, only the arenaviruses are typically associated with a gradual onset) that gives way to more severe constitutional symptoms and prostration. Bleeding is seen in only ~15 to 30% of cases. A maculopapular rash is often noted in light-skinned Lassa patients. Effusions are common, and male-dominant pericarditis may develop late. The fetal death rate is 92% in the last trimester, when maternal mortality is also increased from the usual 15% to 30%; these figures suggest that interruption of the pregnancy of infected women should be considered. White blood cell counts are normal or slightly elevated, and platelet counts are normal or somewhat low. Deafness coincides with clinical improvement in ~20% of cases and is permanent and bilateral in some. Reinfection may occur but has not been associated with severe disease.

High-level viremia or a high serum concentration ofASTstatistically predicts a fatal outcome. Thus patients with an AST level of>150 IU/mL should be treated with intravenous ribavirin. This antiviral nucleoside analogue appears to be effective in reducing mortality from rates among retrospective controls, and its only major side effect is reversible anemia that usually does not require transfusion. The drug should be given by slow intravenous infusion in a dose of 32 mg/kg; this dose should be followed by 16 mg/kg q6h for 4 days and then by 8 mg/kg q8h for 6 days.

SOUTH AMERICANHFSYNDROMES (ARGENTINE, BOLIVIAN, VENEZUELAN, AND BRAZILIAN)

These diseases are similar to one another clinically, but their epidemiology differs with the habits of their rodent reservoirs and the interactions of these animals with humans (Table 198-4). Person-to-person or nosocomial transmission is rare but has occurred.

The basic disease resembles Lassa fever with two marked differences. First, thrombocytopenia -- often marked -- is the rule, and bleeding is quite common. Second,CNSdysfunction is much more common than in Lassa fever and is often manifest by marked confusion, tremors of the upper extremities and tongue, and cerebellar signs. Some cases follow a predominantly neurologic course, with a poor prognosis. The clinical laboratory is helpful in diagnosis since thrombocytopenia, leukopenia, and proteinuria are typical findings.

ArgentineHF is readily treated with convalescent-phase plasma given within the first 8 days of illness. In the absence of passive antibody therapy, intravenous ribavirin in the dose recommended for Lassa fever is likely to be effective in all the South American HF syndromes. The transmission of the disease from men convalescing from Argentine HF to their wives suggests the need for counseling of arenavirus HF patients concerning the avoidance of intimate contacts for several weeks after recovery. A safe, effective, live attenuated vaccine exists for Argentine HF. In experimental animals, this vaccine is cross-protective against the Bolivian HF virus.

RIFT VALLEY FEVER

This mosquito-borne virus is also a pathogen of domestic animals such as sheep, cattle, and goats. It is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes and presumably also has a vertebrate amplifier. Epizootics and epidemics occur when sheep or cattle become infected during particularly heavy rains; developing high-level viremia, these animals infect many different species of mosquitoes. Remote sensing via satellite can detect the ecologic changes associated with high rainfall that predict the likelihood of Rift Valley fever transmission; it can also detect the special depressions from which the floodwater *Aedes* mosquito vectors emerge. In addition, the virus is infectious when transmitted by contact with blood or aerosols from domestic animals or their abortuses. The slaughtered meat is not infectious; anaerobic glycolysis in postmortem tissues results in an acidic environment that rapidly inactivates Bunyaviridae such as Rift Valley fever virus and Crimean-Congo HF virus. The natural range of Rift Valley fever virus is confined to sub-Saharan Africa, where its circulation is markedly enhanced by substantial rainfall such as that which occurred during the El Nino phenomenon of 1997. The virus has also been found in Madagascar and has been introduced into Egypt, where it caused major epidemics in 1977 to 1979, 1993, and subsequently. Neither person-to-person nor nosocomial transmission has been documented.

Rift Valley fever virus is unusual in that it causes at least four different clinical syndromes. Most infections are manifested as the febrile-myalgic syndrome. A small proportion result inHF with especially prominent liver involvement. Perhaps 10% of otherwise mild infections lead to retinal vasculitis; funduscopic examination reveals edema, hemorrhages, and infarction, and some patients have permanently impaired vision. A small proportion of cases (<1 in 200) are followed by typical viral encephalitis. One of the complicated syndromes does not appear to predispose to another.

There is no proven therapy for any of the syndromes described above. The sensitivity of animal models of Rift Valley fever to antibody or ribavirin therapy suggests that either could be given intravenously to persons withHF. Both retinal disease and encephalitis occur after the acute febrile syndrome has ended and serum neutralizing antibody has developed -- events suggesting that only supportive care need be given. Epidemic disease is best prevented by vaccination of livestock. The established ability of this virus to propagate after an introduction into Egypt suggests that other potentially receptive areas, including the United States, should have a response ready for such an eventuality. It seems likely that this disease, like Venezuelan equine encephalitis, can be controlled only with adequate stocks of an effective live attenuated vaccine, and there are no such global stocks. A formalin-inactivated vaccine confers immunity to humans, but quantities are limited and three injections are required; this vaccine is recommended for exposed laboratory workers and for veterinarians working in sub-Saharan Africa.

CRIMEAN CONGO HF

This severe HF syndrome has a wide geographic distribution, potentially being found wherever ticks of the genus *Hyalomma* occur (Table 198-4). The propensity of these ticks to feed on domestic livestock and certain wild mammals means that veterinary

serosurveys are the most effective mechanism for the surveillance of virus circulation in a region. Human infection is acquired via a tick bite or during the crushing of infected ticks. Domestic animals do not become ill but do develop viremia; thus there is danger of infection at the time of slaughter and for a brief interval thereafter (through contact with hides or carcasses). Cases have followed sheep shearing. An epidemic in South Africa was associated with slaughter of tick-infested ostriches. Nosocomial epidemics are common and are usually related to extensive blood exposure or needle sticks.

Although generally similar to otherHFsyndromes, Crimean Congo HF causes extensive liver damage, resulting in jaundice in some cases. Clinical laboratory values indicate disseminated intravascular coagulation and show elevations inAST, creatine phosphokinase, and bilirubin. Patients with fatal cases generally have more marked changes, even in the early days of illness, and also develop leukocytosis rather than leukopenia. Thrombocytopenia is also more marked and develops earlier in cases with a fatal outcome.

No controlled trials have been performed with intravenous ribavirin, but clinical experience and retrospective comparison of patients with ominous clinical laboratory values suggest that ribavirin is efficacious and should be given. No human or veterinary vaccines are recommended.

HFWITH RENAL SYNDROME

This disease, the first to be identified as an HF, is widely distributed over Europe and Asia; the major causative viruses and their rodent reservoirs on these two continents are Puumala virus (bank vole, *Clethrionomys glareolus*) and Hantaan virus (striped field mouse, *Apodemus agrarius*), respectively. Other potential causative viruses exist, including Dobrava virus (yellow-necked field mouse, *A. flavicollus*), which causes severe HF with renal syndrome in the Balkans. Seoul virus is associated with the Norway or sewer rat, *Rattus norvegicus*, and has a worldwide distribution through the migration of the rodent; it is associated with mild or moderate HF with renal syndrome in Asia, but in many areas of the world the human disease has been difficult to identify. Most cases occur in rural residents or vacationers; the exception is Seoul virus disease, which may be acquired in an urban or rural setting or from contaminated laboratory rat colonies. Classic Hantaan disease in Korea (Korean HF) and in rural China (epidemic HF) is most common in spring and fall and is related to rodent density and agricultural practices. Human infection is acquired primarily through aerosols of rodent urine, although virus is also present in saliva and feces. Patients with hantavirus diseases are not infectious. HF with renal syndrome is the most important form of HF today, with more than 100,000 cases of severe disease in Asia annually and milder Puumala infections numbering in the thousands as well.

Severe cases ofHF with renal syndrome caused by Hantaan virus evolve in identifiable stages: the febrile stage with myalgia, lasting 3 to 4 days; the hypotensive stage, often associated with shock and lasting from a few hours to 48 h; the oliguric stage with renal failure, lasting 3 to 10 days; and the polyuric stage with diuresis and hyposthenuria.

The *febrile period* is initiated by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain

on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the V area of the neck, and the back are characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Laboratory evidence of mild to moderate disseminated intravascular coagulation is present. Other laboratory findings include proteinuria and an active urinary sediment.

The *hypotensive phase* is ushered in by falling blood pressure and sometimes by shock. The relative bradycardia typical of the febrile phase is replaced by tachycardia. Kinin activation is marked. The rising hematocrit reflects increasing vascular leakage. Leukocytosis with a left shift develops, and thrombocytopenia continues. Atypical lymphocytes -- which in fact are activated CD8+ and to a lesser extent CD4+ T cells -- circulate. Proteinuria is marked, and the urine's specific gravity falls to 1.010. The renal circulation is congested and compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria.

During the *oliguric phase*, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. The oliguria persists for 3 to 10 days before renal function returns and marks the onset of the *polyuric stage*, which carries the danger of dehydration and electrolyte abnormalities.

Mild cases ofHF with renal syndrome may be much less stereotypical. The presentation may include only fever, gastrointestinal abnormalities, and transient oliguria followed by hyposthenuria.

HFwith renal syndrome should be suspected in patients with rural exposure in an endemic area. Prompt recognition of the disease will permit rapid hospitalization and expectant management of shock and renal failure. Useful clinical laboratory parameters include leukocytosis, which may be leukemoid and is associated with a left shift; thrombocytopenia; and proteinuria. Mainstays of therapy are the management of shock, reliance on pressors, modest crystalloid infusion, intravenous use of human serum albumin, and treatment of renal failure with prompt dialysis for the usual indications. Hydration may result in pulmonary edema, and hypertension should be avoided because of the possibility of intracranial hemorrhage. Use of intravenous ribavirin has reduced mortality and morbidity in severe cases provided treatment is begun within the first 4 days of illness. The case-fatality ratio may be as high as 15% but with proper therapy should be <5%. Sequelae have not been definitely established, but there is a correlation in the United States between chronic hypertensive renal failure and the presence of antibodies to Seoul virus.

Infections with Puumala virus, the most common cause ofHF with renal syndrome in Europe, result in a much attenuated picture but the same general presentation. The syndrome may be referred to by its former name, *nephropathia epidemica*. Bleeding manifestations are found in only 10% of cases, hypotension rather than shock is usually seen, and oliguria is present in only about half of patients. The dominant features may be fever, abdominal pain, proteinuria, mild oliguria, and sometimes blurred vision or glaucoma followed by polyuria and hyposthenuria in recovery. Mortality is<1%.

The diagnosis is readily made by IgM-captureELISA, which should be positive at admission or within 24 to 48 h thereafter. The isolation of virus is difficult, butRT-PCRof a blood clot collected early in the clinical course or of tissues obtained postmortem will give positive results. Such testing is usually undertaken only if definitive identification of the infecting viral species is required or if molecular epidemiologic questions exist.

HANTAVIRUS PULMONARY SYNDROME

Hantavirus pulmonary syndrome was discovered in 1993, but retrospective identification of cases by immunohistochemistry (1978) and serology (1959) support the idea that it is a recently discovered rather than a truly new disease. The causative viruses are hantaviruses of a distinct phylogenetic lineage that is associated with the rodent subfamily Sigmodontinae. Sin Nombre virus chronically infects the deer mouse (*Peromyscus maniculatus*) and is the most important virus causing hantavirus pulmonary syndrome in the United States. The disease is also caused by a Sin Nombre virus variant from the white-footed mouse (*P. leucopus*), by Black Creek Canal virus (*Sigmodon hispidus*, the cotton rat), and by Bayou virus (*Oryzomys palustris*, the rice rat). Several other related viruses cause the disease in South America, but Andes virus is unusual in that it, alone among hantaviruses, has been implicated in human-to-human transmission. The disease is linked to rodent exposure and particularly affects rural residents living in dwellings permeable to rodent entry or working at occupations that pose a risk of rodent exposure. Each rodent species has its own particular habits; in the case of the deer mouse, these behaviors include living in and around human habitation.

The disease begins with a prodrome of about 3 to 4 days (range, 1 to 11 days) comprising fever, myalgia, malaise, and often gastrointestinal disturbances such as nausea, vomiting, and abdominal pain. Dizziness is common and vertigo occasional. Severe prodromal symptoms bring some individuals to medical attention, but patients are usually recognized as the cardiopulmonary phase begins. Typically, there is slightly lowered blood pressure, tachycardia, tachypnea, mild hypoxemia, and early radiographic signs of pulmonary edema. Physical findings in the chest are often surprisingly scant. The conjunctival and cutaneous signs of vascular involvement seen in other types ofHF are absent. During the next few hours, decompensation may progress rapidly to severe hypoxemia and respiratory failure. Most patients surviving the first 48 h of hospitalization are extubated and discharged within a few days, with no apparent residua.

Management during the first few hours after presentation is critical. The goal is to prevent severe hypoxemia by oxygen therapy and, if needed, intubation and intensive respiratory management. During this period, hypotension and shock with increasing hematocrit invite aggressive fluid administration, but this intervention should be undertaken with great caution. Because of low cardiac output with myocardial depression and increased pulmonary vascular permeability, shock should be managed expectantly with pressors and modest infusion of fluid guided by the pulmonary capillary wedge pressure. Mild cases can be managed by frequent monitoring and oxygen administration without intubation. Many patients require intubation to manage hypoxemia and also develop shock. Mortality remains at ~30 to 40% with good management. The antiviral drug ribavirin inhibits the virus in vitro but did not have a

marked effect on patients treated in an open-label study.

During the prodrome, the differential diagnosis of hantavirus pulmonary syndrome is difficult, but by the time of presentation or within 24 h thereafter, a number of diagnostically helpful clinical features become apparent. Cough is not usually present at the outset but may develop later. Interstitial edema is evident on the chest x-ray. Later, bilateral alveolar edema with a central distribution develops in the setting of a normal-sized heart; occasionally, the edema is initially unilateral. Pleural effusions are often visualized. Thrombocytopenia, circulating atypical lymphocytes, and a left shift (often with leukocytosis) are almost always evident; thrombocytopenia has been a particularly important early clue. Hemoconcentration, proteinuria, and hypoalbuminemia should also be sought. Although thrombocytopenia virtually always develops and prolongation of the partial thromboplastin time is the rule, clinical evidence for coagulopathy or laboratory indications of disseminated intravascular coagulation are found in only a minority of cases, usually in severely ill patients. Severely ill patients also have acidosis and elevated serum levels of lactate. Mildly increased values in renal function tests are common, but patients with severe cases often have markedly elevated concentrations of serum creatinine; some of the viruses other than Sin Nombre virus have been associated with more kidney involvement, but few such cases have been studied. The differential diagnosis includes abdominal surgical conditions and pyelonephritis as well as rickettsial disease, sepsis, meningococcemia, plague, tularemia, influenza, and relapsing fever.

A specific diagnosis is best made by IgM testing of acute-phase serum, which has yielded positive results even in the prodrome. Tests using a Sin Nombre virus antigen detect the related hantaviruses causing the pulmonary syndrome in the Americas. Occasionally, heterologous viruses will react only in the IgGELISA, but this finding is highly suspicious given the very low seroprevalence of these viruses in normal populations.RT-PCRis usually positive when used to test blood clots obtained in the first 7 to 9 days of illness as well as tissues; this test is useful in identifying the infecting virus in areas outside the home range of the deer mouse and in atypical cases.

YELLOW FEVER

Yellow fever virus caused major epidemics in the Americas, Africa, and Europe before the discovery of mosquito transmission in 1900 led to its control through attacks on its urban vector, *A. aegypti*. Only then was it found that a jungle cycle also existed in Africa, involving other *Aedes* mosquitoes and monkeys, and that colonization of the New World with *A. aegypti*, originally an African species, had established urban yellow fever as well as an independent sylvatic yellow fever cycle in American jungles involving *Haemagogus* mosquitoes and New World monkeys. Today, urban yellow fever transmission occurs only in some African cities, but the threat exists in the great cities of South America, where reinfestation by *A. aegypti* has taken place and dengue transmission by the same mosquito is common. As late as 1905, New Orleans suffered more than 3000 cases with 452 deaths from "yellow jack." Despite the existence of a highly effective and safe vaccine, several hundred jungle yellow fever cases occur annually in South America, and thousands of jungle and urban cases occur each year in Africa.

Yellow fever is a typicalHFaccompanied by prominent hepatic necrosis. A period of viremia, typically lasting 3 or 4 days, is followed by a period of "intoxication." During the latter phase in severe cases, the characteristic jaundice, hemorrhages, black vomit, anuria, and terminal delirium occur, perhaps related in part to extensive hepatic involvement. Blood leukocyte counts may be normal or reduced and are often high in terminal stages. Albuminuria is usually noted and may be marked; as renal function fails in terminal or severe cases, the level of blood urea nitrogen rises proportionately. Abnormalities detected in liver function tests range from modest elevations ofASTlevels in mild cases to severe derangement.

Urban yellow fever can be prevented by the control of *A. aegypti*. The continuing sylvatic cycle requires vaccination of all visitors to areas of potential transmission. With few exceptions (in the very young and the elderly), reactions to vaccine are minimal; immunity is provided within 10 days and lasts for at least 10 years. An egg allergy dictates caution in vaccine administration. Although there are no documented harmful effects of the vaccine on the fetus, pregnant women should be immunized only if they are definitely at risk of yellow fever exposure. Since vaccination has been associated with several cases of encephalitis in children under 6 months of age, it should be delayed until after 12 months of age unless the risk of exposure is very high. Timely information on changes in yellow fever distribution and yellow fever vaccine requirements can be obtained from Health Information for Travelers, Centers for Disease Control and Prevention, Atlanta, GA 30333; by fax request (404-332-4565; document number 220022#); by phone (404-332-4559); or on the World-Wide Web athttp://www.cdc.gov.

DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME

A syndrome ofHF noted in the 1950s among children in the Philippines and Southeast Asia was soon associated with dengue virus infections, particularly those occurring against a background of previous exposure to another serotype. The transient heterotypic protection after dengue virus infection is replaced within several weeks by the potential for heterotypic infection resulting in typical dengue fever (see above) or -- uncommonly -- for enhanced disease (secondaryDHF/DSS). In rare instances, primary dengue infections lead to an HF syndrome, but much less is known about pathogenesis in this situation. In the past 20 years, *A. aegypti* has progressively reinvaded Latin America and other areas, and frequent travel by infected individuals has introduced multiple strains of dengue virus from many geographic areas. Thus the pattern of hyperendemic transmission of multiple dengue serotypes has now been established in the Americas and the Caribbean and has led to the emergence of DHF/DSS as a major problem there as well. Millions of dengue infections, including many thousands of cases of DHF/DSS, occur annually. The severe syndrome is unlikely to be seen in U.S. citizens since few children have the dengue antibodies that can trigger the pathogenetic cascade when a second infection is acquired.

Macrophage/monocyte infection is central to the pathogenesis of dengue fever and to the origin ofDHF/DSS. Previous infection with a heterologous dengue-virus serotype may result in the production of nonprotective antiviral antibodies that nevertheless bind to the virion's surface and through interaction with the Fc receptor focus secondary dengue viruses on the target cell, the result being enhanced infection. The host is also

primed for a secondary antibody response when viral antigens are released and immune complexes lead to activation of the classic complement pathway, with consequent phlogistic effects. Cross-reactivity at the T cell level results in the release of physiologically active cytokines, including interferon g and tumor necrosis factora. The induction of vascular permeability and shock depends on multiple factors, including the following:

1. *Presence of enhancing and nonneutralizing antibodies* -- Transplacental maternal antibody may be present in infants <9 months old, or antibody elicited by previous heterologous dengue infection may be present in older individuals. T cell reactivity is also intimately involved.

2. *Age* -- Susceptibility toDHF/DSSdrops considerably after 12 years of age.

3. *Sex* -- Females are more often affected than males.

4. *Race* -- Caucasians are more often affected than blacks.

5. *Nutritional status* -- Malnutrition is protective.

6. *Sequence of infection* -- For example, serotype 1 followed by serotype 2 seems to be more dangerous than serotype 4 followed by serotype 2.

7. *Infecting serotype* -- Type 2 is apparently more dangerous than other serotypes.

In addition, there is considerable variation among strains of a given serotype, with Southeast Asian serotype 2 strains having more potential to causeDHF/DSSthan others.

DengueHF is identified by the detection of bleeding tendencies (tourniquet test, petechiae) or overt bleeding in the absence of underlying causes such as preexisting gastrointestinal lesions. Dengue shock syndrome, usually accompanied by hemorrhagic signs, is much more serious and results from increased vascular permeability leading to shock. In mildDHF/DSS, restlessness, lethargy, thrombocytopenia (<100,000/uL), and hemoconcentration are detected 2 to 5 days after the onset of typical dengue fever, usually at the time of defervescence. The maculopapular rash that often develops in dengue fever may also appear in DHF/DSS. In more severe cases, frank shock is apparent, with low pulse pressure, cyanosis, hepatomegaly, pleural effusions, ascites, and in some cases severe ecchymoses and gastrointestinal bleeding. The period of shock lasts only 1 or 2 days, and most patients respond promptly to close monitoring, oxygen administration, and infusion of crystalloid or -- in severe cases -- colloid. The case-fatality rates reported vary greatly with case ascertainment and the quality of treatment; however, most DHF/DSS patients respond well to supportive therapy, and overall mortality in an experienced center in the tropics is probably as low as 1%.

A virologic diagnosis can be made by the usual means, although multiple flavivirus infections lead to a broad immune response to several members of the group, and this situation may result in a lack of virus specificity of the IgM and IgG immune responses. A secondary antibody response can be sought with tests against several flavivirus antigens to demonstrate the characteristic wide spectrum of reactivity.

The key to control of both dengue fever andDHF/DSSis the control of *A. aegypti*, which also reduces the risk of urban yellow fever and chikungunya virus circulation. Control efforts have been handicapped by the presence of nondegradable tires and long-lived plastic containers in trash repositories, insecticide resistance, urban poverty, and an inability of the public health community to mobilize the populace to respond to the need to eliminate mosquito breeding sites. Live attenuated dengue vaccines are in the late stages of development and have produced promising results in early tests. Whether vaccines can provide safe, durable immunity to an immunopathologic disease such as DHF/DSS in endemic areas is an issue that will have to be tested, but it is hoped that vaccination will reduce transmission to negligible levels.

KYASANUR FOREST DISEASE AND OMSK HEMORRHAGIC FEVER

Kyasanur Forest virus and Omsk HFvirus are geographically restricted, tick-borne flaviviruses that cause a syndrome of viral HF during a wave of viremia and that may also enter theCNS to cause subsequent viral encephalitis (see discussion of tick-borne encephalitis above). There is no therapy for these infections, but an inactivated vaccine has been used in India against Kyasanur Forest disease. A new and related virus isolate has been obtained from butchers with HF in the Middle East; the implication is that there are more agents in this group.

FILOVIRUS HEMORRHAGIC FEVER

SeeChap. 199.

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199. FILOVIRIDAE (MARBURG AND EBOLA VIRUSES) - *C. J. Peters*

DEFINITION

Both Marburg virus and Ebola virus cause an acute febrile illness associated with high mortality. This illness is characterized by multisystem involvement that begins with the abrupt onset of headache, myalgias, and fever and proceeds to prostration, rash, shock, and often bleeding manifestations. Epidemics usually begin with a single case acquired from an unknown reservoir in nature and spread mainly through close contact with sick persons or their body fluids, either in the home or at the hospital.

ETIOLOGY

The family Filoviridae comprises two antigenically and genetically distinct viruses: Marburg virus and Ebola virus. Ebola virus has four readily distinguishable subtypes named for their original site of recognition (Zaire, Sudan, Cote d'Ivoire, and Reston). Except for Ebola virus subtype Reston, all the Filoviridae are African viruses that cause severe and often fatal disease in humans. The Reston virus, which has been exported from the Philippines on several occasions, has caused fatal infections in monkeys but only subclinical infections in humans. Different isolates of the four Ebola subtypes made over time and space exhibit remarkable sequence conservation, indicating marked genetic stability in their selective niche. Typical filovirus particles contain a single linear, negative-sense, single-stranded RNA arranged in a helical nucleocapsid. The virions are 790 to 970 nm in length; they may also appear in elongated, contorted forms. The lipid envelope confers sensitivity to lipid solvents and common detergents. The viruses are largely destroyed by heat (60°C, 30 min) and by acidity but may persist for weeks in blood at room temperature. The surface glycoprotein self-associates to form the virion surface spikes, which presumably mediate attachment to cells and fusion. The glycoprotein's high sugar content may contribute to its low capacity to elicit neutralizing antibodies. A smaller form of the glycoprotein, bearing many of its antigenic determinants, is produced by in vitro-infected cells and is found in the circulation in human disease; it has been speculated that this circulating soluble protein may suppress the immune response to the virion surface protein or block antiviral effector mechanisms. Both Marburg virus and Ebola virus are biosafety level 4 pathogens because of their high associated mortality rate and aerosol infectivity.

EPIDEMIOLOGY

Marburg virus was first identified in Germany in 1967, when infected African green monkeys (*Cercopithecus aethiops*) imported from Uganda transmitted the agent to vaccine-laboratory workers. Of the 25 human cases acquired from monkeys, 7 ended in death. The six secondary cases were associated with close contact or parenteral exposure. Secondary spread to the wife of one patient was documented, and virus was isolated from the husband's semen despite the presence of circulating antibodies. Subsequently, isolated cases of Marburg virus infection have been reported from eastern and southern Africa, with limited spread.

In 1999, repeated transmission of Marburg virus to workers in a gold mine in eastern Democratic Republic of Congo was documented. The secondary spread of the virus

among patients' families was more extensive than previously noted, resembling that of Ebola virus and emphasizing the importance of hygiene and proper barrier nursing in the epidemiology of these viruses in Africa.

In 1976, epidemics of severe hemorrhagic fever (550 human cases) occurred simultaneously in Zaire and Sudan, and Ebola virus was found to be the etiologic agent. Later, it was shown that different subtypes of virus -- associated with 90% and 50% mortality, respectively -- caused the two epidemics. Both epidemics were associated with interhuman spread (particularly in the hospital setting) and the use of unsterilized needles and syringes, a common practice in developing-country hospitals. The epidemics dwindled as the clinics were closed and people in the endemic area increasingly shunned affected persons and avoided traditional burial practices.

The Zaire subtype of Ebola virus recurred in a major epidemic (317 cases, 88% mortality) in Democratic Republic of Congo in 1995 and in smaller epidemics in Gabon in 1994-1996. Mortality was high, transmission to caregivers and others who had direct contact with body fluids was common, and poor hygiene in hospitals exacerbated spread. In the Congo epidemic, an index case was infected in Kikwit in January 1995. The epidemic smoldered until April, when intense nosocomial transmission forced closure of the hospitals; samples were finally sent to the laboratory for Ebola testing, which yielded positive results within a few hours. International assistance, with barrier nursing instruction and materials, was provided; nosocomial transmission ceased, hospitals reopened, and patients were segregated to prevent intrafamilial spread. The last case was reported in June 1995.

Three separate emergences of Ebola virus (subtype Zaire) were detected in Gabon from 1994 through 1996, all associated with deep forest exposure and subsequent familial and nosocomial transmission. In the 1996 episode, a physician exposed to Ebola-infected patients traveled to South Africa with a fever; a nurse who assisted in a cutdown on the physician developed Ebola hemorrhagic fever and died in spite of intensive care. The index patient was identified retrospectively on the basis of serum antibodies and virus isolation from semen. Thus, distant transport of Ebola virus is an established risk, and limited nosocomial spread is possible even under hygienic conditions.

The Reston subtype of Ebola virus was first seen in the United States in 1989, when it caused a fatal, highly transmissible disease among cynomolgus macaques imported from the Philippines and quarantined in Reston, VA, pending distribution to biomedical researchers. This and other appearances of the Reston virus have been traced to a single export facility in the Philippines, but no source in nature has been established.

Epidemiologic studies (including a specific search in the Kikwit epidemic) have failed to yield evidence for an important role of airborne particles in human disease. This lack of epidemiologic evidence is surprising and seems to conflict with the viruses' classification as biosafety level 4 pathogens based in part on their aerosol infectivity and with formal laboratory assessments showing a high degree of aerosol infectivity for monkeys. Sick humans apparently do not usually generate sufficient amounts of infectious aerosols to pose a significant hazard to those around them.

Available evidence points to a nonprimate reservoir for these viruses, but an intensive search has failed to elucidate what this reservoir might be. Speculation has centered on a possible role for bats, but that hypothesis has arisen in part merely because of the ubiquity of bats when sought in affected areas and the frustration of researchers in identifying a source of virus.

PATHOLOGY AND PATHOGENESIS

In humans and in animal models, Ebola and Marburg viruses replicate well in virtually all cell types, including endothelial cells, macrophages, and parenchymal cells of multiple organs. Viral replication is associated with cellular necrosis both in vivo and in vitro. Significant findings at the light-microscopic level include liver necrosis with Councilman bodies (intracellular inclusions that correlate with extensive collections of viral nucleocapsids), interstitial pneumonitis, cerebral glial nodules, and small infarcts. Antigen and virions are abundant in fibroblasts, interstitium, and (to a lesser extent) the appendages of the subcutaneous tissues in fatal cases; escape through small breaks in the skin or possibly through sweat glands may occur and, if so, may be correlated with the established epidemiologic risk of close contact with patients and the touching of the deceased. Inflammatory cells are not prominent, even in necrotic areas.

In addition to sustaining direct damage from viral infection, patients infected with Ebola virus (Zaire subtype) have high circulating levels of proinflammatory cytokines, which presumably contribute to the severity of the illness. In fact, the virus interacts intimately with the cellular cytokine system. It is resistant to the antiviral effects of interferon a, although this mediator is amply induced. Viral infection of endothelial cells selectively inhibits the expression of MHC class I molecules and blocks the induction of several genes by the interferons. In addition, glycoprotein expression inhibitsaV integrin expression, an effect that has been shown in vitro to lead to detachment and subsequent death of endothelial cells.

Acute infection is associated with high levels of circulating virus and viral antigen. Clinical improvement takes place when viral titers decrease concomitantly with the onset of a virus-specific immune response, as detected by enzyme-linked immunosorbent assay (ELISA) or fluorescent antibody test. In fatal cases, there is usually little evidence of an antibody response and there is extensive depletion of spleen and lymph nodes. Recovery is apparently mediated by the cellular immune response: convalescent-phase plasma has little in vitro virus-neutralizing capacity and is not protective in passive transfer experiments in monkey and guinea pig models.

CLINICAL MANIFESTATIONS

After an incubation period of ~7 to 10 days (range, 3 to 16 days), the patient abruptly develops fever, severe headache, malaise, myalgia, nausea, and vomiting. Continued fever is joined by diarrhea (often severe), chest pain (accompanied by cough), prostration, and depressed mentation. In light-skinned patients (and less often in blacks), a maculopapular rash appears around day 5 to 7 and is followed by desquamation. Bleeding may begin about this time and is apparent from any mucosal site and into the skin. In some epidemics, fewer than half of patients have had overt bleeding, and this manifestation has been absent even in some fatal cases. Additional

findings include edema of the face, neck, and/or scrotum; hepatomegaly; flushing; conjunctival injection; and pharyngitis. Around 10 to 12 days after the onset of disease, the sustained fever may break, with improvement and eventual recovery of the patient. Recrudescence of fever may be associated with secondary bacterial infections or possibly with localized virus persistence. Late hepatitis, uveitis, and orchitis have been reported, with isolation of virus from semen or detection of polymerase chain reaction (PCR) products in vaginal secretions for several weeks.

LABORATORY FINDINGS

Leukopenia is common early on; neutrophilia has its onset later. Platelet counts fall below (sometimes much below) 50,000/uL. Laboratory evidence of disseminated intravascular coagulation may be found, but its clinical significance and the need for therapy are controversial. Serum levels of alanine and aspartate aminotransferases (particularly the latter) rise progressively, and jaundice develops in some cases. The serum amylase level may be elevated, and this elevation may be associated with abdominal pain suggesting pancreatitis. Proteinuria is usual; decreased kidney function is proportional to shock.

DIAGNOSIS

Most patients acutely ill with Ebola or Marburg viruses have high concentrations of virus in blood. Antigen-detectionELISA is a sensitive, robust diagnostic modality. Virus isolation and reverse transcriptasePCR are also effective and provide additional sensitivity in some cases. Patients who are recovering develop IgM and IgG antibodies that are best detected by ELISA but are also reactive in the less specific fluorescent antibody test. Skin biopsies are an extremely useful adjunct in postmortem diagnosis of Ebola and, to a lesser extent, Marburg virus infections because of the presence of large amounts of viral antigen, the relative safety of obtaining the sample, and the freedom from cold-chain requirements for formalin-fixed tissues.

TREATMENT

No virus-specific therapy is available, and, given the extensive viral involvement in fatal cases, supportive treatment may not be as useful as was once hoped. Vigorous treatment of shock should take into account the likelihood of vascular leak in the pulmonary and systemic circulation and of myocardial functional compromise. The membrane fusion mechanism of Ebola resembles that of retroviruses, and the identification of "fusogenic" sequences suggests that inhibitors of cell entry may be developed. Despite the poor neutralizing capacity of polyclonal convalescent-phase sera, phage display of immunoglobulin mRNA from convalescent bone marrow has produced monoclonal antibodies that have in vitro neutralizing capacity and mediate protection in guinea pig models.

PREVENTION

No vaccine is available, but barrier nursing precautions in African hospitals can greatly decrease the spread of the virus beyond the index case and thus prevent epidemics of filoviruses and other agents as well.

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SECTION 15 -FUNGAL AND ALGAL INFECTIONS

200. DIAGNOSIS AND TREATMENT OF FUNGAL INFECTIONS - *John E. Bennett*

MYCOLOGY FUNDAMENTALS

Fungi can appear microscopically as either rounded, budding forms (yeastlike organisms) or hyphae (molds; Fig. 200-CD1). Yeastlike colonies are smooth, while mold colonies are fuzzy; fungi that grow as yeasts include species of *Candida* and *Cryptococcus*, while fungi that grow as molds include species of *Aspergillus*, *Rhizopus*, and dermatophytes (ringworm fungi). The fungi that cause histoplasmosis, blastomycosis, sporotrichosis, coccidioidomycosis, and paracoccidioidomycosis are called *dimorphic* ("having two forms") because they are spherical in tissue but grow like molds when cultured at room temperature. *Candida* species other than *Candida glabrata* appear in tissue as both budding yeasts and tubular elements called *pseudohyphae*. *Pneumocystis carinii* is closer to fungi than to parasites by ribosomal sequences (Chap. 209). Because the drugs used to treat *Pneumocystis* pneumonia are also used to treat parasitic or bacterial infections, those drugs will not be discussed in this chapter.

Many fungi can form two different types of spores and are given different names, depending on the spore-bearing structures. When the spores are produced by mitosis, the fungus is said to be an *anamorph*, or to be in the imperfect state. Many fungi can have different sporulating structures in which genetic recombination occurs, often as a result of coculture with a strain of the opposite mating type. A fungus producing those distinctive spores is said to be a *teleomorph*, or to be in the perfect state. Diagnostic laboratories usually use the name of the anamorph because they do not use culture conditions that would produce the teleomorph. One exception is *Scedosporium apiospermum*, which is often observed as a teleomorph in the diagnostic laboratory and identified as *Pseudallescheria boydii*.

Most fungi that are pathogenic for humans are saprophytes in nature; they cause infection when airborne spores reach the lung or paranasal sinus or when hyphae or spores are accidentally inoculated into the skin or cornea. Acquisition of infection from another person or an animal has been reported in the case of ringworm but is very rare in other mycoses. Thus, hospitalized patients with fungal infections do not require special isolation. Most fungi infect hosts preferentially by one route and only infrequently by other routes. For example, the agents of ringworm, pityriasis versicolor, and piedra infect the epidermis and its appendages. Sporotrichosis and mycetoma usually arise from subcutaneous inoculation. Inhalation is the route of inoculation for the agents of most deep mycoses. Ingestion of fungi rarely causes infection; *Candida albicans*, a normal commensal in the mouth and intestine, reaches deeper tissues only when mucosal or cutaneous barriers are breached by disease, surgery, trauma, or catheterization. Histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis have been called "endemic" mycoses to emphasize their restricted geographic distribution. Some fungi, such as *Aspergillus*, are said to be opportunists in that they usually infect hosts with compromised immunity. This distinction is relative, not absolute.

Immunity after exposure to fungi may confer partial protection against reinfection. Residents of areas in which mycoses are endemic are less subject to infection than are newcomers. Predisposing factors are helpful in defining host defense. Immunoglobulin deficiencies do not appear to predispose to any mycosis, whereas neutropenia is common among patients who develop invasive aspergillosis or deep candidiasis. Cell-mediated immunity appears to be of paramount importance in most other deep mycoses.

DIAGNOSIS

Many fungi can be identified to the genus or even the species level by microscopic examination of smears or biopsy specimens. Calcofluor white staining with fluorescence microscopy is a sensitive technique for smears of sputum, bronchoalveolar lavage fluid, or pus. India ink smear remains the method of choice for detecting cryptococci in cerebrospinal fluid (CSF). *Candida* yeast cells and pseudohyphae are the only fungi that are usually gram-positive on smears. For other fungi, Gram's staining is distinctly suboptimal. For histopathology slides, Gomori methenamine silver and a neutral counterstain are preferred.

The method used has a marked effect on the rapidity and sensitivity of blood cultures for fungi except in the case of *Candida* species, which are relatively easy to grow. For most other fungi, concentration of the blood by lysis centrifugation and culture on solid medium constitute the optimal technique. Commercially available nucleic acid hybridization techniques can speed the identification of slow-growing molds, such as *Histoplasma capsulatum* and *Coccidioides immitis*. Serology has limited value, but testing of serum orCSF for cryptococcal antigen or antibody to *C. immitis* can be diagnostic. Detection of *Histoplasma* antigen in urine or serum is helpful in diagnosis and in following the results of treatment for disseminated histoplasmosis. Skin testing with fungal antigens is not useful in detecting active infection.

ANTIFUNGAL THERAPY

TOPICAL AGENTS

Imidazoles and Triazoles (See also "Systemic Antifungals," below) These synthetic compounds act by inhibiting ergosterol synthesis in the fungal cell wall and, when given topically, may cause direct damage to the fungal cytoplasmic membrane. The imidazoles available for cutaneous application include clotrimazole, econazole, ketoconazole, sulconazole, oxiconazole, and miconazole. Vaginal formulations include four imidazoles (miconazole, clotrimazole, tioconazole, and butoconazole) and one triazole (terconazole). As yet, no substantial differences in the efficacy of or local intolerance to the various topical azoles have become apparent. All are effective in the treatment of cutaneous candidiasis, tinea (pityriasis) versicolor, and mild to moderately severe ringworm of the glabrous skin. Vaginal formulations are effective for vulvovaginal candidiasis. Clotrimazole is poorly absorbed from the gastrointestinal tract, but the oral troche is useful as a topical treatment for oral and esophageal candidiasis.

Polyene Macrolide Antibiotics These broad-spectrum antifungal agents combine with sterol in the fungal cytoplasmic membrane, increasing membrane permeability.

Topically, they are not active against ringworm but are effective against candidiasis of the skin and mucous membranes. Nystatin and amphotericin B suspensions are effective in oral thrush, and vaginal troches are effective in vulvovaginal candidiasis. Both nystatin and amphotericin B are available in topical preparations for cutaneous candidiasis.

Other Topical Antifungals Ciclopirox olamine, haloprogin, terbinafine, and naftifine have the same clinical spectrum among the cutaneous mycoses as the imidazoles. Tolnaftate and undecylenic acid are effective against ringworm but not candidiasis. Keratolytic agents, such as salicylic acid, are helpful as accessory drugs for some hyperkeratotic skin lesions.

SYSTEMIC ANTIFUNGALS

Griseofulvin Griseofulvin is a useful drug in the treatment of certain kinds of ringworm; however, it is ineffective in the treatment of candidiasis. The microcrystalline and ultramicrocrystalline preparations differ in dose but not in efficacy. Absorption of both is enhanced when the drug is ingested with fat-containing foods. Griseofulvin interacts with phenobarbital and coumarin-type anticoagulants.

Terbinafine Oral terbinafine (250 mg once daily) is at least as effective as itraconazole and more effective than griseofulvin in onychomycosis and ringworm. Treatment duration ranges from 3 months for fingernails to 6 months for toenails. Gastrointestinal distress is the most common side effect. Rash, hepatitis, and pancytopenia have occurred, but serious adverse effects have been uncommon. Terbinafine decreases cyclosporine levels. Cimetidine increases and rifampin decreases terbinafine levels in blood.

Imidazoles and Triazoles

General Features The azole antifungals include imidazoles and triazoles. Fluconazole, itraconazole, and investigational azoles are all triazoles, so named because they have three nitrogens in the ring structure. This class has less impact on human hormonal synthesis and less hepatotoxicity than the only widely used systemic imidazole, ketoconazole. Itraconazole has many structural features in common with ketoconazole; however, it has a broader spectrum of activity and has largely replaced ketoconazole.

Reported interactions of itraconazole and fluconazole with other drugs are listed inTable 200-1. Ketoconazole interactions (not listed) appear to be the same as those listed for itraconazole. Azole interactions with any one class of drugs, such as benzodiazepines, HMG-CoA reductase inhibitors, or drugs that decrease gastric acidity, should be considered to apply to all drugs of that class until proven otherwise. Fluconazole differs substantially from itraconazole: unlike that of itraconazole, the absorption of fluconazole is independent of food or gastric acid, and fluconazole has much less effect on the hepatic metabolism of other drugs than does itraconazole. High fluconazole blood levels engendered by azotemia or by dosages above those used in pharmacologic studies may lead to new and profound drug interactions.

All azoles have the potential for embryotoxicity and teratogenicity. In fact, it seems likely

that azoles should not be given during pregnancy without a discussion of the serious risks and possible benefits with the mother. Four infants born to mothers taking at least 400 mg of fluconazole daily for coccidioidal meningitis have had severe bone, craniofacial, or cardiac abnormalities. Similarity of these abnormalities to those in pregnant animals given fluconazole suggests that fluconazole caused the defects.

Itraconazole Itraconazole is useful in the treatment of blastomycosis, histoplasmosis, candidiasis, coccidioidomycosis, sporotrichosis, pseudallescheriasis, onychomycosis, ringworm, tinea versicolor, and some cases of aspergillosis. Its efficacy in mycoses of the central nervous system has been modest at best. Almost no bioactive drug appears in urine. Itraconazole is metabolized in the liver, with the hydroxy metabolite accounting for at least half of the antifungal activity in serum. Food increases absorption of itraconazole capsules by about threefold but substantially reduces absorption of the cyclodextrin suspension. Ability of the suspension to exert a topical as well as a systemic effect probably accounts for its improved efficacy in oropharyngeal candidiasis. The usual dosage of either oral itraconazole formulation is 100 to 200 mg once daily for oropharyngeal and esophageal candidiasis. For deep infections, itraconazole capsules are given at an initial dosage of 600 to 800 mg daily for 3 days and a subsequent dosage of 200 to 400 mg once daily continued for 6 to 12 months. Itraconazole blood levels are helpful in documenting absorption of oral itraconazole when the drug is used for the treatment of deep mycoses. An intravenous formulation is commercially available and should be considered for initial therapy in hospitalized patients in whom itraconazole absorption may be suboptimal. Immunosuppressed patients with rapidly progressing pseudallescheriasis, an infection that does not respond to amphotericin B, are candidates for intravenous itraconazole treatment.

Fluconazole This triazole can be administered in tablet form, as a suspension, or as an intravenous infusion. With a half-life of about 31 h, fluconazole can be given once a day. Approximately 80% of the drug is excreted unchanged in the urine. Patients with creatinine clearance rates of 21 to 50 mL/min and 11 to 20 mL/min should have their fluconazole doses reduced by 50 and 75%, respectively. The drug penetrates the CSFand other body fluids very well.

Nausea and abdominal distress are the most common forms of dose-limiting fluconazole toxicity. An allergic rash may develop and is particularly common among patients infected with HIV. Fatal cases of Stevens-Johnson syndrome have been described in the HIV-infected population. Alopecia commonly follows prolonged administration of ³400 mg daily but resolves when therapy is discontinued. Rare cases of anaphylaxis, hepatic necrosis, and neutropenia have been described.

Fluconazole is useful in the treatment of oropharyngeal and esophageal candidiasis in adults. A single 150-mg tablet is effective in vulvovaginal candidiasis. Catheter-acquired candidemia in the immunocompetent host responds to 400 mg of fluconazole daily in conjunction with the removal of the infected catheter. Treatment should be continued for 10 to 14 days after the patient has become afebrile. Fluconazole is also effective in initial and maintenance therapy for cryptococcal meningitis in patients with AIDS, although most of these patients should initially receive a 2-week course of intravenous amphotericin B. Patients with coccidioidal meningitis can often be given fluconazole rather than intrathecal amphotericin B as maintenance therapy.

The incidence of deep candidiasis among recipients of allogeneic bone marrow transplants can be reduced by the administration of fluconazole (400 mg daily) for 75 days after initiation of the transplantation-preparative regimen. Prophylaxis in other neutropenic patients has not appeared useful. Fluconazole (200 mg daily) reduced the incidence of cryptococcosis and mucosal candidiasis among AIDS patients whose CD4+ cell counts were <200/uL and was particularly effective among those with counts of<50/uL. However, this regimen is not recommended because it does not reduce mortality, is expensive, and can lead to drug resistance.

Fluconazole is less effective than itraconazole in blastomycosis, histoplasmosis, and sporotrichosis. The drug is not active in aspergillosis or mucormycosis.

Amphotericin B A colloidal deoxycholate complex of the polyene drug amphotericin B is available for intravenous or intrathecal administration. In-line filters with a 0.22-um pore diameter may trap some of the colloid. The catabolism of amphotericin B is extremely slow and is not influenced by renal failure, hepatic failure, or hemodialysis. The drug's penetration intoCSF and vitreous humor is poor; however, the concentrations in pleural, peritoneal, and articular exudates are adequate for many mycoses. Histoplasmosis, blastomycosis, paracoccidioidomycosis, candidiasis, and cryptococcosis are the most responsive mycoses; coccidioidomycosis, extraarticular sporotrichosis, aspergillosis, and mucormycosis are less responsive; and chromoblastomycosis, mycetoma, and pseudallescheriasis respond little, if at all. The usual course is 0.5 to 0.7 mg/kg daily for 8 to 10 weeks. Infusions are generally given in 5% dextrose over 2 to 4 h.

Initial doses of amphotericin B occasionally cause marked febrile reactions that may be poorly tolerated by adult patients with limited cardiac or pulmonary function. It may be prudent to give such patients an initial 1-mg test dose followed by rapidly escalating doses, depending on tolerance. Premedication with aspirin or acetaminophen or the addition of hydrocortisone (25 mg) to the infusion decreases chills and fever. Azotemia during treatment is usual, the extent depending on the daily dose. Saline infusions have been advocated to reduce azotemia. Permanent loss of renal function is related to the total dose of amphotericin B; this condition is generally noted in adults who have received >3 g. Other side effects include anemia, hypokalemia, renal tubular acidosis, nausea, anorexia, weight loss, phlebitis, and occasionally hypomagnesemia. Intrathecal amphotericin B has been used in coccidioidal meningitis and refractory cryptococcal meningitis, although this therapy is associated with considerable toxicity.

Three lipid formulations of amphotericin B are commercially available in the United States: amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AB). All cause less nephrotoxicity than the older amphotericin B deoxycholate complex (ABD). Acute, febrile infusion-related reactions occur with all three lipid formulations but are most severe with ABCD. The recommended duration for initial infusions of ABCD is 1 mg/kg per hour, somewhat slower than the 2-h duration of ABLC or L-AB infusions, with the intent of decreasing febrile reactions. Premedication with acetaminophen is also an option. Use of these remarkably expensive formulations should be confined to patients who cannot tolerate the nephrotoxicity of ABD. Although the lipid formulations are also approved for patients

failing to respond to ABD, there is no indication that these formulations are more effective than ABD for any mycosis.

Flucytosine Flucytosine (5-fluorocytosine) is a synthetic oral drug useful in cryptococcosis, candidiasis, and chromoblastomycosis. Within the fungal cell, flucytosine is converted to the antimetabolite 5-fluorouracil. Drug resistance appears rather rapidly when flucytosine is used alone. For this reason, the drug is generally used in combination with amphotericin B. The usual dose of flucytosine is 25 to 37.5 mg/kg every 6 h. Flucytosine is well absorbed from the gastrointestinal tract. The drug penetrates well into theCSF and is excreted unchanged in the urine. Even modest reductions in renal function may elevate flucytosine blood levels into the toxic range (³100 to 125 ug/mL). Elevated levels are associated with a significant incidence of neutropenia and thrombocytopenia and also seem to predispose to colitis, the other major toxic effect of this drug. Hepatotoxicity is idiosyncratic and uncommon. An allergic rash may develop.

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201. HISTOPLASMOSIS - *John E. Bennett*

ETIOLOGIC AGENT

Histoplasma capsulatum is a dimorphic fungus that grows as a mold in nature or on Sabouraud's agar at room temperature. Hyphae bear both large and small spores, which are used for identification. Nucleic acid hybridization can also be used to identify the organism in culture. *H. capsulatum* grows as a small budding yeast in host tissue and on enriched agar, such as blood cysteine glucose, at 37°C. Despite its name, the fungus is unencapsulated. Coculture of isolates with opposite mating types can produce different sporulating structures in which genetic recombination occurs. When these structures, referred to as a *teleomorph* or the *perfect state*, are seen in culture, the name *Ajellomyces capsulatus* is used.

EPIDEMIOLOGY

Infection with *H. capsulatum* has been encountered in many areas of the world but is much more frequent in certain areas. Within the United States, infection is most common in the southeastern, mid-Atlantic, and central states. Endemicity is probably contingent on the availability of proper conditions in nature for growth of the fungus. *H. capsulatum* prefers moist surface soil, particularly soil enriched by droppings of certain birds and bats. The fungus has been isolated repeatedly from such sites, and many case clusters have occurred 5 to 18 days after the exposure of groups of people to dust while (for example) cleaning dirt-floored chicken coops; raking soil beneath bird-roosting sites; exploring caves; and cleaning, remodeling, or demolishing old buildings. Skin-test reactivity in many endemic areas indicates that³80% of residents over age 16 have been exposed.

PATHOGENESIS AND PATHOLOGY

Microconidia, or small spores, of *H. capsulatum* are small enough to reach the alveoli on inhalation and are transformed there to budding forms. With time, an intense granulomatous reaction occurs. Caseation necrosis or calcification may mimic tuberculosis. In children, the primary infection usually heals completely but may leave spotty calcification in the hilar nodes or lung. Transient dissemination may leave calcified granulomas in the spleen. In adults, a rounded mass of scar tissue, with or without central calcification, may remain in the lung. This mass has been called a *histoplasmoma*. Previous exposure is thought to confer some protection against reinfection, but infection in persons with prior positive skin tests clearly has occurred.

In a small proportion of patients, histoplasmosis becomes a progressive, potentially fatal infection. The disease occurs either as chronic fibrocavitary pneumonia or, less commonly, as disseminated infection. Patients with either form lack a history of acute primary pulmonary histoplasmosis. Chronic pulmonary infection favors otherwise healthy males over the age of 40. A history of cigarette use or the presence of emphysema is elicited from nearly all patients with chronic progressive pulmonary histoplasmosis. An acute, rapidly fatal disseminated infection is most likely to be encountered among young children and immunosuppressed patients, including those with AIDS. A more chronic but equally lethal disseminated infection is more common

among previously healthy adults.

CLINICAL MANIFESTATIONS

The vast majority of infections are either asymptomatic or mild, and the diagnosis is elusive. Cough, fever, malaise, and chest x-ray findings of hilar adenopathy with or without one or more areas of pneumonitis are typical features. Erythema nodosum and erythema multiforme have been reported in a few outbreaks. Hilar adenopathy may cause temporary compression of the right-middle-lobe bronchus in children and young adults. Subacute pericarditis may develop, probably by extension from contiguous lymph nodes. Rarely, hilar nodes undergo a caseous, granulomatous reaction with perinodal fibrosis. Mediastinal structures become encased by progressive fibrosis, and compression of the pulmonary veins, superior vena cava, pulmonary arteries, and esophagus may take place over many years. Late in mediastinal disease, only rare nonviable *Histoplasma* cells can be found in caseous residua of lymph nodes.

Chronic pulmonary histoplasmosis is characterized by a gradual onset (over weeks or months) of increasing productive cough, weight loss, and sometimes night sweats. Chest x-ray reveals uni- or bilateral fibronodular apical infiltrates. Approximately one-third of cases stabilize or improve spontaneously early in the course. The remainder progress insidiously. Retraction and cavitation of the upper lobes occur, with spread to the apex of the lower lobes and other areas of the lung. Emphysema and bulla formation further compromise pulmonary function. Death from cor pulmonale, bacterial pneumonia, or histoplasmosis occurs after months or years.

Acute disseminated histoplasmosis may be mistaken for miliary tuberculosis (Chap. 169). Common findings include fever, emaciation, hepatosplenomegaly, lymphadenopathy, jaundice, anemia, leukopenia, and thrombocytopenia. A high index of suspicion is necessary in patients with AIDS, in whose cases there may be other explanations for the abnormalities caused by disseminated histoplasmosis (Fig. 201-CD1). All these features may be noted in chronic dissemination as well, but chronic disease tends to be more localized. Indurated ulcers of the mouth, tongue, nose, or larynx are reported in about one-fourth of cases. Other focal findings include granulomatous hepatitis, Addison's disease, gastrointestinal ulceration, endocarditis, and chronic meningitis. Chest x-ray abnormalities are evident in half of cases and characteristically consist of discrete nodules or a miliary pattern.

Infection with *H. capsulatum var. duboisii* is rare outside of Africa. The yeast form is larger in tissue than that of *H. capsulatum var. capsulatum*. Clinical manifestations resemble those of blastomycosis more than those of histoplasmosis in that skin and bone lesions are very common.

DIAGNOSIS

Culture of the etiologic organism is the preferred method for diagnosis of histoplasmosis but is often difficult. Blood cultures are best done by the lysis-centrifugation technique, with plates held at 30°C for at least 2 weeks. Approximately 15 mL of blood should be cultured from adults. Routine blood cultures in broth are generally unsuitable. Cultures of bone marrow, mucosal lesions, liver, and bronchoalveolar lavage fluid are

diagnostically useful in disseminated histoplasmosis. Sputum culture is the preferred method for the diagnosis of chronic pulmonary histoplasmosis. However, growth may require 2 to 4 weeks to become visible, and other organisms may overgrow the plate. Diagnosis based on Giemsa-stained smears of blood or bronchoalveolar lavage fluid or on methenamine silver staining of infected lung, bone marrow, lymph node, or mucosal lesions requires considerable expertise, although these techniques yield results rapidly and provide specimens that can easily be sent to a referral laboratory. Organisms may be very scanty in lesions with marked caseous necrosis. An assay for *Histoplasma* antigen in blood or urine is commercially available and is useful both for diagnosis and for monitoring of the response to therapy in patients with AIDS who have disseminated infection. Diagnosis by antigen detection requires confirmation by culture or histopathology because false-positive results have occasionally been obtained. Tests for antibody to *H. capsulatum* have been of limited value in diagnosis. Histoplasmin skin testing has proven useful in epidemiologic studies but not in clinical diagnosis. Neither skin testing nor serology has been predictive of histoplasmosis in patients infected with HIV.

TREATMENT

Acute pulmonary histoplasmosis requires no therapy. Oral itraconazole (200 mg/d) can be given to shorten the course of illness, although this effect has not been proven. Patients with mediastinal fibrosis may benefit from surgery, but their ultimate prognosis is poor. All patients with disseminated or chronic fibronodular pulmonary histoplasmosis should receive chemotherapy. Intravenous amphotericin B (0.6 mg/kg daily) is the drug of choice for the initial treatment of patients with disseminated histoplasmosis who are severely ill or immunosuppressed or whose infection involves the central nervous system; the regimen can be changed to itraconazole (200 mg twice daily) once clinical improvement is evident in these patients. Measuring itraconazole trough blood levels should be considered in those patients (e.g., patients with AIDS) who may not be absorbing the drug well (Chap. 200). Itraconazole suspension, taken fasting, is better absorbed than the capsule formulation. Fluconazole is reliably absorbed, even in patients taking drugs to block gastric acid secretion, but at doses up to 400 mg/d has been less effective in treatment of chronic pulmonary or disseminated histoplasmosis. Patients with AIDS whose disseminated histoplasmosis has responded to 10 weeks of therapy should receive itraconazole (200 mg/d) for life to prevent relapse. It remains unknown whether patients with a sustained response to highly active antiretroviral therapy can discontinue maintenance therapy with itraconazole.

Immunocompetent patients can initially be given itraconazole (200 mg twice daily) and are generally treated for 6 to 12 months. Ketoconazole (400 to 800 mg once daily) can be used instead of itraconazole for the treatment of immunocompetent patients without central nervous system disease when the lower cost is more important than the higher incidence of side effects. Alternatively, immunocompetent patients can be given a 10-week course of amphotericin B (0.5 mg/kg daily).

Long-term maintenance therapy with an azole is not recommended for patients other than those with AIDS. However, relapse of chronic pulmonary and disseminated histoplasmosis is not rare and warrants careful follow-up for 1 year after therapy.

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202. COCCIDIOIDOMYCOSIS - *John E. Bennett*

ETIOLOGIC AGENT

Coccidioides immitis has two forms, growing as a white fluffy mold on most culture media but as a nonbudding spherical form (a spherule) in host tissue or under special conditions. The organism reproduces in host tissue by forming small endospores within mature spherules. After rupture of the spherule, the released endospores enlarge, become spherules, and repeat the cycle. The fungus is identified by its appearance and by the formation of thick-walled, barrel-shaped spores, called *arthrospores*, in the hyphae of the mold form.

EPIDEMIOLOGY, PATHOGENESIS, AND PATHOLOGY

C. immitis is a soil saprophyte found in certain arid regions of the United States, Mexico, Central America, and South America. Within the United States, most cases of infection with *C. immitis* are acquired in California, Arizona, and western Texas. A few cases are acquired by exposure to fomites from endemic areas (e.g., in cotton bales).

Infection in humans and animals results from inhalation of wind-borne arthrospores from soil sites. This primary pulmonary infection is symptomatic in only 40% of cases, with symptoms ranging from a mild influenza-like illness to severe pneumonia. Mild self-limited infections may come to medical attention because of case clusters or hypersensitivity reactions: erythema nodosum, erythema multiforme, toxic erythema, arthralgia, arthritis, conjunctivitis, or episcleritis. Case clusters occur 10 to 14 days after a group of susceptible individuals is exposed to dust in an endemic area through such activities as archaeologic excavation, rock hunting, military maneuvers, or construction work. Windstorms can carry spores to adjacent nonendemic areas and cause case clusters. The usual course of primary pneumonia is complete healing, although an area of pneumonitis (detected on radiographs) may heal by the formation of a coinlike lesion called a *coccidioidoma*. Less commonly, a single thin-walled cavity remains as a chronic sequela in the area of consolidation. Alternatively, an area of consolidation may persist as chronic pneumonia or progress to fibronodular cavitary disease.

Pleural effusion may be the only manifestation of primary infection. Spontaneous healing of this form is common.

An uncommon but dreaded complication of coccidioidomycosis is dissemination beyond the lung and hilar lymph nodes. Dissemination is especially frequent among blacks, Filipinos, Native Americans, Mexican-Americans, pregnant women, and immunosuppressed patients, including those with AIDS.

C. immitis incites a chronic granulomatous reaction in host tissue, often with caseation necrosis. Lung and hilar node lesions may show calcification. Both IgM and IgG antibodies to *C. immitis* are induced by infection, but neither type of antibody appears to be protective. The amount of specific IgG antibody is a rough measure of the antigenic mass (i.e., of the intensity of infection), and a high titer is a poor prognostic sign. Appearance of delayed hypersensitivity to antigens of *C. immitis* is most common in clinical forms of disease with a good prognosis, such as self-limited primary pulmonary

disease. In skin tests for *Coccidioides* antigens, about half of patients with disseminated disease have negative results that portend a poor outcome.

CLINICAL MANIFESTATIONS

Symptomatic primary pulmonary infection is manifested by fever, cough, chest pain, malaise, and sometimes the hypersensitivity reactions listed above. Chest radiographs may show an infiltrate, hilar adenopathy, or pleural effusion. Mild peripheral-blood eosinophilia may be found. Spontaneous improvement begins after several days to 2 weeks of illness and usually culminates in complete recovery.

The symptoms of a chronic thin-walled cavity include cough or hemoptysis in half of cases; the other half are asymptomatic. Chronic progressive pulmonary coccidioidomycosis causes cough, sputum production, variable degrees of fever, and weight loss. The first indications of dissemination usually appear during primary infection. Reactivation with dissemination in later years occurs occasionally, especially if Hodgkin's disease, non-Hodgkin's lymphoma, renal transplantation, AIDS, or immunosuppression of some other etiology has supervened. Dissemination should be suspected when fever, malaise, hilar or paratracheal lymphadenopathy, elevated sedimentation rate, and high complement fixation titers signal abnormal persistence in patients with primary pulmonary coccidioidomycosis. With time, lesions appear in the bone, skin, subcutaneous tissue, meninges, joints, and other sites. Chronic meningitis presents as headache of indolent onset, with or without other signs of disseminated coccidioidomycosis. Cultures and smears of cerebrospinal fluid (CSF) are most often negative, but antibody is usually detectable in CSF by complement fixation. Skin lesions are indolent and maculopapular; soft tissue and bony lesions contain pus and may present as a draining sinus. Without treatment, disseminated coccidioidomycosis progresses to death over weeks to years.

Disseminated coccidioidomycosis can progress rapidly in patients with advanced HIV infection. Fever with skin or bone lesions may be the first sign. Those who present with diffuse pulmonary infiltrates have a poor prognosis. Blood cultures are positive late in the disease, if at all.

DIAGNOSIS

When coccidioidomycosis is suspected, sputum, urine, and pus should be examined for *C. immitis* by wet smear and culture. *The laboratory request should indicate clearly that coccidioidomycosis is suspected, because the mold form must be handled with extreme care to prevent infection of laboratory personnel.* On biopsy, smaller spherules must be distinguished from nonbudding forms of *Blastomyces* and *Cryptococcus*, but the appearance of the mature spherule is diagnostic.

Serologic tests are very helpful in the diagnosis of coccidioidomycosis. Latex agglutination and agar gel diffusion tests are useful in screening sera for antibody to *Coccidioides*. The complement fixation test is used forCSFdeterminations and for the confirmation and quantitation of serum antibody detected by screening tests. The number of cases with a positive complement fixation test depends on the severity of disease and on the laboratory performing the test. Positive tests are least common

among patients with solitary pulmonary cavities or primary pulmonary infection, while sera from patients with disseminated disease in multiple organs are nearly all positive. Seroconversion is helpful in primary pulmonary coccidioidomycosis but may not occur for up to 8 weeks after onset. A positive complement fixation test of unconcentrated CSF is diagnostic of meningitis. Rarely, a parameningeal focus causes a positive complement fixation test of CSF.

Conversion of the skin test from negative to positive (³5 mm of induration at 24 or 48 h) with spherulin may take place between days 3 and 21 of symptoms in primary pulmonary coccidioidomycosis. Skin testing can be helpful in epidemiologic studies, such as investigations of case clusters or the definition of endemic areas. The utility of skin testing as a diagnostic tool is limited by the persistence of positive tests resulting from remote exposures to *Coccidioides* and by the frequency of negative skin tests among patients with either thin-walled cavities or disseminated coccidioidomycosis. A positive skin test has not predicted dissemination in HIV-infected patients. The presence of complement-fixing antibody to *C. immitis* in AIDS patients should prompt a search for active infection.

TREATMENT

Primary pulmonary coccidioidomycosis usually resolves spontaneously. Some physicians give a few weeks of treatment with intravenous amphotericin B or itraconazole to patients with unusually severe or protracted primary infection in the hope of aborting disseminated or chronic pulmonary disease.

Patients with severe or rapidly progressing disseminated coccidioidomycosis are first given intravenous amphotericin B at a dose of 0.5 to 0.7 mg/kg daily. Patients whose condition improves after 2 to 3 months of treatment with amphotericin B or who have more indolent disseminated infection are given itraconazole (200 mg twice daily) or fluconazole (400 to 600 mg/d). These oral agents are useful for long-term suppression of infection, and treatment should be continued for years. Patients with coccidioidal meningitis usually are initially given fluconazole (400 to 800 mg/d) but may require intrathecal amphotericin B. Hydrocephalus is a frequent complication of uncontrolled meningitis. Surgical debridement of bone lesions or drainage of abscesses can be helpful. The prognosis for ultimate cure of disseminated coccidioidomycosis is guarded.

Resection of chronic progressive pulmonary lesions is a helpful adjunct to chemotherapy when infection is confined to the lung and to one lobe. A single thin-walled cavity tends to close spontaneously and ordinarily is not resected. Such a cavity responds poorly to chemotherapy.

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203. BLASTOMYCOSIS - *John E. Bennett*

ETIOLOGIC AGENT

Blastomyces dermatitidis is a dimorphic fungus that grows at room temperature as a white or tan mold but grows within the host or at 37°C as budding, round yeastlike cells. The fungus can be identified on the basis of its appearance, its dimorphism, the small spores borne on hyphae of the mold form, or the results of nucleic acid hybridization. When isolates of the two opposite mating types are grown close together on special culture medium, such as yeast extract or soil extract agar, sporulating structures that characterize the perfect state (teleomorph), called *Ajellomyces dermatitidis*, appear.

EPIDEMIOLOGY

The infection is restricted by geography and age. Blastomycosis is uncommon in any locality, but most cases occur in the southeastern, central, and mid-Atlantic areas of the United States, with occasional cases in other localities in the United States and Canada. Cases have also been encountered in Africa, Mexico, Central America, and (rarely) South America. Most patients are between 20 and 69 years old. The male-to-female ratio is about 10:1. There is no occupational predisposition to the development of blastomycosis.

PATHOGENESIS AND PATHOLOGY

Infection with *B. dermatitidis* appears to be acquired by inhalation of the fungus from soil, decomposed vegetation, or rotting wood. Several case clusters have resulted from participation in recreational activities in wooded areas along waterways. Infection is not transmissible from person to person. The initial pulmonary infection may either heal spontaneously or become chronic. Spread to other portions of the lung, cavitation, or endobronchial lesions may be found in patients with chronic disease. Whether or not the lung lesion resolves spontaneously, infection commonly spreads hematogenously to the skin, subcutaneous tissue, bone, prostate, epididymis, or mucosa of the nose, mouth, or larynx. Less commonly, infection spreads to the brain, meninges, liver, lymph nodes, or spleen. Dissemination may not be evident for weeks or years after the appearance of the lung lesion. Progressive infection is only rarely attributable to an underlying disease, to HIV infection, or to immunosuppressive treatment. The inflammatory response includes lymphocytes, giant cells, and neutrophils. Pseudoepitheliomatous hyperplasia may be striking and may lead to a mistaken diagnosis of squamous cell carcinoma.

CLINICAL MANIFESTATIONS

A few patients have acute, self-limited pneumonia. Fever, productive cough, myalgia, and malaise usually resolve within a month. Pulmonary infiltrates clear slowly as *B. dermatitidis* disappears from the sputum.

In the vast majority of patients, blastomycosis has an indolent onset and a chronically progressive course. Fever, cough, weight loss, lassitude, skin lesions, and chest ache are common. Skin lesions favor exposed areas and enlarge over many weeks from pimples to well-circumscribed, verrucous, crusted, or ulcerated lesions (Fig. 203-CD1).

Pain and regional lymphadenopathy are minimal. Large chronic lesions may undergo central healing with scarring and contracture. Mucous membrane lesions resemble squamous cell carcinoma. Chest x-ray findings are abnormal in two-thirds of patients, with one or more pneumonic or nodular infiltrates. Calcification, hilar adenopathy, and large pleural effusions are rare. Osteolytic lesions may be found in nearly any bone and present as a cold abscess or a draining sinus. Extension to a contiguous joint may cause indolent swelling, pain, and restricted motion. Prostatic and epididymal lesions clinically resemble those of tuberculosis.

DIAGNOSIS

The diagnosis of blastomycosis is made by demonstration of the fungus in a culture of sputum, pus, or urine. An expert can diagnose blastomycosis on the basis of the appearance of the organism in wet smear or histopathologic section. The fungus may be visible in a sputum cytology smear but is easily overlooked.

TREATMENT

A few patients have developed only transitory lung lesions, but no guidelines are known to distinguish these patients from those whose disease will progress locally or disseminate. Therefore, every patient should receive treatment. Intravenous amphotericin B is the drug of choice for patients with rapidly progressive infections, severe illness, or central nervous system lesions. Skin and noncavitary lung lesions should be treated for about 8 to 10 weeks. The recommended total dose for an adult is about 2 g. Cavitary lung disease or infection extending beyond the lung and skin should be treated for about 10 to 12 weeks with ³2.5 g.

Oral itraconazole (200 mg twice daily with food) is the drug of choice for the treatment of patients who have indolent nonmeningeal blastomycosis of mild to moderate severity and who take the drug reliably. Therapy with itraconazole is continued for 6 to 12 months.

The mortality rate in appropriately treated cases is£15%.

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204. CRYPTOCOCCOSIS - *John E. Bennett*

ETIOLOGIC AGENT

Cryptococcosis is an infection caused by the yeastlike fungus *Cryptococcus neoformans*. This fungus reproduces by budding and forms round, yeastlike cells. Within the host and on certain culture media, a large polysaccharide capsule surrounds each yeast cell. The fungus grows well in smooth, creamy-white colonies on Sabouraud's or other simple media at 20 to 37°C. Identification of the organism is based on gross and microscopic appearance, biochemical test results, and growth at 37°C. The results of nucleic acid hybridization or the formation of brown pigment on Niger seed agar can also be used for identification.

The fungus has four capsular serotypes, designated A, B, C, and D. There are also two mating types. Coculture of opposite mating types creates a transient diploid state called *Filobasidiella neoformans* var. neoformans for serotypes A and D and *F. neoformans* var. bacillispora for serotypes B and C. Organisms not cultured under mating conditions are designated *C. neoformans* var. neoformans for serotypes A and D and *C. neoformans* var. gattii for serotypes B and C; a simple color medium distinguishes the two varieties.

EPIDEMIOLOGY

Weathered pigeon droppings commonly contain serotype A or D (*C. neoformans* var. *neoformans*). *C. neoformans* var. *gattii* has been isolated from the litter around trees of the species *Eucalyptus camaldulensis* and *E. tereticornis*. Eucalyptus isolates have so far typed as serotype B. The distribution of these eucalyptus species in Australia corresponds to the distribution of infections due to *C. neoformans* var. *gattii* in that country. The high prevalence of these trees in other subtropical climates has been postulated to explain the relative restriction of such infections to warm climates.

Cryptococcosis due to *C. neoformans* var. *neoformans* is a common complication of late infection with HIV. The incidence appears to be declining in some areas of the United States, probably as a result of highly active antiretroviral therapy and use of fluconazole for oropharyngeal candidiasis. Patients who have undergone solid-organ transplantation or glucocorticoid therapy and those with sarcoidosis are also at increased risk for infections with *C. neoformans* var. *neoformans*. Almost all such infections are caused by serotype A, although serotype D occurs in up to 20% of cases in Western Europe. Infections with var. *gattii* have been rare among AIDS patients and other immunocompromised patients, even in subtropical climates, where var. *gattii* infection occurs in previously healthy individuals.

Animals, particularly cats, can acquire cryptococcosis but have not transmitted the infection to other animals or to humans. The source from which humans acquire the infection is unknown, with the rare exception of cases acquired through a transplanted cornea, kidney, or other solid organ. Cryptococcosis is rare before puberty.

PATHOGENESIS AND PATHOLOGY

Infection is thought to be acquired by inhalation of fungus into the lungs. Pulmonary infection has a tendency toward spontaneous resolution and is frequently asymptomatic. Silent hematogenous spread to the brain leads to clusters of cryptococci in the perivascular areas of cortical gray matter, in the basal ganglia, and, to a lesser extent, in other areas of the central nervous system. The inflammatory response around these foci is usually scant. In the more chronic cases, a dense basilar arachnoiditis is typical. Lung lesions are characterized by intense granulomatous inflammation. Cryptococci are best seen in tissue by staining with methenamine silver or periodic acid-Schiff. Although a strongly positive result on mucicarmine staining of tissue is diagnostic, staining varies from intense to absent.

CLINICAL MANIFESTATIONS

Most patients have *meningoencephalitis* at the time of diagnosis. This form of the infection is invariably fatal without appropriate therapy; death occurs any time from 2 weeks to several years after the onset of symptoms. Early manifestations include headache, nausea, staggering gait, dementia, irritability, confusion, and blurred vision. Both fever and nuchal rigidity are often mild or lacking. Papilledema is evident in one-third of cases at the time of diagnosis. Cranial nerve palsies, typically asymmetric, occur in about one-fourth of cases. Other lateralized signs are rare. With progression of the infection, deepening coma and signs of brainstem compression appear. Autopsy often reveals cerebral edema in more acute cases and hydrocephalus in more chronic cases.

Pulmonary cryptococcosis causes chest pain in about 40% of patients and cough in 20%. The chest x-ray shows one or more dense infiltrates, which are often well circumscribed. Cavitation, pleural effusions, and hilar adenopathy are infrequent. Calcification is not evident, and fibrotic stranding is rarely noticeable.

Ten percent of patients with cryptococcosis have skin lesions, and the vast majority of patients with skin lesions have disseminated infection (Fig. 204-CD1). One or a few asymptomatic tiny papular lesions appear and slowly enlarge; they display a tendency toward central softening leading to ulceration. Osteolytic lesions occur in 4% of cases and usually present as a cold abscess. Rare manifestations of cryptococcosis include prostatitis, endophthalmitis, hepatitis, pericarditis, endocarditis, and renal abscess.

DIAGNOSIS

Fever and headache in a patient with AIDS or with risk factors forHIVinfection suggest the possibility of cryptococcosis, toxoplasmosis, or central nervous system lymphoma. Evidence of a focal lesion on magnetic resonance imaging is unusual in cryptococcosis. Most cryptococcal cerebral mass lesions occur in patients infected with *C. neoformans* var. *gattii* who also have meningitis. In patients without AIDS, meningitis due to *C. neoformans* resembles that due to *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, *Coccidioides immitis*, or metastatic cancer. Lumbar puncture is the single most useful diagnostic test. An india ink smear of centrifuged cerebrospinal fluid (CSF) sediment reveals encapsulated yeast in more than half of cases, although artifacts can cause confusion. In patients without AIDS, levels of glucose in CSF are reduced in half of all cases; protein levels are usually increased; and lymphocytic pleocytosis is usually

found. CSF abnormalities are less pronounced in patients with AIDS, although india ink smear is more often positive.

Approximately 90% of patients with cryptococcal meningoencephalitis, including all those with a positiveCSFsmear, have capsular antigen detectable in CSF or serum by latex agglutination. An enzyme immunoassay for cryptococcal antigen is also available. Occasional false-positive results in the above tests make culture the definitive diagnostic test and have prevented serum antigen from being a useful screening test in asymptomatic patients with AIDS. *C. neoformans* is often present in urine from patients with meningoencephalitis. Fungemia occurs in 10 to 30% of patients and is particularly common among patients with AIDS.

Pulmonary cryptococcosis mimics malignancy with regard to radiographic findings and symptoms. Sputum culture is positive in only 10% of cases, and serum antigen tests are positive in only one-third. Occasionally, *C. neoformans* appears in one or more sputum specimens as an endobronchial saprophyte. Biopsy is usually required for diagnosis.

Cutaneous cryptococcosis may be mistaken for a comedo, basal cell carcinoma, or sarcoidosis. In patients with AIDS, skin lesions may be numerous and are sometimes mistaken for molluscum contagiosum. Biopsy reveals myriad cryptococci. Osseous cryptococcosis resembles tuberculosis.

TREATMENT

Patients with AIDS and cryptococcosis are treated initially with intravenous amphotericin B (0.7 mg/kg daily) for at least 2 weeks and until their clinical condition is stable; thereafter, they receive fluconazole. The addition of flucytosine (25 mg/kg every 6 h) to amphotericin B for 2 weeks has minimal impact on morbidity and mortality. After treatment with amphotericin B, fluconazole (400 mg) is given once daily. Daily doses of 800 mg have been used with marginal changes in toxicity or efficacy. The addition of flucytosine to fluconazole increases gastrointestinal intolerance. After infection is controlled, treatment with a smaller dose of fluconazole (200 mg/d) is continued indefinitely. Itraconazole is less effective than fluconazole for maintenance therapy. It is not yet known whether patients whose CD4+ T lymphocyte counts have exhibited a sustained rise in response to antiretroviral therapy can safely discontinue fluconazole maintenance therapy.

In patients without AIDS, the therapeutic goal is to cure the infection, not merely to control its symptoms. A single intensive course is given until cultures from all previously positive sites (particularlyCSF) become convincingly negative. Normalization of the glucose level in lumbar CSF is desirable, but complete clearing of CSF or serum antigen during therapy is not essential. Amphotericin B (0.6 to 0.7 mg/kg daily for^{3}10 weeks) is the best-studied regimen. Flucytosine has been added to amphotericin B to accelerate the culture response, but grave toxicity can result unless flucytosine blood levels are kept below 100 ug/mL. Case reports have described patients without HIV infection who have responded to fluconazole or liposomal amphotericin B, but the dose and duration of treatment required to cure cryptococcal meningitis are undefined. Amphotericin B lipid complex and amphotericin B colloidal dispersion are not recommended pending further study.

Hydrocephalus may be the presenting manifestation or a later complication of cryptococcosis. Blindness, dementia, and personality change are among the other sequelae. Daily lumbar puncture orCSFshunting has been advocated -- in the hope of averting permanent blindness -- for patients with marked cerebral edema who have incipient blurred vision.

Patients with extraneural cryptococcosis most often require treatment with intravenous amphotericin B, with or without flucytosine. Observation or excision of lesions may suffice for some patients who have previously been healthy; who have a single focus in lung, skin, or bone; and who have no cryptococci in CSF, urine, or blood.

PREVENTION

Fluconazole (200 mg/d) has been shown to decrease the incidence of cryptococcosis in HIV-infected patients with CD4+ cell counts of<200/uL and particularly in those with counts of<50/uL. Weekly fluconazole has not provided this protection. Daily fluconazole has not conferred a survival advantage; in light of its cost and the currently low incidence of cryptococcosis in patients with AIDS in the United States, prophylaxis is strongly discouraged.

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205. CANDIDIASIS - *John E. Bennett*

ETIOLOGIC AGENTS

Candida albicans is the most common cause of mucosal candidiasis and is responsible for about half of all cases of candidemia in hospitalized patients. A small proportion of *C. albicans* isolates have been transferred to a new species, *C. dubliniensis*. *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*, *C. glabrata* (formerly *Torulopsis glabrata*), *C. krusei*, and a few other *Candida* species also cause potentially fatal bloodstream infection. Many of these non-*albicans* species can enter the bloodstream through an intravascular catheter. *Candida* species, taken together, are the fifth most common cause of nosocomial bloodstream infections in the United States.

All *Candida* species pathogenic for humans are also encountered as commensals of humans, particularly in the mouth, stool, and vagina. These species grow rapidly at 25° to 37°C on simple media as oval, budding cells. In special culture media and in tissue, hyphae or elongated branching structures called *pseudohyphae* are formed. *C. glabrata* differs from other members of the genus in that it forms no true hyphae or pseudohyphae in vitro or in infected tissue. *C. albicans* and *C. dubliniensis* can be identified presumptively by their ability to form germ tubes in serum or by the formation of thick-walled large spores called *chlamydospores*. Final identification of all *Candida* species requires biochemical tests.

PATHOGENESIS

Candidiasis is often preceded by increased colonization of the mouth, vagina, and stool with *Candida* due to broad-spectrum antibiotic therapy. Additional local and systemic factors favor infection. Oropharyngeal thrush is particularly likely to occur in neonates and in patients with diabetes mellitus, HIV infection, or dentures. Vulvovaginal candidiasis (Chap. 132) is especially common in the third trimester of pregnancy. *Candida* from the perineum can enter the urinary tract via an indwelling bladder catheter. Cutaneous candidiasis most often involves macerated skin, such as that in the diapered area of infants, under pendulous breasts, or on hands constantly in water or covered by occlusive gloves. *Candida* can pass from the colonized surface into deep tissue when the integrity of the mucosa or skin is violated, as, for example, by perforation of the gastrointestinal tract through trauma, surgery, or peptic ulceration or by mucosal damage due to cytotoxic agents used for cancer chemotherapy. Although *Candida* is not normally a resident of the skin, secretions from the mouth, rectum, or vagina as well as drainage from surgical wounds or tracheostomy sites can contaminate the hub or skin site of a catheter in an umbilical or central vein. Intravenous drug abuse or third-degree burns can also provide a skin portal for *Candida* that can lead to deep candidiasis. Once *Candida* has passed the integumentary barrier, very low birth weight (in neonates) and neutropenia or glucocorticoid therapy (in any patient) markedly compromise host defense. Hematogenous seeding is particularly evident in the retina, kidney, spleen, and liver.

CLINICAL MANIFESTATIONS

Oral thrush (Figs. 205-CD1 and205-CD2) presents as discrete and confluent adherent

white plaques on the oral and pharyngeal mucosa, particularly in the mouth and on the tongue. These lesions are usually painless, but fissuring at the corners of the mouth can be painful. Unexplained oropharyngeal thrush raises the possibility of HIV infection. Oral thrush is common in acute HIV infection and becomes increasingly common as the CD4+ cell count falls. At CD4+ counts <50/uL, esophageal thrush also becomes common. HIV infection appears not to be an independent risk factor for vulvovaginal thrush.

Cutaneous candidiasis (Figs. 205-CD3,205-CD4, and205-CD5) presents as red macerated intertriginous areas, paronychia, balanitis (Fig. 205-CD6), or pruritus ani. Candidiasis of the perineal and scrotal skin may be accompanied by discrete pustular lesions on the inner aspects of the thighs. *Chronic mucocutaneous candidiasis* or *candidal granuloma* typically presents as circumscribed hyperkeratotic skin lesions, crumbling dystrophic nails, partial alopecia in areas of scalp lesions, and both oral and vaginal thrush. Systemic infection is very rare, but disfigurement of the face and hands can be severe. Other findings may include chronic epidermophytosis, dental dysplasia, and hypofunction of the parathyroid, adrenal, or thyroid gland. A variety of defects in T cell function have been described in these patients. Vulvovaginal thrush (Chap. 132, Fig 205-CD7) causes pruritus, discharge, and sometimes pain on intercourse or urination. Speculum examination reveals an inflamed mucosa and a thin exudate, often with white curds.

Esophageal candidiasis is often asymptomatic but can cause substernal pain or a sense of obstruction on swallowing. Most lesions are in the distal third of the esophagus and appear on endoscopy as areas of redness and edema, focal white patches, or ulcers. Biopsy or brushing is required for diagnosis and for detection of concomitant infections, particularly herpes simplex in patients with hematologic malignancies and cytomegalovirus infection in AIDS patients. Esophagography (barium swallow) is diagnostically insensitive but may reveal spasm or mucosal irregularities. *Candida* esophagitis can cause bleeding and impaired alimentation. Hematogenous dissemination from the esophagus probably occurs in some neutropenic patients but is rarely reported in HIV-infected patients.

Candida can cause cystitis, pyelitis, or renal papillary necrosis in an obstructed urinary tract. When a colonized urinary tract is operated on or instrumented, candidemia may result. However, most patients with *Candida* cultured from the urine simply have bladder colonization from a Foley catheter or a sizable volume of residual urine. Contamination of a voided midstream specimen by vaginal *Candida* is also common.

Candidemia originating from an intravascular catheter may clear in the immunocompetent patient when the catheter is removed. Focal seeding of the retina can take place even if candidemia clears and the patient becomes afebrile. Unilateral or bilateral small white retinal exudates appear within 2 weeks of the onset of candidemia. Lesions may regress spontaneously or enlarge slowly. The vitreous humor becomes cloudy, and the patient notices blurring, ocular pain, or a scotoma. Retinal detachment, vitreous abscess, and extension to the anterior chamber can occur over the ensuing weeks. These retinal lesions, present in ~10% of nonneutropenic patients with candidemia, are the principal reason that systemic antifungal therapy is recommended for all patients with candidemia. Funduscopy should be performed to be certain that

retinal lesions, if present, resolve completely. Most cases with ocular involvement have occurred in nonneutropenic patients. In contrast, so-called hepatosplenic candidiasis is usually recognized in patients with acute leukemia who are recovering from profound neutropenia. This entity, better called *chronic disseminated candidiasis*, originates from intestinal seeding of the portal and venous circulation. Fever, modestly elevated serum concentrations of alkaline phosphatase, and multiple small abscesses evident on ultrasonography, magnetic resonance imaging, or computed tomography of the liver, spleen, or kidney suggest the diagnosis. During acute candidemia in neutropenic patients, small erythematous papules may appear anywhere on the skin (Plate IID-57D,Fig. 205-CD8). If the patient does not expire promptly from disseminated candidiasis, the lesions will develop a necrotic center. Painful muscle lesions may also be found. Punch biopsy of a skin lesion helps distinguish this extremely grave condition from *Malassezia* folliculitis, a similar-appearing but benign condition that can involve the cape area of the chest or the extremities of a sweaty febrile patient.

Hematogenous seeding in the neutropenic patient is occasionally visible radiologically as tiny pulmonary nodules. *Candida* pneumonia, apart from hematogenous candidiasis, is very rare. Organisms seeding a native or prosthetic cardiac valve originate principally from central venous catheters; occasionally, valvular seeding is encountered in intravenous drug abusers. Emboli to large arteries, such as the iliac or femoral artery, are characteristic. Intravenous injection of impure brown heroin has caused a clinical syndrome consisting of *Candida* endophthalmitis and purulent folliculitis, sometimes accompanied by vertebral osteomyelitis. This diffuse folliculitis favors hairy areas, including the scalp and bearded facial skin.

Candida can cause indolent arthritis, most commonly of the knee, in patients who have received glucocorticoid injections into the joint, in patients who are immunosuppressed, and in low-birth-weight neonates. Prosthetic joints may become infected during implantation. Scanty growth of *Candida* from joint fluid can cause the laboratory to incorrectly dismiss the organism as a contaminant.

Hematogenous dissemination can lead to brain abscess or chronic meningitis. Diagnosis of infections of ventriculoperitoneal shunts is difficult because symptoms are indolent and cultures of lumbar fluid are usually sterile.

DIAGNOSIS

Demonstration of pseudohyphae on wet smear with confirmation by culture is the procedure of choice for diagnosing superficial candidiasis (Fig. 205-CD9). Scrapings for the smear may be obtained from skin, nails, and oral and vaginal mucosa. Culture alone is not diagnostic; however, recovery of *Candida* species from multiple superficial sites in immunosuppressed patients may portend visceral invasion.

Deeper lesions due to *Candida* may be diagnosed by histologic section of biopsy specimens or by culture of cerebrospinal fluid, blood, joint fluid, or surgical specimens. Blood cultures are useful in the diagnosis of *Candida* endocarditis and intravenous catheter-induced sepsis but are positive less often in other forms of disseminated disease. Serologic tests for antibody or antigen are not useful.

TREATMENT

Cutaneous candidiasis of macerated areas responds to measures that reduce moisture and chafing plus topical application of an antifungal agent in a nonocclusive base. Nystatin powder or a cream containing ciclopirox or an azole is useful. Clotrimazole, miconazole, econazole, ketoconazole, sulconazole, and oxiconazole are available as creams or lotions. *Candida* vulvovaginitis responds better to an azole than to nystatin suppositories. There is little difference in efficacy among miconazole, clotrimazole, tioconazole, butoconazole, and terconazole vaginal formulations. Systemic treatment of *Candida* vulvovaginitis with a single 150-mg capsule of fluconazole is more convenient than topical treatment but also poses a higher risk of adverse effects. Clotrimazole troches, used five times a day, are more effective in oral and esophageal candidiasis than nystatin suspension. Oral fluconazole (100 to 200 mg once daily) is more convenient and more effective in esophagitis than clotrimazole troches. Esophagitis not responding to fluconazole may warrant repeat endoscopy to exclude other conditions. Itraconazole suspension (100 to 200 mg/d) alleviates *Candida* esophagitis in some patients in whom fluconazole treatment fails. Amphotericin B suspension has limited use but can be tried in patients whose oropharyngeal candidiasis does not respond to azoles.

Management of recurrent oropharyngeal candidiasis in the HIV-infected patient presents special problems. Patients with CD4+ cell counts <100/uL who have received prolonged fluconazole therapy are at risk of developing azole resistance, requiring an increased dose to mount a response, relapsing early, and eventually failing to respond well to any dose of fluconazole. The increasing azole resistance in this population suggests that HIV-infected patients with oropharyngeal candidiasis should be treated for each individual episode and that only when episodes become intolerably frequent should weekly or daily preventive therapy be given and even then at the lowest dose required to maintain remission. In contrast, AIDS patients with *Candida* esophagitis are so prone to relapse that preventive therapy with fluconazole is recommended for all proven cases. Most HIV-infected patients with azole-resistant oropharyngeal candidiasis also have esophagitis. Nearly all patients with azole-resistant oropharyngeal or esophageal candidiasis respond to intravenous amphotericin B (0.3 to 0.5 mg/kg daily) but relapse promptly after the completion of therapy.

Bladder thrush responds to bladder irrigations with amphotericin B (50 ug/mL for 5 days). If no bladder catheter is in place, oral fluconazole can be used to control candiduria. In all forms of superficial candidiasis, relapse after successful treatment is common unless the underlying factor can be eliminated.

Intravenous amphotericin B is the drug of choice in disseminated candidiasis. The deoxycholate formulation is usually given at a dosage of 0.5 to 0.7 mg/kg daily. Open, noncomparative studies of the lipid formulations of amphotericin B have suggested that they may be useful in disseminated candidiasis, but the optimal dose and formulation remain unknown. Fluconazole in an adult dose of 100 mg/d is probably the drug of choice for chronic mucocutaneous candidiasis.

In immunocompetent patients with intravenous catheter-acquired *C. albicans* fungemia, the catheter should be removed in conjunction with the administration of either

fluconazole (400 mg/d) or amphotericin B (0.5 mg/kg daily). Patients with suppurative phlebitis of a peripheral vein should have the infected portion of the vein excised. Therapy for candidemia is continued for 2 weeks after the patient becomes afebrile. The *Candida* species involved should be considered in choosing between fluconazole and amphotericin B. *C. krusei* and *C. inconspicua* are rare causes of candidemia but are resistant to fluconazole in vitro. *C. glabrata* exhibits intermediate susceptibility to fluconazole, but too few cases have been studied to determine whether candidemia involving that species will respond as well to fluconazole as to amphotericin B. Strains of *C. lusitaniae* resistant to amphotericin B but susceptible to azoles have been encountered. Intravenous amphotericin B, with or without flucytosine, is the preferred treatment for *Candida* endophthalmitis, although cures have been reported with fluconazole. Pars plana vitrectomy may facilitate diagnosis and cure when a *Candida* vitreous abscess is present. Injection of amphotericin B into the vitreous humor can also be helpful.

Injection of amphotericin B into an infected joint, pleural cavity, or peritoneum is rarely indicated. Removal of prostheses, including prosthetic joints, cardiac valves, peritoneal dialysis catheters, and central venous catheters, is usually essential. Collections of pus, such as those in the postoperative abdomen, need to be drained surgically or by percutaneous, computed tomography-guided catheterization; an exception relates to the numerous small abscesses in liver, spleen, or kidney in chronic disseminated candidiasis, which cannot be drained effectively and require prolonged antifungal therapy. In general, treatment should continue until the patient with chronic disseminated candidiasis has been afebrile and nonneutropenic for at least 2 weeks. Defects may persist on imaging studies long after cure. Relapse during another episode of neutropenia is common unless the patient is receiving amphotericin B. Repeat cytotoxic therapy or even bone marrow transplantation can be undertaken in patients with prior chronic disseminated candidiasis, but amphotericin B should be given prophylactically during neutropenia.

Fluconazole can decrease the incidence of deep candidiasis in recipients of allogeneic bone marrow transplants when 400 mg is given daily until engraftment. Although the incidence of superficial candidiasis is also decreased by fluconazole prophylaxis, superficial infection can be readily detected and treated. Aspergillosis is not prevented by prophylactic fluconazole. Studies of leukemic and other neutropenic patients have found no beneficial effect of prophylactic fluconazole.

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206. ASPERGILLOSIS - *John E. Bennett*

ETIOLOGIC AGENTS

Aspergillus fumigatus is the most common cause of aspergillosis, but *A. flavus*, *A. niger*, and several other species can also cause disease. *Aspergillus* is a mold with septate hyphae about 2 to 4 um in diameter. The fungus is identified by its gross and microscopic appearance in culture.

PATHOGENESIS AND PATHOLOGY

All the common species of *Aspergillus* that cause disease in humans are ubiquitous in the environment, growing on dead leaves, stored grain, compost piles, hay, and other decaying vegetation. Inhalation of *Aspergillus* spores must be extremely common, but disease is rare. Invasion of lung tissue is confined almost entirely to immunosuppressed patients, in roughly 90% of whom two of the following three conditions will be operative: a granulocyte count in peripheral blood of<500/uL, treatment with supraphysiologic doses of adrenal glucocorticoids, and a history of treatment with cytotoxic drugs such as cyclosporine. Invasive aspergillosis is an occasional complication of AIDS. *Aspergillus* infection is characterized by hyphal invasion of blood vessels, thrombosis, necrosis, and hemorrhagic infarction. Chronic granulomatous disease of childhood also predisposes to invasive pulmonary aspergillosis, but in that situation the inflammatory response is a pyogranuloma and blood vessel invasion is rare.

Massive inhalation of *Aspergillus* spores by healthy persons can lead to acute, diffuse, self-limited pneumonitis. Epithelioid granulomas with giant cells and central pyogenic areas containing hyphae are detected in these cases. Spontaneous recovery taking several weeks is the usual course.

Aspergillus can colonize the damaged bronchial tree, pulmonary cysts, or cavities of patients with underlying lung disease. Balls of hyphae within cysts or cavities (aspergillomas), usually in the upper lobe, may reach several centimeters in diameter and may be visible on chest x-ray. Tissue invasion does not occur. The term *allergic bronchopulmonary aspergillosis* denotes the condition of patients with preexisting asthma who have eosinophilia, IgE antibody to *Aspergillus*, and fleeting pulmonary infiltrates from bronchial plugging.

CLINICAL MANIFESTATIONS

Endobronchial saprophytic pulmonary aspergillosis presents as chronic productive cough, often with hemoptysis, in a patient with prior chronic lung disease, such as tuberculosis, sarcoidosis, bronchiectasis, or histoplasmosis. *Aspergillus* may be spread from its endocavitary or endobronchial site to the pleura during the course of bacterial lung abscess or surgery. Patients reported to have chronic necrotizing *Aspergillus* pneumonia appear in most instances to have had saprophytic endobronchial colonization and a pulmonary process attributable to another disease, with or without superimposed bacterial infections. Patients with chronic pneumonia and *Aspergillus* in the sputum should be assumed to have either pneumonia of a different etiology (e.g., histoplasmosis) or *Aspergillus* pneumonia with underlying immunosuppression (e.g.,

chronic granulomatous disease or infection with HIV).

Invasive aspergillosis in the immunocompromised host presents as an acute, rapidly progressive, densely consolidated pulmonary infiltrate and is most common among patients with acute leukemia and recipients of tissue transplants. Infection progresses by direct extension across tissue planes and by hematogenous dissemination to lung, brain, and other organs. Computed tomography (CT) has been particularly valuable in suggesting the diagnosis of invasive pulmonary aspergillosis in patients with neutropenia. The earliest CT finding is one or more small pulmonary nodules. As a nodule enlarges, the dense central core of infarcted tissue becomes surrounded by edema or hemorrhage, forming a hazy rim called the *halo sign*. This rim disappears in a few days as the dense core enlarges. When bone marrow function recovers, the infarcted central core cavitates, creating the *crescent sign*. *Aspergillus* may invade immunosuppressed patients through the skin at a site of minor trauma or through the upper airway mucosa. Early lesions in the nose should be sought in patients with neutropenia who have fever and minimal epistaxis. Scarlet-red patches of the mucosa rapidly become necrotic and white, then black. Rapid extension into the adjacent paranasal sinus, orbit, or face is usual, with or without the appearance of lung lesions.

Aspergillus sinusitis in immunocompetent patients may take three forms. A ball of hyphae may form in a chronically obstructed paranasal sinus, without tissue invasion. Much less commonly, a chronic, fibrosing granulomatous inflammation associated with *Aspergillus* hyphae within tissue may begin in the sinus and spread slowly to the orbit and the brain. *Aspergillus* is also a cause of allergic fungal sinusitis, but dark-walled fungi (e.g., *Cladosporium*, *Alternaria*) are more common in this setting. Patients usually have a history of chronic allergic rhinitis, sometimes with nasal polyps, but are otherwise healthy, presenting with painless proptosis, nasal obstruction, or dull aching pain. OnCT or magnetic resonance imaging, a solid soft tissue mass pushing out the lateral wall of the ethmoid sinus or the medial wall of the maxillary sinus may be detected. On sinus exploration, the mucosa is found to be thickened and inflamed but intact. Within the sinus cavity, sticky mucopus with strands of neutrophils, eosinophils, Charcot-Leyden crystals, and occasional hyphae can be found.

Aspergillosis in HIV-infected patients most commonly involves the lung, presenting as fever, cough, and dyspnea. Typically, the CD4 cell count is below 50/uL. Roughly half of these patients have neutropenia or have recently been treated with glucocorticoids. Bilateral diffuse or focal pulmonary infiltrates with a tendency to cavitate constitute the most common radiologic manifestation. Well-localized, white, necrotic pseudomembranes full of hyphae or ulcers may develop in the trachea or the major bronchi. Progression of bronchitis to pneumonia is usual, but hematogenous dissemination is uncommon. Either allergic or invasive *Aspergillus* sinusitis can occur in HIV-infected patients; the allergic form can develop even at CD4 cell counts above 50/uL.

The growth of *Aspergillus* on cerumen and detritus within the external auditory canal is termed *otomycosis*. Trauma to the cornea may cause *Aspergillus* keratitis. Endophthalmitis follows the introduction of *Aspergillus* into the globe by trauma or surgery. *Aspergillus* may infect intracardiac or intravascular prostheses.

DIAGNOSIS

The repeated isolation of *Aspergillus* from sputum or the demonstration of hyphae in sputum or bronchoalveolar lavage fluid suggests endobronchial colonization or infection. Even a single isolation of *Aspergillus* from the sputum of a neutropenic patient with pneumonia, particularly a child or a nonsmoker, suggests the diagnosis of invasive aspergillosis. In patients with advanced AIDS, fever, and cough, the isolation of *Aspergillus* from respiratory secretions raises the possibility of aspergillosis and thus should prompt bronchoscopy. Fungus ball of the lung is usually detectable by chest x-ray. IgG antibody to *Aspergillus* antigens is demonstrable in the serum of many colonized patients and of virtually all patients with fungus ball.

Biopsy is usually required for the diagnosis of invasive aspergillosis of the lung, nose, paranasal sinus, bronchi, or sites of dissemination. Blood cultures are rarely positive, even in patients with infected cardiac valves (native or prosthetic). Detection of galactomannan antigen in serum suggests the diagnosis, but false-positives are frequent, particularly in children. *Aspergillus* hyphae can be identified presumptively by histology, but culture is required for confirmation and for determination of the species. Only culture can reliably distinguish aspergillosis from pseudallescheriasis; drug therapy for these two diseases differs.

TREATMENT

Patients with severe hemoptysis due to fungus ball of the lung may benefit from lobectomy. Poor pulmonary function in residual lung and dense pleural adhesions around the lesion can complicate the resection. Systemic chemotherapy is of no value in endobronchial or endocavitary aspergillosis.

Treatment with intravenous amphotericin B (1.0 to 1.5 mg/kg daily) has resulted in the arrest or cure of invasive aspergillosis when immunosuppression is not severe. Liposomal amphotericin B at daily doses of 1 to 4 mg/kg has given results that seem roughly comparable to those obtained with amphotericin B deoxycholate. Itraconazole (200 mg twice daily) is useful in some less immunosuppressed patients with indolent or slowly progressive invasive aspergillosis. Surgery is the only treatment needed for fungus ball of the sinus and for allergic fungal sinusitis. Antifungal therapy has little effect on either entity if used alone, but chronic suppressive therapy has been begun postoperatively for relapse of allergic fungal sinusitis. The prognosis for cure of invasive aspergillosis in the paranasal sinus is very poor when the patient has profound and unremitting neutropenia. The prognosis is better in less immunosuppressed patients.

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207. MUCORMYCOSIS - *John E. Bennett*

ETIOLOGIC AGENTS

Species of *Rhizopus*, *Rhizomucor*, and *Cunninghamella* are the most common causes of mucormycosis, but species of *Apophysomyces*, *Saksenaea*, *Mucor*, and *Absidia* also are occasionally responsible for this infection. The organism in tissue is composed of broad, rarely septate hyphae of uneven diameter (6 to 50 um). The organisms are inexplicably difficult to grow from infected tissue. When growth does take place, it is rapid and profuse on most media at room temperature. Identification is based on the gross and microscopic appearance of the mold.

Zygomycosis is a term that includes mucormycosis and entomophthoramycosis. The latter is a tropical infection of the subcutaneous tissue or paranasal sinuses caused by species of *Basidiobolus* and *Conidiobolus*, respectively.

EPIDEMIOLOGY AND PATHOLOGY

Rhizopus and *Rhizomucor* species are ubiquitous, appearing on decaying vegetation, dung, and foods of high sugar content. Mucormycosis is uncommon and is largely confined to patients with serious preexisting diseases. Mucormycosis originating in the paranasal sinuses and nose predominantly affects patients with poorly controlled diabetes mellitus. Patients who have undergone organ transplantation, who have a hematologic malignancy, or who are receiving long-term deferoxamine therapy are predisposed to mucormycosis of either sinus or lung. Gastrointestinal mucormycosis occurs in a variety of conditions, including uremia, severe malnutrition, and diarrheal diseases. The infection is acquired from nature, with no person-to-person spread. In all forms of mucormycosis, vascular invasion by hyphae is a prominent feature. Ischemic or hemorrhagic necrosis is the foremost histologic finding.

CLINICAL MANIFESTATIONS

Mucormycosis originating in the nose and paranasal sinuses produces a characteristic clinical picture. Low-grade fever, dull sinus pain, and sometimes nasal congestion or a thin, bloody nasal discharge are followed in a few days by double vision, increasing fever, and obtundation. Examination reveals a unilateral generalized reduction of ocular motion, chemosis, and proptosis. The nasal turbinates on the involved side may be dusky red or necrotic. A sharply delineated area of necrosis, strictly respecting the midline, may appear in the hard palate. The skin of the cheek may become inflamed. Fungal invasion of the globe or ophthalmic artery leads to blindness. Opacification of one or more sinuses is detected by computed tomography (CT) or by magnetic resonance imaging (MRI). Carotid arteriography may show invasion or obstruction of the carotid siphon. Coma is due to direct invasion of the frontal lobe. Early symptoms mimic those of bacterial sinusitis. Clouding of the sensorium may be attributed to diabetic acidosis. Cavernous sinus thrombosis may be considered when orbital invasion occurs. Without treatment, the patient may die after an interval ranging from a few days to a few weeks.

Pulmonary mucormycosis manifests as progressive severe pneumonia accompanied by

high fever and toxicity. The necrotic center of large infiltrates may cavitate. Hematogenous spread to other areas of the lung, as well as to the brain and other organs, is common. Survival beyond 2 weeks is unusual. Gastrointestinal invasion presents as one or more ulcers that tend to perforate. Hematogenous dissemination can originate from the gastrointestinal tract, lung, or paranasal sinuses. Sometimes no portal of entry can be found.

DIAGNOSIS

CTor MRIis very helpful in assessing the extent of sinusitis before surgery and in evaluating the patient afterward. CT is better for detecting bony erosion; MRI better visualizes extension into the frontal lobe or carotid artery in the siphon. Lesions of the lung and craniofacial structures are best diagnosed by biopsy and histologic section. Cultural confirmation should be attempted. Wet smear of crushed tissue can provide a rapid diagnosis. Cultures of blood and cerebrospinal fluid are negative. Smear and culture of sputum may be positive during cavitation of a lung lesion.

TREATMENT

Regulation of diabetes mellitus and a decrease in the dose of immunosuppressive drugs facilitate the treatment of mucormycosis. Extensive debridement of craniofacial lesions appears to be very important. Orbital exenteration may be required. Intravenous amphotericin B is clearly of value in craniofacial mucormycosis and should be employed in the other forms of mucormycosis as well. The maximal tolerated doses are given until progression is halted. With the deoxycholate formulation, 1 to 1.5 mg/kg daily is indicated. Therapy is continued for a total of 10 to 12 weeks. Azoles are of no value. Appropriate management results in cure of about half of craniofacial infections. The survival of patients with pulmonary, gastrointestinal, or disseminated mucormycosis is rare.

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208. MISCELLANEOUS MYCOSES AND ALGAL INFECTIONS - *John E. Bennett*

CHROMOBLASTOMYCOSIS (FIG. 208-CD1)

This chronic subcutaneous mycosis, rarely seen in the United States, presents as a verrucoid, ulcerated, or crusted skin lesion. The disease follows the introduction of any of several fungi into subcutaneous tissue by thorns or bits of vegetation. The infection spreads over ensuing months and years to contiguous tissue, causing few symptoms. The appearance of thick-walled, dark-colored, rounded forms ("copper pennies") in histopathologic section is diagnostic. Surgical excision is the treatment of choice. Itraconazole has ameliorated some relatively small and incompletely excised lesions.

DERMATOPHYTOSIS

Definition Dermatophytosis, also known as ringworm or tinea, is a chronic fungal infection of the skin, hair, or nails.

Etiology Species of *Trichophyton*, *Microsporum*, and *Epidermophyton* are called *dermatophytes.* These organisms grow in and remain confined to the keratinous structures of the body. Other mycoses, such as candidiasis, pityriasis versicolor, and tinea nigra, sometimes include fungal invasion of keratinous structures but traditionally are not called dermatophytoses.

Pathology and Pathogenesis Dermatophyte species are referred to as *anthropophilic*, *zoophilic*, or *geophilic*, depending on whether their usual reservoir in nature appears to be humans, animals, or soil, respectively. The infectivity of organisms from all these sources is low, and outbreaks are largely confined to occasional clusters of cases of scalp infection in children. Acquisition of a dermatophytosis appears to be favored by minor trauma, maceration, and poor hygiene of the skin. Infection does not seem to confer solid immunity: Repeated infection with the same species is common, particularly with anthropophilic species. The infrequency of scalp infection among adults has been attributed to local factors rather than immunity.

Invasion of the stratum corneum by dermatophytes may cause inflammation that is either mild or (particularly with zoophilic fungi) intense. Shedding of the stratum corneum is increased by inflammation. To the extent that fungal growth cannot keep up with shedding, inflammation may help terminate infection. Conversely, infection is probably favored when shedding is reduced by treatment with glucocorticoids and cytotoxic drugs. Antifungal drugs interfere with the ability of fungal growth to keep up with shedding.

Clinical Manifestations The disease varies with the site of infection and the fungal species involved. Foot infection (athlete's foot, tinea pedis) may present as fissuring of the toe webs, scaling of the plantar surfaces, or vesicles around the toe webs and soles. Interdigital lesions may be pruritic or, when bacterial superinfection occurs, may be painful. Hand infection is less common but resembles foot infection.

Scalp dermatophytosis (tinea capitis; Fig. 208-CD4) is characterized by areas of alopecia and scaling. In so-called endothrix infection, the hair shaft breaks off at the skin

surface, leaving the hairs visible as black dots in the scalp. Some forms of scalp infection include an area of intense boggy suppuration called a *kerion*.

Dermatophytosis of the glabrous skin (tinea corporis, Plate IID-51) presents as circumscribed lesions with a wide variety of appearances, including scales, vesicles, and pustules. Inflammation may be minimal or intense. Central healing of less inflamed lesions may take place. The serpiginous border of inflammation is the source of the name *ringworm*.

Dermatophytosis of the bearded area (tinea barbae) appears as a pustular folliculitis. Onychomycosis (tinea unguium; Fig. 208-CD5) presents as a white discoloration of the nails or as thickening, chalkiness, and crumbling of the nails. Peeling and fissuring of paronychial nail folds or keratotic debris under the nail edge also may be evident.

Diagnosis Discolored hairs, scales, and keratotic debris under infected nails should be collected for KOH smear and culture. In the scraping of skin lesions, a drop of water on the skin site may keep the removed scales from flying off and thus may aid in their collection. Culture is important in distinguishing dermatophytes from *Candida* and fungal saprophytes growing in keratinaceous debris.

TREATMENT

Noninflammatory lesions of the trunk, groin, hands, and feet usually respond to twice-daily applications of clotrimazole, miconazole, ketoconazole, econazole, naftifine, terbinafine, or ciclopirox olamine cream. Hyperkeratotic lesions of the palms and soles respond slowly to these agents and may benefit from Whitfield's ointment initially to thin the keratin. Ointment should not be used between the toes, in the groin, or in the gluteal crease because maceration promotes bacterial infection.

Ringworm that is moderately severe, that is unresponsive to topical therapy, or that involves the scalp, nails, or bearded area should be treated systemically. Once-daily therapy with itraconazole (200 mg), terbinafine (250 mg), microcrystalline griseofulvin (500 mg), or ultramicrocrystalline griseofulvin (375 mg) is effective. Treatment must be continued until all infected keratin is gone. Cutting off infected hair and cleansing interdigital webs can expedite cure. Secondary bacterial infection of the foot may require soaks or antibacterial agents. The likelihood of relapse of dermatophyte foot infections may be decreased by keeping the feet clean and dry. For nail infections, itraconazole or terbinafine is preferred. In distal subungual onychomycosis, a single course of either drug results in initial improvement in half of patients, of whom half relapse. Results are better with fingernails than with toenails and for more distal rather than lateral nail involvement. To save money, itraconazole can be given as a double dose (400 mg) for 1 week each month with only marginal loss of efficacy. The duration of therapy is 2 to 3 months for fingernails and 4 to 6 months for toenails.

PROTOTHECOSIS

Prototheca species are ubiquitous achlorophyllic algae that enter the skin through contaminated wounds and cause localized infections in the olecranon bursa, skin, subcutaneous tissue, tendon sheaths, or deeper tissue. Diagnosis is based on culture or

histopathologic demonstration of sporangia with endospores in tissue. Surgical debridement and treatment with intravenous amphotericin B are useful.

FUSARIOSIS

Fusarium species can cause localized or hematogenously disseminated infection. Localized infection results from contaminated wounds. Almost all patients with hematogenously disseminated infection are severely immunosuppressed and profoundly neutropenic. Skin lesions occur in two-thirds of patients. Several painful red indurated lesions appear on the extremities or sometimes the trunk. These lesions often develop an ecchymotic center that ulcerates. A portal of infection is not usually apparent. Blood cultures have been positive in 59% of cases. Amphotericin B is probably the drug of choice for the treatment of fusariosis, but recovery depends on the diminution of neutropenia.

MALASSEZIA INFECTION (PITYRIASIS)

Malassezia furfur is part of the normal flora of the human skin but can cause tinea (pityriasis) versicolor (Fig. 208-CD6) or catheter-acquired sepsis. Tinea versicolor appears as asymptomatic, well-delineated, hyperpigmented or hypopigmented macules centered on the upper trunk and upper arms. Confluent lesions may cover large areas, making the border difficult to find. A fine "branny" scale or folliculitis is sometimes visible. When examined microscopically by KOH mount, skin sections are seen to contain characteristic round and elongated cells (Fig. 208-CD7). On inspection with Wood's light, lesions either do not fluoresce or appear yellow-green. *Erythrasma* (Fig. 141-CD1) resembles tinea versicolor but is characterized by gram-positive bacilli on smear and coral-red fluorescence. Azole creams are effective for the treatment of small areas of tinea versicolor; however, the application of selenium sulfide shampoo (Selsun) for 10 min daily, followed by showering to remove the shampoo, is more practical for large areas. Itraconazole is also effective. Catheter-acquired sepsis due to *M. furfur* develops in patients (particularly neonates) receiving intravenous lipid. The organism requires special culture conditions for growth, and the infection is cured by catheter removal.

MYCETOMA

Etiology *Actinomycetoma* refers to infection by actinomycetes of the genera *Nocardia*, *Nocardiopsis*, *Streptomyces*, and *Actinomadura*. *Eumycetoma* (Fig. 208-CD8) is caused by true fungi of many different genera. The predominant agent varies with the locality.

Pathogenesis and Pathology The pathogens live in the soil and enter the skin through minor trauma. The most common site of infection is the foot. The infection runs a relentless course over many years, with destruction of contiguous bone and fascia. Grains are found in purulent foci surrounded by fibrosis and a mononuclear cell inflammatory response.

Clinical Manifestations Mycetoma is a chronic suppurative infection originating in subcutaneous tissue and characterized by the presence of grains, which are tightly clumped colonies of the causative agent. The infected site is characterized by painless

swelling, woody induration, and sinus tracts that discharge pus intermittently. Systemic symptoms do not develop, and spread to distant sites in the body does not take place.

Diagnosis Although the clinical picture is characteristic, mycetoma is sometimes confused with chronic osteomyelitis or botryomycosis. The diagnosis requires demonstration of grains in pus from the draining sinus or in biopsy sections. Many histologic sections may need to be examined to locate a grain.

TREATMENT

Actinomycetoma may respond to prolonged combination chemotherapy -- e.g., with streptomycin and either dapsone or trimethoprim-sulfamethoxazole. Eumycetoma rarely responds to chemotherapy; some cases caused by *Madurella mycetomatis* have appeared to respond to ketoconazole or itraconazole.

PARACOCCIDIOIDOMYCOSIS

Etiology Formerly called *South American blastomycosis*, this mycosis is caused by *Paracoccidioides brasiliensis*. A dimorphic fungus, *P. brasiliensis* grows as a budding yeast in tissue but may be grown as either a yeast or a mold on culture medium. The organism is identified by its gross and microscopic appearance.

Pathogenesis and Pathology Infection is thought to be acquired by inhalation of spores from environmental sources, possibly soil. Pulmonary infection produces few symptoms initially. Hematogenous spread to the mucous membranes of the mouth and nose, the lymph nodes, and other sites causes patients to seek medical attention. In fatal cases, the infection spreads to the adrenals, the gastrointestinal tract, and many other viscera.

Clinical Manifestations Common signs include indurated ulcers of the mouth, oropharynx, larynx, and nose; enlarged and draining lymph nodes; lesions of the skin and genitalia; and productive cough, weight loss, dyspnea, and sometimes fever. Paracoccidioidomycosis is acquired only in South America, Central America, and Mexico, but its extreme indolence may delay its recognition until many years after the patient has left the endemic area. Chest radiography most often shows bilateral patchy pneumonia.

Diagnosis Cultures of sputum, pus, and mucosal lesions are often diagnostic. The diagnosis can be made by smear or histologic section, although confirmation by culture is preferable. Serologic tests are useful in suggesting the diagnosis and monitoring the response to therapy.

TREATMENT

Relatively mild cases of paracoccidioidomycosis may be cured by 1 year of treatment with oral ketoconazole or itraconazole (200 to 400 mg daily). More advanced cases are treated with intravenous amphotericin B followed by itraconazole.

PHAEOHYPHOMYCOSIS

This is the name given to infections caused by fungi with dark-walled hyphae, excluding those given conventional names like chromoblastomycosis. Although an extraordinary variety of fungi and clinical syndromes are encompassed by this definition, most patients have brain abscess, subcutaneous abscess, or allergic fungal sinusitis. Most of the brain abscesses are due to *Cladophialophora bantiana*, *Ochroconis gallopavum*, *Exophiala dermatitidis*, *Bipolaris* species, and *Ramichloridium mackenziei*. Patients are previously healthy. Subcutaneous abscesses are usually single, arise at the site of minor trauma, and occur in both immunosuppressed and immunocompetent individuals. A large number of dematiaceous (dark-walled) mold species cause subcutaneous phaeohyphomycosis as well as allergic fungal sinusitis. The latter entity develops in patients with allergic rhinitis and presents as an expanding mucoid mass in one or more paranasal sinuses. The tenacious mucus contains eosinophils, Charcot-Leyden crystals, and occasional hyphae. Surgical excision of phaeohyphomycotic lesions is important. Antifungal therapy may retard recurrences but is of little value unless surgical excision has been performed.

PSEUDALLESCHERIASIS

Etiology Also called *Petriellidium boydii*, *Pseudallescheria boydii* is a mold frequently found in soil. When the fungus is isolated in the imperfect state, it is called *Scedosporium apiospermum*.

Pathogenesis and Pathology Wind-borne spores of *P. boydii*, arising from the soil, are the presumed source of infection. The fungus grows as a mold within tissue, causing necrosis and abscess formation.

Clinical Manifestations *P. boydii* resembles *Aspergillus* in its ability to colonize the endobronchial tree, to form fungus balls in the lungs or paranasal sinuses, and to invade the cornea or globe of the eye, the soft tissues, the joints, or the bones after trauma or surgery and in its propensity to invade the lungs and paranasal sinuses of immunosuppressed hosts, including patients with AIDS. Hyphae of *P. boydii* in tissue may be difficult to distinguish from those of *Aspergillus*. Infection with *P. boydii* is much less common than that with *Aspergillus*. Intravascular hyphae, a hallmark of invasive aspergillosis, are also found in pseudallescheriasis. Near-drowning in polluted water has led to severe *P. boydii* pneumonia, often with dissemination and fatal brain abscesses.

Diagnosis Demonstration of hyphae in tissue and culture confirmation are required for diagnosis.

TREATMENT

Itraconazole at the maximal tolerated doses is the regimen of choice. Surgical drainage or debridement can be helpful. The prognosis is poor.

Scedosporium prolificans, a fungus closely related to *P. boydii*, has caused infections in bones, joints, or soft tissue, usually after trauma. These infections have responded to surgical debridement. Disseminated infection with *S. prolificans* in immunosuppressed patients has been fatal. The response to treatment with all antifungal agents has been

poor.

SPOROTRICHOSIS

Etiology *Sporothrix schenckii* lives as a saprophyte on plants in many areas of the world. In nature and on culture at room temperature, the fungus grows as a mold; within host tissue or at 37°C on enriched media, it grows as a budding yeast. It is identified by its appearance in mold and yeast forms.

Pathogenesis and Pathology Infection results from the inoculation of *S. schenckii* into subcutaneous tissue through minor trauma. Nursery workers, florists, and gardeners acquire the illness from roses, sphagnum moss, and other plants. Infection may be limited to the site of inoculation (plaque sporotrichosis) or extend along proximal lymphatic channels (lymphangitic sporotrichosis). Spread beyond an extremity -- the usual site of infection -- is rare, and hematogenous dissemination from the skin remains unproven. The portal for osteoarticular, pulmonary, and other extracutaneous forms of sporotrichosis is unknown but is likely the lung.

Untreated sporotrichosis persists for months. The inflammatory response includes both the clustering of neutrophils and a marked granulomatous response with epithelioid cells and giant cells.

Clinical Manifestations In lymphangitic sporotrichosis, which is by far the most common manifestation, a nearly painless red papule forms at the site of inoculation. Over the next several weeks, similar nodules form along proximal lymphatic channels (Fig. 208-CD9). The nodules intermittently discharge small amounts of pus. Ulceration may occur. The proximal extension of these lesions, often with skip areas, is quite distinctive but may be mimicked by lesions of *Nocardia brasiliensis*, *Mycobacterium marinum*, or (in rare cases) *Leishmania brasiliensis* or *Mycobacterium kansasii*.

Plaque sporotrichosis manifests as a nontender red maculopapular granuloma confined to the site of inoculation. Osteoarticular sporotrichosis presents as mono- or polyarticular arthritis of indolent onset and progression over months or years, involving the elbows, knees, wrists, ankles, and (rarely) smaller joints of the extremities. Periarticular bone develops areas of demineralization detectable on x-ray, and draining sinuses may appear over joints and bursae. Hematogenous spread to the skin may take place during polyarticular disease, but none of the skin lesions shows lymphangitic spread. Immunosuppression, including that due to advanced infection with HIV, predisposes to hematogenous spread. Pulmonary sporotrichosis usually presents as a single chronic cavitary upper-lobe lung lesion. Chronic meningitis can develop in the absence of skin or lung lesions. *S. schenckii* is difficult to recover from cerebrospinal fluid.

Diagnosis Culture of pus, joint fluid, sputum, or a skin biopsy specimen is the preferred method of diagnosis. The appearance of *S. schenckii* in tissue is quite variable. In skin lesions, the organisms are hard to find.

TREATMENT

Cutaneous sporotrichosis can be cured with a saturated solution of potassium iodide given orally in increasing divided doses of up to 4.5 to 9 mL/d for adults, as tolerated. Gastrointestinal disturbance or acneiform rash over the cape area and face is common, but therapy should be continued for 1 month after the resolution of all lesions. Itraconazole (100 to 200 mg daily) is an effective and better-tolerated alternative. Extracutaneous sporotrichosis rarely responds to iodides, but more than half of cases have been cured by prolonged courses of intravenous amphotericin B. Itraconazole (200 mg once or twice daily) is effective in some cases of extracutaneous sporotrichosis.

TRICHOSPORONOSIS

A recent change in taxonomy of the genus *Trichosporon* has moved most of the agents causing deep infections from *T. beigelii* into the species *T. asahii*, with a few categorized as *T. mucoides*. White piedra of the scalp is caused by *T. ovoides* and that of the pubic hair by *T. inkin*. *T cutaneum* and *T. asteroides* cause superficial infections. Most of what is currently known about *Trichosporon* infections is not species specific, so the following description refers to *T. beigelii*. *T. capitatum*, which causes disseminated infection in patients with neutropenia, was previously reclassified as *Blastoschizomyces capitatus* and will not be covered here.

T. beigelii can colonize the human gastrointestinal tract and skin and can enter the bloodstream of patients with severe neutropenia through an inapparent source. Hematogenously disseminated infection is manifested by fever and often by the development of several erythematous or purpuric tender papules anywhere on the body. Lesions can form large, tense hemorrhagic bullae. In some patients, native or prosthetic cardiac valves become infected. In tissue, hyphae and yeastlike cells are seen. Amphotericin B is probably the drug of choice for treatment, but recovery is dependent on the return of bone marrow function.

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209. *PNEUMOCYSTIS CARINII* INFECTION - *Peter D. Walzer*

DEFINITION AND DESCRIPTION

Pneumocystis carinii is an opportunistic pathogen whose natural habitat is the lung. The organism is an important cause of pneumonia in the compromised host.

Although the taxonomic status of *P. carinii* has long been controversial, molecular studies during the past decade have clearly placed the organism among the fungi. This classification is based on analysis of gene sequences for ribosomal RNA, mitochondrial proteins, and major enzymes. The cell wall of *P. carinii* containsb-1,3-glucan; drugs that inhibitb-glucan synthesis in fungi are highly active against *P. carinii* in animal models. However, in contrast to most fungi, *P. carinii* lacks ergosterol and is not susceptible to antifungal drugs that inhibit ergosterol synthesis.

Study of the basic biology of *P. carinii* has been severely hampered by the lack of a reliable in vitro cultivation system. Major developmental stages of the organism include the small (1- to 4-um) pleomorphic trophozoite or trophic form; the 5- to 8-um cyst, which has a thick cell wall and contains up to eight intracystic bodies; and the precyst, an intermediate stage. The life cycle of *P. carinii* probably involves asexual replication by the trophic form and sexual reproduction by the cyst, which ends in release of the intracystic bodies; an intracellular stage has not been identified. Ultrastructurally, *P. carinii* has a primitive organelle system, but little is known about its metabolism.

P. carinii contains two prominent antigen groups. The 95- to 140-kDa major surface glycoprotein (MSG) complex represents a family of proteins encoded by multiple genes. The MSG complex is highly immunogenic, contains shared and species-specific antigenic determinants, and exhibits protective B and T cell epitopes in animal models. The MSG complex plays a pivotal role in the host-parasite relationship in *P. carinii* infection. It facilitates adherence to host proteins via extracellular matrix proteins, surfactant proteins, and the mannose receptor; and its ability to undergo antigenic variation may represent a mechanism by which *P. carinii* evades the host immune response. The other antigen, which migrates as a band of 35 to 55 kDa, is the most common antigen recognized by the host and thus may serve as a marker of infection.

EPIDEMIOLOGY

P. carinii has a worldwide distribution among humans and has been detected in a variety of animals. The organisms found in these hosts are morphologically identical, but recent studies have revealed a high degree of genetic diversity and host specificity. Serologic surveys indicate that most healthy children have been exposed to the organism by 3 to 4 years of age. Animal model experiments have demonstrated that *P. carinii* is transmitted by the airborne route. Person-to-person transmission has been suggested by the occurrence of outbreaks of pneumocystosis among institutionalized debilitated infants and in hospitals caring for immunosuppressed patients. On the basis of animal studies, the incubation period is thought to be 4 to 8 weeks.

PATHOGENESIS AND PATHOLOGY

The host factors that predispose to the development of pneumocystosis involve defects in cellular and humoral immunity. People at risk for the disease include patients infected with HIV; persons receiving immunosuppressive therapy (particularly glucocorticoids) for cancer, organ transplantation, and other disorders; children with primary immunodeficiency diseases; and premature malnourished infants. The central role of CD4+ cells in host resistance to *P. carinii* has been shown by research in experimental animals and by studies that have correlated the risk of pneumocystosis in HIV-infected patients with CD4+ cell counts. Evidence supporting the importance of impaired humoral immunity consists of the occurrence of pneumocytosis in patients and animals with B cell defects and the beneficial effect of passively administered antibodies.

The principal host effector cells against *P. carinii* are alveolar macrophages, which ingest and kill the organism, releasing a variety of inflammatory mediators. Tumor necrosis factora and interleukin (IL) 1 are important in the early host defenses against *P. carinii*, but the role of other cytokines is less clear. Recent evidence suggests that HIV alters the mannose receptor-mediated binding and phagocytosis of *P. carinii*.

After being inhaled, *P. carinii* takes up residence in the alveoli, where it attaches tightly to type I cells but maintains an extracellular existence. In some cases, the organism remains in the host for long periods, and pneumonia develops by reactivation of latent infection; in other cases, pneumonia arises from a new bout of infection. As the immune system of the host becomes compromised, *P. carinii* organisms propagate and gradually fill the alveoli. This scenario is accompanied by a complex series of events that result in increased alveolar-capillary permeability and damage to type I cells. Surfactant abnormalities include a fall in bronchoalveolar lavage (BAL) fluid phospholipids and an increase in surfactant proteins A and D. Contributions of the host inflammatory response to lung injury are suggested by the correlation of increasedIL-8 levels and neutrophil counts in BAL fluid from patients with relatively severe disease.

On lung sections stained with hematoxylin and eosin, the alveoli are filled with a typical foamy, vacuolated exudate. Severe disease may include interstitial edema, fibrosis, and hyaline membrane formation. The host inflammatory changes usually consist of hypertrophy of alveolar type II cells, a typical reparative response, and a mild mononuclear cell interstitial infiltrate. Malnourished infants display an intense plasma cell infiltrate that gave the disease its early name: interstitial plasma cell pneumonia.

CLINICAL FEATURES

Patients with *P. carinii* pneumonia develop dyspnea, fever, and nonproductive cough. Symptoms in non-HIV-infected patients often begin after the glucocorticoid dose has been tapered and typically last 1 to 2 weeks. HIV-infected patients are usually ill for several weeks or longer and have relatively subtle manifestations. However, the clinical picture in individual patients is quite variable, and a high index of suspicion and elicitation of a careful history are key factors in early detection.

Physical findings include tachypnea, tachycardia, and cyanosis, but lung auscultation reveals few abnormalities. The white blood cell count is variable and is usually governed by the patient's underlying disease. Assessment of arterial blood gases demonstrates hypoxia, an increased alveolar-arterial oxygen gradient (PA_{O2}-Pa_{O2}), and respiratory

alkalosis. There also may be changes in pulmonary function test values (diffusing capacity) and increased uptake with nuclear imaging techniques (gallium scan). Elevated serum concentrations of lactate dehydrogenase (LDH) have been reported; they probably reflect lung parenchymal damage but are not specific to *P. carinii* infection. In general, laboratory abnormalities are less severe in HIV-infected patients than in non-HIV-infected patients.

The classic findings on chest radiography consist of bilateral diffuse infiltrates beginning in the perihilar regions (Fig. 209-1), but various atypical manifestations (nodular densities, cavitary lesions) have also been reported. Patients who receive aerosolized pentamidine have an increased frequency of upper-lobe infiltrates and pneumothorax. Early in the course of pneumocystosis, the chest radiograph may be normal.

Although *P. carinii* usually remains confined to the lungs, cases of disseminated infection have occurred in both HIV-infected and non-HIV-infected patients. One risk factor for extrapulmonary spread in patients with HIV is the administration of aerosolized pentamidine. The most common sites of extrapulmonary involvement are the lymph nodes, spleen, liver, and bone marrow. Clinical manifestations range from incidental findings at autopsy to specific organ involvement. Histopathologic examination reveals the presence of *P. carinii* and the characteristic associated foamy material. Treatment for the extrapulmonary forms of pneumocystosis is the same as that for pneumonia.

DIAGNOSIS

Because the clinical picture of *P. carinii* infection can be produced by many other infectious and noninfectious agents, the diagnosis must be based on specific identification of the organism. A definitive diagnosis is made by histopathologic staining. Traditional stains have included reagents such as methenamine silver, toluidine blue, and cresyl echt violet, which selectively stain the wall of *P. carinii* cysts, and reagents such as Wright-Giemsa, which stain the nuclei of all developmental stages. Other reagents include nonspecific fluorochrome stains (calcofluor white) and Papanicolaou's stain. Immunofluorescence with monoclonal antibodies is more sensitive than histologic staining but is also more expensive. DNA amplification by the polymerase chain reaction offers the greatest sensitivity and may find a place in the routine diagnosis of *P. carinii* when commercial kits become available.

The successful diagnosis of pneumocystosis depends upon the collection of proper specimens. In general, the yield from different diagnostic procedures is higher in HIV-infected patients than in non-HIV-infected patients because of the higher organism burden in the former group. Sputum induction has gained popularity as a simple, noninvasive technique; this procedure requires trained and dedicated personnel, and its success has varied at different institutions. Fiberoptic bronchoscopy withBAL, which is more sensitive than sputum induction, remains the mainstay of *P. carinii* diagnosis. This procedure also provides information about the organism burden, the host inflammatory response, and the presence of other opportunistic infections. Transbronchial biopsy and open lung biopsy, which are the most invasive procedures, are reserved for situations in which a diagnosis cannot be made by BAL.

COURSE AND PROGNOSIS

In the typical case of untreated *P. carinii* pneumonia, progressive respiratory embarrassment leads to death. Therapy is most effective when instituted early in the course of the disease, before there is extensive alveolar damage. If induced sputum is nondiagnostic andBALcannot be performed in a timely manner, it is reasonable to begin empiric therapy with drugs active against *P. carinii*. However, this practice does not obviate the need for a specific etiologic diagnosis. With improvements in management, the case-fatality rate has been lowered to about 15% in HIV-infected patients but remains high (40%) in non-HIV-infected patients. The most widely used prognostic indicators have been the arterial oxygen pressure and the alveolar-arterial oxygen gradient. Other factors that may influence survival include neutrophil counts and IL-8 levels in BAL fluid, chest radiographic abnormalities, serumLDH and albumin levels, and the expertise of the hospital in caring for patients with HIV infection. Concurrent pulmonary infections complicate management, but the presence of cytomegalovirus usually does not affect the outcome of pneumocystosis.

TREATMENT

Trimethoprim-sulfamethoxazole (TMP-SMZ), which acts by inhibiting folic acid synthesis, is considered the drug of choice for all forms of pneumocystosis. The daily dosage, administered orally or intravenously in three or four divided doses, is 15 to 20 mg TMP/kg and 75 to 100 mg SMZ/kg. Therapy is continued for 14 days in non-HIV-infected patients and for 21 days in persons infected with HIV. Since HIV-infected patients respond more slowly than non-HIV-infected patients, it is prudent to wait at least 7 days after the initiation of treatment before concluding that therapy has failed. The addition of drugs to an existing regimen is no more effective than switching regimens and may increase the risk of toxicity. TMP-SMZ is well tolerated by non-HIV-infected patients, but more than half of HIV-infected patients experience serious adverse reactions, including fever, rash, neutropenia, thrombocytopenia, hepatitis, and hyperkalemia.

Several alternative regimens are available for the treatment of mild to moderate cases of *P. carinii* pneumonia: TMP (15 mg/kg per day orally) plus dapsone (100 mg/d orally), clindamycin (600 mg every 6 h intravenously or 300 to 450 mg every 6 h orally) plus primaquine (15 to 30 mg of base per day orally), or atovaquone alone (750 mg twice daily orally). Dapsone and primaquine should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency.

Two alternative drugs are available for the treatment of moderate to severe forms of pneumocystosis. Pentamidine, which has been used against *P. carinii* for many years, is administered as a single daily dose of 4 mg/kg by slow intravenous infusion. Pentamidine is highly toxic; its major side effects are hypotension, cardiac arrhythmias, dysglycemias, azotemia, electrolyte changes, and neutropenia. Trimetrexate is administered intravenously as a single daily dose of 45 mg/m^2; in conjunction with trimetrexate therapy, folinic acid is given orally or intravenously at a dose of 20 mg/m^2every 6 h to prevent bone marrow suppression.

Patients with HIV frequently experience deterioration in respiratory function shortly after receiving anti-*P. carinii* drugs. Several studies have shown that the administration of

glucocorticoids to patients with HIV and moderate to severe pneumocystosis (a P_{O2} of£70 mmHg or a PA_{O2}-Pa_{O2} of³35 mmHg) can prevent this problem and improve the rate of survival. The administration of steroids should be started early in the course of the illness (usually when antimicrobial drugs are begun) for maximal benefit; the recommended regimen is 40 mg of prednisone orally twice daily on days 1 to 5, 40 mg/d on days 6 to 10, and 20 mg/d on days 11 to 20. This regimen has generally proven to be safe despite concern about its effects on other opportunistic infections. The use of steroids as adjunctive therapy in HIV-infected patients with mild pneumocystosis or in non-HIV-infected patients remains to be evaluated.

PREVENTION

Primary prophylaxis is indicated for HIV-infected patients at high risk of developing pneumocystosis -- that is, those who have CD4+ cell counts of <200/uL, unexplained fever [>37.8°C (100° F)] for ³2 weeks, or a history of oropharyngeal candidiasis. Guidelines for the administration of primary prophylaxis to other immunocompromised hosts are less clear. Secondary prophylaxis is indicated for all patients who have recovered from *P. carinii* pneumonia. Among HIV-infected patients, the risk of recurrent episodes of pneumocystosis is high and lifelong; among non-HIV-infected patients, the risk is lower and exists for as long as the immunosuppressive condition persists.

Several antimicrobial drugs are effective in preventing pneumocystosis, although some concern has been raised about possible resistance. One double-strength tablet ofTMP-SMZ(160 mg TMP, 800 mg SMZ) per day is the prophylactic regimen of choice. The major limitation of TMP-SMZ treatment is the high frequency of adverse reactions among HIV-infected patients. Recommended alternative regimens include TMP-SMZ at a reduced dose (80 mg TMP, 400 mg SMZ) or frequency (3 times per week), dapsone alone at a daily oral dose of 100 mg, dapsone at a dose of 50 mg/d combined with weekly oral doses of pyrimethamine (50 mg) and folinic acid (25 mg), pentamidine at a monthly dose of 300 mg administered by Respigard nebulizer, and atovaquone at an oral dose of 1500 mg/d.

Although there are no specific recommendations for preventing the spread of *P. carinii* in health care facilities, it seems prudent to prevent direct contact between patients with pneumocystosis and other susceptible hosts.

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SECTION 16 -PROTOZOAL AND HELMINTHIC INFECTIONS: GENERAL CONSIDERATIONS

210. APPROACH TO THE PATIENT WITH PARASITIC INFECTION - *Peter F. Weller*

Because diverse parasitic organisms may infect humans, a range of factors are germane to an assessment of the possible parasitic etiology of a patient's disease. These factors include issues related to the patient's history, immune status, and presenting clinical and laboratory characteristics, especially eosinophilia. Complementing historical information, a full clinical evaluation and laboratory testing provide additional data to direct the assessment for parasitic infection. The specific tests required, ranging from standard blood biochemical assays to imaging of selected organs, are dictated by the nature of the patient's illness. Additional diagnostic testing for parasitic infections (Chap. 211) completes the evaluation.

HISTORY

Geographic History The history can provide valuable information about potential exposures to parasitic infections. A history of travel to, residence or work in, or immigration from areas of the world in which various parasites not endemic in the United States are encountered offers a clue to possible parasitic or other infectious etiologies of a patient's disease (Chap. 123). Some parasitic infections may become manifest early after a traveler's return home; paramount among these in terms of preventable mortality is malaria. If a patient has been in a region of the world where malaria is endemic (even only briefly, as in an airport layover), fever mandates a consideration of malaria, whether or not malaria chemoprophylaxis has been used. Falciparum malaria, which in a nonimmune patient may progress rapidly to serious and even life-threatening consequences (Chap. 214), is a potential medical emergency and must be considered at the initial evaluation, even if symptoms and fever patterns are suggestive of less specific flulike or gastrointestinal illness. Rarely, malaria transmission has been reported within the United States.

For patients with a history of recent travel, the onset of gastrointestinal symptoms only after return suggests protozoal diseases characterized by a 1- to 2-week delay between acquisition and appearance of symptoms -- notably, giardiasis, cyclosporiasis, and cryptosporidiosis (Chap. 218). Gastrointestinal symptoms lasting longer than a week also suggest protozoan etiologies, including giardiasis, amebiasis, and cyclosporiasis. For patients who have traveled less recently, information on the specific countries and the types of regions (urban or rural) visited and on the nature and duration of the visit, whether for general tourism or for activities related to specific occupations, is helpful in concert with presenting clinical features and hematologic and other laboratory findings. Diseases that may become manifest only some years after an individual leaves an endemic region include schistosomiasis, some forms of filariasis, strongyloidiasis, echinococcosis, and cysticercosis.

For the illnesses of patients who have never left the United States, various parasitic etiologies should be considered, depending on the presenting disease. Trichomoniasis, trichinellosis, strongyloidiasis, giardiasis, cryptosporidiosis, cyclosporiasis, echinococcosis, and pinworm are among the parasitic infections endemic in settings

within the United States. Diseases that are more frequent where there is fecal contamination of soil or other environmental sites include hookworm, ascariasis, trichuriasis, amebiasis, and strongyloidiasis; dermal exposure, as by walking barefoot on soil contaminated with parasitic larvae, predisposes residents of such an area as well as travelers to the acquisition of cutaneous larva migrans, hookworm, and strongyloidiasis.

Dietary History If more than one patient develops similar symptoms in a given situation, common-source water- or foodborne diseases (giardiasis, cryptosporidiosis, cyclosporiasis) should be considered. Waterborne infections are more likely to be acquired from surface water supplies, ranging from mountain streams to municipal reservoirs. Likewise, attention to dietary history may be helpful. Trichinellosis should be considered when the patient may have consumed contaminated pork, bear, walrus, or other meat from carnivores. Ingestion of undercooked fish predisposes to anisakiasis and to infection with other fish-dwelling nematodes, tapeworms (*Diphyllobothrium latum*), or flukes (*Nanophyetus salmincola*). Ingestion of snails or of produce contaminated with land snails can lead to infection with *Angiostrongylus cantonensis* (eosinophilic meningitis;Chap. 219). Ingestion of more exotic animal foodstuffs, including snakes, can result in the transmission of gnathostomiasis (Chap. 219). For children with a propensity for pica, ingestion of soil containing *Toxocara* eggs may lead to visceral larva migrans. Consumption of ground-grown vegetables, including those shipped in from distant fields contaminated with human feces, provides an opportunity for the ingestion of nematode eggs of *Ascaris lumbricoides* or *Trichuris trichiura*.

Other Exposure Histories An antecedent blood transfusion raises the possibility of malaria (especially that due to *Plasmodium malariae* or *P. falciparum*), babesiosis, or Chagas' disease. A history of wading or swimming in fresh water is germane to the acquisition of schistosomiasis or avian schistosome dermatitis. Fresh water may be a source of infection with free-living amebae, and these protozoa may cause meningoencephalitis or ocular infections. Arthropod vector-borne parasitic infections include malaria and lymphatic filariasis (carried by mosquitoes) and babesiosis (carried by ticks); the latter is transmitted in some regions of the United States.

Residence in an institutional setting where fecal-oral hygiene may be imperfect raises the possibility of giardiasis, cryptosporidiosis, or strongyloidiasis. Child-care centers provide opportunities for young children and their family members to acquire giardiasis, cryptosporidiosis, and pinworm infections. Trichomoniasis is transmitted sexually; giardiasis, cryptosporidiosis, amebiasis, and strongyloidiasis can be transmitted during anal intercourse or oral-anal contact.

IMMUNE STATUS

The patient's immune status is relevant in determining which parasitic infections need to be considered. In patients infected with HIV-1, especially those with depressed CD4+ lymphocyte counts, specific protozoan diseases may develop opportunistically. These infections include toxoplasmosis, isosporiasis, cyclosporiasis, cryptosporidiosis, visceral leishmaniasis, American trypanosomiasis, microsporidiosis, and infections with free-living amebae (*Acanthamoeba* and related genera). In individuals infected with human T-lymphotropic virus type 1, strongyloidiasis is a prominent consideration.

Patients who are asplenic are at risk not only for overwhelming infections due to encapsulated bacteria but also for fulminant infections caused by intraerythrocytic protozoa, including malaria and babesiosis. Patients with hypogammaglobulinemia or cystic fibrosis may develop refractory giardiasis. In patients developing symptoms of enterocolitis while receiving glucocorticoids, the possibility of an exacerbation of unsuspected strongyloidiasis or amebic colitis should be considered.

EOSINOPHILIA

Eosinophilia may offer a hematologic clue to the presence of some parasites. Only two protozoan parasites have been associated with eosinophilia: *Isospora belli* and, on occasion, *Dientamoeba fragilis*. The detection of eosinophilia generally mandates a consideration of the multicellular helminthic parasites that characteristically elicit interleukin 5-mediated eosinophilia. (Helminth-elicited eosinophilia, however, may be suppressed by glucocorticoid therapy or by intercurrent bacterial or viral infections.) The magnitude of eosinophilia tends to correlate with the extent of tissue invasion by helminths. Marked blood eosinophilia (more than 3000 eosinophils per microliter) develops during the early transpulmonary migration of intestinal nematodes, including *Ascaris* and hookworms, at a time when eggs (whose presence confirms the diagnosis) have not yet been produced in the intestinal tract.

Eosinophilia is also marked in the early stages of fluke infections, including schistosomiasis (Katayama fever), paragonimiasis, clonorchiasis, and fascioliasis; during the stage of muscle invasion in trichinellosis; during tissue migration of adult worms in loiasis and gnathostomiasis; and with heavy infections in visceral larva migrans. Eosinophilia persisting for more than a year may be indicative of hookworm infection, strongyloidiasis, visceral larva migrans (especially in children), filarial infection (including onchocerciasis, loiasis, and tropical pulmonary eosinophilia), fluke infections (including schistosomiasis, fascioliasis, clonorchiasis, and paragonimiasis), and cysticercosis. Leakage of fluids from echinococcal cysts can cause intermittent increases in eosinophilia.

Eosinophilia sometimes provides the only clue to the presence of helminthic infection and should prompt an evaluation for such infection. Serologic testing for schistosomiasis, filariasis, visceral larva migrans, and strongyloidiasis will be helpful in an assessment for some of the diseases most likely to elicit eosinophilia. Serologic evaluation for strongyloidiasis is especially important since autoinfection may permit persistence of the organisms for decades and put the patient at risk for disseminated disease if immunosuppressive glucocorticoids are later administered for any reason.

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211. LABORATORY DIAGNOSIS OF PARASITIC INFECTIONS - *Charles E. Davis*

The cornerstone for the diagnosis of parasitic infections is a thorough history of the patient's illness. Epidemiologic aspects of the illness are especially important because the risks of acquiring many parasites are closely related to occupation, recreation, or travel to areas of high endemicity. Without a basic knowledge of the epidemiology and life cycles of the major parasites, it is difficult to approach the diagnosis of parasitic infections systematically. Accordingly, the medical classification of important human parasites in this chapter emphasizes their geographic distribution, their transmission, and the anatomic location and stages of their life cycle in humans. The text and tables are intended to serve as a guide to the correct diagnostic procedures for the major parasitic infections and to direct the reader to other chapters that contain more comprehensive information about each infection.Tables 211-1,211-2, and211-3summarize the geographic distributions, the anatomic locations, and the laboratory methods employed for the diagnosis of flatworm, roundworm, and protozoal infections, respectively.

In addition to selecting the correct diagnostic procedures, physicians must counsel their patients to ensure that specimens are collected properly and arrive at the laboratory promptly. For example, the diagnosis of bancroftian filariasis is unlikely to be confirmed by the laboratory unless blood is drawn near midnight, when the nocturnal microfilariae are active. Laboratory personnel and surgical pathologists should be notified in advance when a parasitic infection is suspected. Continuing interaction with the laboratory staff and the surgical pathologists increases the likelihood that parasites in body fluids or biopsy specimens will be examined carefully by the most capable individuals.

INTESTINAL PARASITES

Most helminths and protozoa exit the body in the fecal stream. The patient or the patient's attendant should be instructed to collect feces in a clean cardboard container and to record the time of collection on the container. Contamination with water, which could contain free-living protozoa, or with urine should be avoided. Fecal samples should be collected before ingestion of barium or other contrast agents for radiologic procedures and before treatment with antidiarrheal agents and antacids, because these substances change the consistency of the feces and interfere with microscopic detection of parasites. Because of the cyclic shedding of most parasites in the feces, a minimum of three samples collected on alternate days should be examined. When delays in transport to the laboratory are unavoidable or specimens must be shipped by mail, fecal samples should be kept in polyvinyl alcohol to preserve protozoal trophozoites. Refrigeration will also preserve trophozoites for a few hours and protozoal cysts and helminthic ova for several days.

Analysis of fecal samples consists of both a macroscopic and a microscopic examination. Watery or loose stools are more likely to contain protozoal trophozoites, but protozoal cysts and all stages of helminths may be found in formed feces. If adult worms or tapeworm segments are observed, they should be transported promptly to the laboratory or washed and preserved in fixative for later examination. The only tapeworm with motile segments is *Taenia saginata*, the beef tapeworm, which patients sometimes bring to the physician. Motility is an important distinguishing characteristic, because the

ova of *T. saginata* and *T. solium*, the cause of cysticercosis, are morphologically indistinguishable.

Microscopic examination of feces (Table 211-4) is not complete until direct wet mounts have been evaluated and concentration techniques as well as permanent stains have been applied. Before accepting a report of negativity for ova and parasites as final, the physician should insist that the laboratory undertake each of these procedures. Some intestinal parasites are more readily detected in material other than feces. For example, use of the string test (or one of its commercial substitutes) to sample duodenal contents is sometimes necessary to detect *Giardia lamblia*, *Cryptosporidium*, and *Strongyloides* larvae. Use of the "Scotch tape" technique to detect pinworm ova on the perianal skin sometimes also reveals ova of *T. saginata* deposited perianally when the motile segments disintegrate (Table 211-4).

Two routine solutions are used to make wet mounts for the identification of the various life stages of helminths and protozoa: physiologic saline for trophozoites, cysts, ova, and larvae and dilute iodine solution for protozoal cysts and ova. Iodine solution must never be used to examine specimens for trophozoites because it kills the parasites and thus eliminates their characteristic motility.

The two most common concentration procedures for detecting small numbers of cysts and ova are formalin-ether sedimentation and zinc sulfate flotation. The formalin-ether technique is preferable, because all parasites sediment but not all float. Slides permanently stained for trophozoites should be prepared before concentration. Additional slides stained for cysts and ova may be made from the concentrate.

In many instances, especially in the differentiation of *Entamoeba histolytica* from other amebas, identification of parasites from wet mounts or concentrates must be considered tentative. Permanently stained smears allow study of the cellular detail necessary for definitive identification. The iron-hematoxylin stain is excellent for critical work, but trichrome staining, which can be completed in 1 h, is a satisfactory alternative that also reveals parasites in specimens preserved in polyvinyl alcohol fixative.

BLOOD AND TISSUE PARASITES

Invasion of tissue by protozoa and helminths renders the choice of diagnostic techniques more difficult. For example, physicians must understand that aspiration of an amebic liver abscess rarely reveals *E. histolytica* because the trophozoites are located primarily in the abscess wall. They must remember that the urine sediment offers the best opportunity to detect *Schistosoma haematobium* in the Ethiopian youngster or the American traveler who returns from Africa with hematuria (Table 211-5).Tables 211-1,211-2, and211-3, which offer a quick guide to the geographic distribution and anatomic locations of the major tissue parasites, should help the physician to select the appropriate body fluid or biopsy site for microscopic examination.Tables 211-5,211-6, and211-7provide additional information about the identification of parasites in samples from specific anatomic locations. The laboratory procedures for detection of parasites in other body fluids are similar to those used in the examination of feces. The physician should insist on wet mounts, concentration techniques, and permanent stains for all body fluids. The trichrome or iron-hematoxylin stain is satisfactory for all tissue

helminths in body fluids other than blood, but microfilarial worms and blood protozoa are more easily visualized when stained with Giemsa or Wright's stain.

The most common parasites detected in Giemsa-stained blood smears are the plasmodia, microfilariae, and African trypanosomes (Table 211-5). Most patients with Chagas' disease present in the chronic phase, when *Trypanosoma cruzi* is no longer microscopically detectable in blood smears. Wet mounts are sometimes more sensitive than stained smears for the detection of microfilariae and African trypanosomes because these active parasites cause noticeable movement of the erythrocytes in the microscopic field. Nuclepore filtration of blood facilitates the detection of microfilariae. The intracellular amastigote forms of *Leishmania* spp. and *T. cruzi* can sometimes be visualized in stained smears of peripheral blood, but aspirates of the bone marrow, liver, and spleen are the best sources for microscopic detection and culture of *Leishmania* in kala-azar and of *T. cruzi* in chronic Chagas' disease.

The diagnosis of malaria and the critical distinction among the various *Plasmodium* spp. are made by microscopic examination of stained thick and thin blood films (Table 211-6;Plates VI-3,VI-4,VI-5,VI-6,VI-7,VI-8,VI-9,VI-10,VI-11,VI-12,VI-13,VI-14,VI-15,VI-16,VI-17,VI-18, VI-19,VI-20,VI-21,VI-22,VI-23,VI-24,VI-25,VI-26,VI-27,VI-28,VI-29,VI-30,VI-31,VI-32, andVI-33). Most malariologists prefer Giemsa stain because of its overall high quality, suitability for staining of both thick and thin smears, and stability in tropical climates. Wright's stain can produce high-quality thin smears and is widely used in the Americas, but it deteriorates rapidly in the tropics because its methanol base is highly hygroscopic. Specimens of capillary or venous blood should be obtained every 4 to 12 h until a diagnosis is established. The thin smear is made on clean slides exactly like a blood film for a white blood cell differential. The thick film is made by placing one drop of blood on the slide and stirring it in a circular motion to a diameter of about 2 cm. The erythrocytes in the thick film are lysed with water, but the thin film is fixed in methanol to preserve erythrocyte morphology.

Although most tissue parasites stain with the traditional hematoxylin and eosin, surgical biopsy specimens should also be stained with appropriate special stains. The surgical pathologist who is accustomed to applying silver stains for *Pneumocystis carinii* to induced sputum and transbronchial biopsies may have to be reminded to examine wet mounts and iron-hematoxylin-stained preparations of pulmonary specimens for helminthic ova and *E. histolytica*. The clinician should also be able to advise the surgeon and pathologist about optimal techniques for the identification of parasites in specimens obtained by certain specialized minor procedures (Table 211-7). For example, the excision of skin snips for the diagnosis of onchocerciasis, the collection of rectal snips for the diagnosis of schistosomiasis, and punch biopsy of skin lesions for the identification and culture of cutaneous and mucocutaneous species of *Leishmania* are simple procedures, but the diagnosis can be missed if the specimens are improperly obtained or processed.

NONSPECIFIC TESTS

Eosinophilia is a common accompaniment of infections with most of the tissue helminths; absolute numbers of eosinophils may be high in trichinosis and the migratory

phases of filariasis (Table 211-8). Intestinal helminths provoke eosinophilia only during pulmonary migration of the larval stages. Eosinophilia is not a manifestation of protozoal infections, with the possible exceptions of those due to *Isospora* and *Dientamoeba fragilis*.

Like the hypochromic, microcytic anemia of heavy hookworm infections, other nonspecific laboratory abnormalities may suggest parasitic infection in patients with appropriate geographic and/or environmental exposures. Biochemical evidence of cirrhosis or an abnormal urine sediment in an African immigrant certainly raises the possibility of schistosomiasis, and anemia and thrombocytopenia in a febrile traveler or immigrant are among the hallmarks of malaria. Computed tomography and magnetic resonance imaging also contribute to the diagnosis of infections with many tissue parasites and have become invaluable adjuncts in the diagnosis of neurocysticercosis and cerebral toxoplasmosis.

ANTIBODY AND ANTIGEN DETECTION

Useful antibody assays for many of the important tissue parasites are available; those listed inTable 211-9 can be obtained from the Centers for Disease Control and Prevention (CDC) in Atlanta. The results of most serologic tests not listed in the tables and not offered by the CDC should be interpreted with caution.

The value of antibody assays is limited in the case of the filarial worms and plasmodia. The detection of antibody to plasmodia is of limited use for establishing the diagnosis of malaria in individual patients because diagnostic titers develop slowly and the tests must be sent to the CDC. Filarial antigens cross-react with those from other nematodes, and antibody assays do not distinguish between past and current infection. In contrast, a negative result in an American or European traveler virtually rules out the diagnosis of bancroftian or brugian filariasis. Promising new assays for filarial antigens and antibodies in lymphatic filariasis are not yet available in commercial kits or from theCDC.

Despite these specific limitations, the restricted geographic distribution of many tropical parasites increases the diagnostic usefulness of antibody detection in travelers from industrialized countries. On the other hand, a large proportion of the world has been exposed to *Toxoplasma gondii*, and the presence of IgG antibody does not constitute proof of active disease.

Fewer antibody assays are available for the diagnosis of infection with intestinal parasites. Cross-reactivity and lack of efficient cultivation techniques, along with the ability to establish diagnoses without invasive procedures, have discouraged intensive investigation of these methods. *E. histolytica* is the major exception. Sensitive, specific serologic tests are invaluable in the diagnosis of amebiasis. Commercial kits for the detection of antigen by enzyme-linked immunosorbent assay or of whole organisms by fluorescent antibody assay are now available for several protozoan parasites (Table 211-9).

MOLECULAR TECHNIQUES

DNA hybridization with probes that are repeated many times in the genome of a specific

parasite and amplification of a specific DNA fragment by the polymerase chain reaction (PCR) are promising techniques for the diagnosis of parasitic infections. Although molecular techniques for the detection of many parasites are already being used in insect vectors, animal models, and human trials, few are available for routine use in patients at this time. The only available commercial kit is that for the identification of *Trichomonas vaginalis* by hybridization of secretions from vaginal swabs with synthetic oligonucleotide probes. TheCDC will perform PCR for microsporidia, cryptosporidia, *Cyclospora*, and *E. histolytica* on stools (frozen or fixed in either potassium dichromate or ethanol) and on biopsy and bronchoalveolar lavage samples (fixed in methanol or ethanol). For *Plasmodium* and *Babesia*, PCR is performed on blood treated with EDTA or collected in IsoCode Stix (Schleicher and Schuell).

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212. THERAPY FOR PARASITIC INFECTIONS - *Thomas A. Moore*

Over the last few decades, the reach of some parasitic diseases such as malaria has extended because of factors such as deforestation, population shifts, global warming, and other climatic events (e.g., "El Nino"). Efforts to combat this trend are complicated by the development and spread of drug resistance among parasites and the limited introduction of new antiparasitic agents. However, significant advances toward the reduction of the burden of parasitic disease have been made. The generous donation of ivermectin and albendazole for global eradication programs has improved the health of countless individuals and offers the promise of disease eradication. The expanded use of traditionally nonparasitic agents, such as amphotericin B for visceral leishmaniasis, has offered hope against the specter of drug resistance. The introduction of newer agents, such as triclabendazole, also appears promising.

Currently recommended treatment options for most parasitic diseases of humans are listed inTable 212-1. A brief summary of some of the agents can be found below; each agent is listed by its generic name. Many of the agents are approved by the Food and Drug Administration (FDA) but are considered investigational for the treatment of certain infections; these drugs are marked accordingly in Table 212-1. Drugs marked in the text with an asterisk (*) are available only through the Centers for Disease Control and Prevention (CDC) Drug Service (telephone: 404-639-3670). Other drugs, marked with a dagger (+), are available only through the manufacturer; contact information for these manufacturers may be available from the CDC. Information on dosing in children and pregnant women can be obtained in the references at the end of the chapter.

Albendazole This benzimidazole derivative has recently become generally available and is active against a broad range of helminths and protozoa. All benzimidazoles act by binding to freeb-tubulin, inhibiting the polymerization of tubulin and the microtubule-dependent uptake of glucose. In helminths, the result is the depletion of glycogen stores, but this fundamental disruption of cellular metabolism also offers treatment for a wide range of parasitic diseases. Like all benzimidazoles, albendazole is poorly absorbed from the gastrointestinal tract. However, since the active metabolite attains higher serum and cyst concentrations than mebendazole, it is more effective against echinococcal disease. Significant adverse reactions are usually limited to prolonged use and include abdominal pain and reversible hepatic dysfunction. Rarely, leukopenia and reversible alopecia occur. Albendazole is contraindicated in early pregnancy.

Artesunate and Artemether Artesunate, artemether, and the parent compound artemisinin are sesquiterpene lactones derived from the wormwood plant *Artemisia annua*. These agents have become first-line treatments for severe falciparum malaria in some areas of the world where drug resistance is a major problem. They are rapidly effective against the asexual blood forms of *Plasmodium* spp., including multidrug-resistant *P. falciparum*, but they are not active against intrahepatic forms. Their mechanism of action is not completely understood, but they are believed to act by converting to free radicals and other intermediates in the presence of intraparasitic iron; the result is alkylation of parasite proteins or membrane damage. Artemisinin derivatives presently show no cross-resistance with known antimalarials and thus are important for treating severe malaria in areas of multidrug resistance. However, long treatment

courses are required and, when these agents are used alone, recrudescence may occur. Artemisinin and its derivatives are cleared rapidly from the circulation, and their short half-lives limit their use for prophylaxis. Adverse events are usually infrequent and mild and include drug fever and contact dermatitis. Animal data suggest that neurotoxicity can develop if the compounds are administered chronically, and cerebellar dysfunction has been reported in persons treated with artesunate. These drugs are not available in the United States.

Amphotericin B Amphotericin exerts its effect by inserting itself into the cytoplasmic membrane of the organism and binding sterols, causing membrane permeability. Amphotericin B deoxycholate, a lipophilic polyene drug, is an effective agent for the treatment of leishmaniasis and amebic meningoencephalitis due to *Naegleria* spp., but its use is associated with significant nephrotoxicity and occasional allergic reactions. Three lipid-complexed formulations of amphotericin B have been released: amphotericin B colloidal dispersion (ABCD), amphotericin B lipid complex (ABLC), and liposomal amphotericin B. These agents are effective against antimony-resistant visceral leishmaniasis and offer the benefits of shorter courses and less toxicity.

Atovaquone Atovaquone is a hydroxynaphthoquinone that exerts its broad-spectrum antiprotozoal activity via inhibition of parasite mitochondrial electron transport. Although it has relatively poor bioavailability, atovaquone exhibits potent activity against toxoplasmosis when used with pyrimethamine. When combined with proguanil or doxycycline, it is effective for both treatment and prophylaxis of malaria. Side effects are rare but can include nausea and a maculopapular rash.

Azithromycin An azalide antibiotic, azithromycin has been used to treat a number of protozoal infections such as babesiosis, malaria, toxoplasmosis, and cryptosporidiosis. Azithromycin acts by inhibiting protein synthesis; in apicomplexan parasites, this inhibition occurs in the plastid. Most adverse reactions are gastrointestinal (diarrhea, nausea, abdominal pain) and uncommon and rarely require discontinuation of the drug.

Benznidazole This oral nitroimidazole derivative is used to treat acute Chagas' disease, and cure rates of 80 to 90% have been recorded. Benznidazole acts by generating oxygen radicals to which the parasite is more sensitive than mammalian cells because of a relative deficiency in antioxidant enzymes. Adverse effects are frequent and include rashes, nausea, paresthesias, and leukopenia. The safety of benznidazole in early pregnancy has not been established, but the drug should be used immediately after the first trimester to prevent congenital transmission. Benznidazole is currently unavailable in the United States.

Bithionol* Bithionol is a phenolic substance structurally related to hexachlorophene. Its antihelminthic activity is poorly understood, but the agent is believed to inhibit oxidative phosphorylation. Bithionol is no longer manufactured. A dwindling supply is available from the CDC for treatment of fascioliasis and paragonimiasis. The drug's distribution is limited to physicians treating patients with one of these diseases who are unable to use praziquantel because of previous idiosyncratic or allergic reactions or in whom a course of praziquantel has failed to eradicate infection. Significant side effects are common and include abdominal pain, diarrhea, and urticaria.

Chloroquine The best-known of the 4-aminoquinolines, chloroquine has marked, rapid schizonticidal and gametocidal activity against blood forms of *P. ovale* and *P. malariae* and against susceptible strains of *P. vivax* and *P. falciparum*. It is not active against intrahepatic forms (*P. vivax* and *P. ovale*). Chloroquine is concentrated in the acidic food vacuoles of intraerythrocytic parasites, where it reaches levels 600-fold higher than plasma levels. The drug inhibits a parasite heme polymerase that protects the parasite from the membrane-damaging byproducts of hemoglobin degradation; as a result of this inhibition, the parasite is effectively killed with its own metabolic waste. Chloroquine resistance appears to arise as a result of a decreased level of chloroquine uptake. This drug is safe for use in pregnancy. Adverse reactions include pruritus, transient headaches, and nausea.

Clindamycin This macrolide is an effective adjunct for the treatment of several protozoal infections, including toxoplasmosis, malaria, and babesiosis. The most significant potential adverse reaction is the development of *Clostridium difficile*-associated diarrhea. When administered with quinine, clindamycin is active against drug-resistant falciparum malaria; this combination is the therapy of choice for babesiosis.

Diethylcarbamazine* A piperazine derivative with a long history of successful use, this drug remains the treatment of choice for lymphatic filariasis and loiasis and has also been used for visceral larva migrans. Diethylcarbamazine exerts effects on helminths, including immobilization due to a decrease in muscle activity, disruption of microtubule formation, and alteration of helminthic surface membranes resulting in enhanced killing by the host's immune system. In addition, this agent enhances adherence properties of eosinophils. It is safe for use in pregnancy and well tolerated. Significant adverse events associated with the drug, including encephalopathy and death, are attributable to the parasite burden, which is best assessed by the degree of microfilaremia. Use in patients with onchocerciasis can precipitate a Mazzotti reaction with pruritus, fever, and arthralgias. Untoward effects produced directly by diethylcarbamazine usually involve the gastrointestinal tract and are dose-related.

Eflornithine (Difluoromethylornithine, DFMO)+ This ornithine derivative has specific activity against all stages of infection with *Trypanosoma brucei gambiense* and acts by irreversibly inhibiting ornithine decarboxylase -- an enzyme critical to the formation of polyamines, which are essential to trypanosomatids. Eflornithine readily crosses the blood-brain barrier and is excreted mainly by the kidneys. Its use is contraindicated in pregnancy. Adverse reactions, which are usually mild and reversible, include pancytopenia, diarrhea, and transient hearing loss.

Furazolidone This nitrofuran derivative, which is an effective alternative agent for the treatment of giardiasis, acts by damaging parasite DNA. Since it is the only agent active against *Giardia* that is available in liquid form, it is often used to treat young children. Side effects include allergic reactions, nausea, vomiting, and disulfiram-like reactions when ingested with alcohol. Because hemolytic anemia due to glutathione instability can occur, furazolidone treatment is contraindicated in mothers who are breast-feeding and in neonates.

Halofantrine An oral alternative drug for treatment of malaria due to

chloroquine-resistant *P. falciparum*, this 9-phenanthrenemethanol is one of three classes of arylaminoalcohols first identified as potential antimalarial agents by the World War II Malaria Chemotherapy Program. Its activity is believed to be similar to that of chloroquine. Halofantrine is generally well tolerated; the most commonly reported adverse effects are abdominal pain and diarrhea. The incidence of pruritus is lower than that with chloroquine. Halofantrine causes dose-related prolongation of the PR and QT intervals, and its use is contraindicated in persons who have cardiac disease or who have taken mefloquine in the preceding 3 weeks. Halofantrine treatment is also contraindicated in pregnant and lactating women. The drug is currently unavailable in the United States.

Iodoquinol This hydroxyquinoline is an effective luminal agent for the treatment of amebiasis, balantidiasis, and infection with *Dientamoeba fragilis*. Its mechanism of action is unknown. Adverse effects include headache, diarrhea, nausea, vomiting, abdominal pain, pruritus, fever, seizures, and encephalopathy. Most serious are the reactions related to prolonged high-dose therapy, which should not occur if the dosage regimens recommended inTable 212-1 are followed. Because the drug contains iodine, it should be used with caution in patients with thyroid disease.

Ivermectin This derivative of avermectin is used to treat infections caused by a wide range of helminths. It is the drug of choice for the treatment of onchocerciasis, strongyloidiasis, and cutaneous larva migrans. While active against the intestinal helminths *Ascaris lumbricoides* and *Enterobius vermicularis*, it is variably effective in trichuriasis and ineffective against hookworms. Recent data suggest that ivermectin acts by opening neuromuscular membrane-associated glutamate-dependent chloride channels (unique to nematodes and arthropods) -- an event resulting in an influx of chloride ions, worm paralysis, and subsequent death by immune or other mechanisms. Ivermectin is generally safe, easy to administer, and well tolerated, but encephalopathy and occasional deaths have been reported when the drug is given to persons with high burdens of *Loa loa* microfilaremia. Ivermectin is not approved for use during pregnancy.

Mebendazole This benzimidazole derivative is widely used for treatment of intestinal helminths and exhibits activity against *Echinococcus granulosus*. Benzimidazoles block parasite microtubule assembly and glucose uptake. Because mebendazole is poorly absorbed, its incidence of side effects is low, but its usefulness in treating tissue helminths is limited. Transient abdominal pain and diarrhea sometimes occur, usually in persons with massive parasite burdens. The use of mebendazole is contraindicated in pregnancy.

Mefloquine Like quinine and chloroquine, this quinoline is active only against the asexual erythrocytic stages of malarial parasites. The mode of action of mefloquine is similar to that of chloroquine, but mefloquine is not concentrated so extensively in the food vacuole and may act on alternative targets in the parasite. Taken as a single dose, it is the preferred drug for prophylaxis of chloroquine-resistant malaria; high doses can be used for treatment. The development of drug-resistant strains of *P. falciparum* in parts of Africa and Southeast Asia is ominous, but mefloquine is still an effective drug in most of the world. It is well tolerated by most persons, but its safety in pregnancy is unknown. Adverse effects are usually dose-related and include nausea and dizziness. Psychosis and seizures occur rarely, but treatment of patients with neuropsychiatric

conditions warrants caution. Concomitant use of quinine, quinidine, or drugs causing b-adrenergic blockade may produce electrocardiographic disturbances or cardiac arrest.

Melarsoprol* This trivalent arsenical is used for the treatment of late-stage East African trypanosomiasis and is not uniformly effective. The drug enters the parasite via an adenosine transporter; resistant strains lack this transport system. Arsenicals react avidly with sulfhydryl groups on proteins and inhibit their function. This is the likely mechanism of action and the cause of the severe adverse effects commonly seen. Encephalopathy is the most serious side effect, usually occurring within 4 days of the initiation of therapy and resulting in death in 6% of recipients.

Metrifonate This organophosphorus compound has selective activity against *Schistosoma haematobium*. It is partially metabolized to 2,2-dimethyldichlorovinyl phosphate (DDVP), a highly active chemical that irreversibly inhibits the acetylcholinesterase enzyme. Schistosomal cholinesterase is more susceptible to this metabolite than is the corresponding human enzyme. Metrifonate's exact mechanism of action is uncertain, but it is believed to inhibit tegumental acetylcholine receptors that mediate glucose transport. Although the drug is well tolerated, recipients experience a transient decrease in plasma cholinesterase activity and should not be exposed to neuromuscular blocking agents or organophosphate insecticides for at least 48 h after treatment. Metrifonate's safety in pregnancy is not established. The drug is currently unavailable in the United States.

Metronidazole Of the nitroimidazoles, only metronidazole has been licensed in the United States. This drug hasFDAapproval only for the treatment of amebiasis and trichomoniasis, although it is currently the drug of choice for giardiasis and trichomoniasis and is an alternative agent for balantidiasis. Metronidazole is reduced by anaerobic metabolism, and the metabolite acts as an electron sink, depriving anaerobes of reducing equivalents. Covalent binding or other interactions of intermediate metabolites of metronidazole with parasite macromolecules may partly explain the efficacy of this agent. Its benefit in dracunculiasis appears to be due to a reduction in inflammation rather than to any specific antihelminthic effect. Metronidazole is generally well tolerated despite common side effects such as nausea, headache, and a metabolic aftertaste. Alcohol should be avoided due to disulfiram-like effects. Although metronidazole has not been approved or recommended for use during pregnancy, it has not been associated with birth defects.

Nifurtimox* This nitrofuran compound is an effective oral agent for the treatment of acute Chagas' disease. Intracellular reduction followed by auto-oxidation yielding oxygen radicals has been suggested as the mode of action of nifurtimox on *Trypanosoma cruzi* and as the basis of its toxicity in humans. Prolonged use is required, but the course may have to be interrupted due to drug toxicity, which develops in 40 to 70% of recipients. Adverse reactions are common, dose related, and reversible. They include nausea, vomiting, abdominal pain, insomnia, seizures, and polyneuritis. Nifurtimox should be avoided in early pregnancy.

Nitazoxanide+This 5-nitrothiazole compound appears to be a safe and effective alternative agent for the treatment of cryptosporidiosis. Its mechanism of action is unknown. It is currently available only from Romark Laboratories in the United States.

Oxamniquine This tetrahydroquinoline derivative is an effective alternative agent for the treatment of schistosomiasis, although susceptibility to this drug exhibits regional variation. In treated adult schistosomes, oxamniquine produces marked tegumental alterations similar to those seen with praziquantel but less rapid (evident 4 to 8 days after treatment). Patients should be warned that their urine may have an intense orange-red color. Side effects are uncommon and usually mild, although hallucinations and seizures have been reported. Oxamniquine has not been shown to be teratogenic or embryotoxic, but its use in pregnancy has not been approved.

Paromomycin This aminoglycoside is an effective oral agent for the treatment of infections due to intestinal protozoa. Like other aminoglycosides, it is poorly absorbed after oral administration and binds to the 30S ribosomal RNA in the aminoacyl-tRNA site, resulting in inhibition of protein synthesis. Paromomycin is well tolerated and safe for use in pregnancy.

Pentamidine Isethionate This diamine is an effective alternative agent for some forms of leishmaniasis and trypanosomiasis. While its mechanism of action remains undefined, it is known to exert a wide range of effects, including interaction with trypanosomal kinetoplast DNA, interference with polyamine synthesis through a decrease in the activity of ornithine decarboxylase, and inhibition of RNA polymerase, ribosomal function, and the synthesis of nucleic acids and proteins. Adverse reactions are common and include hypotension, pancreatitis, hypoglycemia, arrhythmias, and reversible renal failure.

Praziquantel This heterocyclic prazino-isoquinoline derivative is highly active against a broad spectrum of trematodes and cestodes. It disrupts the parasite tegument, resulting in contracture with loss of adherence to host tissues and ultimately disintegration or expulsion. Drug levels are reduced by concomitantly administered glucocorticoids, but cimetidine can be used to offset this problem. Praziquantel is generally well tolerated, but seizures may result in persons with neurocysticercosis. Patients with schistosomiasis who have heavy parasite burdens may develop abdominal discomfort, nausea, headache, dizziness, and drowsiness. Although praziquantel has not been shown to be mutagenic, teratogenic, or embryotoxic, it is preferable to delay treatment until after delivery unless immediate intervention is essential. Because praziquantel is excreted in breast milk, it is recommended that women not nurse on the day(s) of drug administration or for 72 h thereafter.

Primaquine Phosphate This drug is the only agent available for eradication of the hepatic stage of malarial parasites. In order to be effective, it must be metabolized by the host. Although their parasiticidal activity remains unclear, the metabolites are believed to affect both pyrimidine synthesis and the mitochondrial electron transport chain. The major adverse effect of this drug is acute hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Primaquine phosphate is otherwise well tolerated. Its use in pregnancy is contraindicated.

Proguanil (Chloroguanide) This agent, which inhibits plasmodial dihydrofolate reductase, is used with atovaquone for oral treatment of uncomplicated malaria or with chloroquine for prophylaxis in parts of Africa without widespread chloroquine-resistant *P.*

falciparum. Proguanil is quite well tolerated at the usually prescribed doses, but higher doses can produce nausea, vomiting, abdominal pain, and diarrhea. It is not available in the United States.

Pyrantel Pamoate This safe, well-tolerated, and inexpensive pyrimidine derivative depolarizes the neuromuscular junctions of most intestinal nematodes, resulting in irreversible paralysis and allowing natural expulsion of the worms with the host's feces. The drug is poorly absorbed from the gastrointestinal tract and is usually effective in a single dose. It has minimal toxicity at the oral doses used to treat intestinal helminthic infection.

Pyrimethamine When combined with short-acting sulfonamides, this diaminopyrimidine is effective in malaria, toxoplasmosis, and isosporiasis. Unlike mammalian cells, the parasites that cause these infections cannot utilize preformed pyrimidines obtained through salvage pathways but rather rely completely on de novo synthesis of pyrimidines, for which folate derivatives are essential cofactors.

Pyrimethamine-sulfadoxine is an effective adjunctive agent for the oral treatment of uncomplicated malaria due to chloroquine-resistant organisms. However, its usefulness as a first-line agent is limited by the development of resistant strains of *P. falciparum* and *P. vivax*.

When combined with sulfadiazine, pyrimethamine is the treatment of choice for toxoplasmosis, but the duration of the required course of therapy often results in the development of folate deficiency requiring folinic acid supplementation. Sulfadiazine crystals can cause hematuria, and allergic drug reactions due to sulfadiazine often require a switch to clindamycin.

Quinacrine* Quinacrine is the only drug approved by theFDA for the treatment of giardiasis. It is not commercially available but can be obtained from alternative sources through theCDC Drug Service. Quinacrine intercalates into parasite DNA and inhibits nucleic acid synthesis. Side effects are common and include nausea and vomiting, headache, and skin discoloration. Alcohol is best avoided due to a disulfiram-like effect.

Quinine and Quinidine When combined with another agent, the cinchona alkaloid quinine is effective for the oral treatment of both uncomplicated malaria due to chloroquine-resistant strains and babesiosis. Quinine acts rapidly against the asexual blood stages of all forms of human malaria. For severe malaria, only quinidine (the dextroisomer of quinine) is available in the United States. Its use requires cardiac monitoring, and dose reduction is necessary in persons with severe renal impairment. Both quinine and quinidine can produce hypoglycemia. Symptoms of cinchonism (tinnitus, headache, nausea, and visual disturbances) are dose-related and reversible.

Spiramycin+This macrolide antibiotic is used to treat acute toxoplasmosis in pregnancy and congenital toxoplasmosis. Although not yet licensed in the United States, it is available through theFDA. Complications of treatment are rare but can include life-threatening ventricular arrhythmias in neonates.

Sodium Stibogluconate* and Meglumine Antimonate These pentavalent antimony

compounds are first-line agents for the treatment of all forms of leishmaniasis. Despite their use in leishmaniasis for almost 100 years, their mechanism of action against *Leishmania* spp. remains unknown. Presumably, the compounds interfere with parasite metabolism. The drugs are taken up by the reticuloendothelial system, and their activity against *Leishmania* spp. may be enhanced by this localization. Resistance is a major problem in some areas of the world. Side effects are common and generally reversible but require temporary interruption of therapy in many cases. Chemical pancreatitis is almost universal, although it is often asymptomatic. In rare instances, pentavalent antimony compounds produce prolongation of the QT interval, and sudden death due to arrhythmia or cardiac failure has been reported. Arthralgias, myalgias, and headaches occur frequently. Since the drugs' safety in pregnancy has not been established, their use should be avoided if possible in pregnant women. These agents may be used in children >18 months of age.

Suramin* This derivative of urea is the drug of choice for the early stage of African trypanosomiasis. The drug acts by forming stable complexes with proteins, inhibiting multiple enzymes. Suramin has a variety of potentially severe side effects, including anaphylaxis, exfoliative dermatitis, paresthesias, photophobia, and renal dysfunction.

Tetracycline and Doxycycline These antibiotics are useful in the treatment of balantidiasis and *D. fragilis* infection as well as in the oral treatment of uncomplicated malaria due to chloroquine-resistant strains. The tetracyclines inhibit protein synthesis in prokaryotic ribosomes, and they probably have the same activity in parasites. Potential side effects in adults include nausea, vomiting, and photosensitivity dermatitis. Because they can impair normal development of bones and teeth, tetracyclines are contraindicated in pregnant women and children <8 years of age.

Thiabendazole This benzimidazole derivative is a potent antihelminthic agent, but its use in strongyloidiasis and other infections is limited by frequent, severe side effects. Patients most often report dizziness, headache, nausea, and vomiting. Less commonly, hepatitis and severe hypersensitivity reactions develop. The drug's mechanism of action is similar to that of other benzimidazoles. Treatment with thiabendazole is contraindicated in pregnancy.

Tinidazole This nitroimidazole is effective for the treatment of amebiasis, giardiasis, and trichomoniasis. Its mechanism of action and side effects are similar to those seen with metronidazole, but adverse events appear to be less frequent and severe with tinidazole. In addition, tinidazole is potentially curative in a single dose. This agent is currently unavailable in the United States.

Triclabendazole This benzimidazole is effective against paragonimiasis and all stages of *Fasciola hepatica*, a trematode with inherent resistance to praziquantel. The sulfoxide metabolite, which is believed to be responsible for the drug's activity, binds to fluke tubulin and disrupts microtubule-based processes. Triclabendazole is safe and well tolerated and offers single-dose cure. It is currently unavailable in the United States.

Trimethoprim-Sulfamethoxazole This synergistic antifolate compound is active against cyclosporiasis, isosporiasis, and encephalitis due to *Toxoplasma gondii*. Trimethoprim is a dihydrofolate reductase inhibitor whose effect is enhanced by

sulfamethoxazole. Adverse effects, which can be severe, are usually attributable to the sulfonamide component and involve allergic skin reactions, bone marrow suppression, and hemolysis.

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SECTION 17 -PROTOZOAL INFECTIONS

213. AMEBIASIS AND INFECTION WITH FREE-LIVING AMEBAS - *Sharon L. Reed*

AMEBIASIS

DEFINITION

Amebiasis is an infection with the intestinal protozoan *Entamoeba histolytica*. About 90% of infections are asymptomatic, and the remaining 10% produce a spectrum of clinical syndromes ranging from dysentery to abscesses of the liver or other organs.

LIFE CYCLE AND TRANSMISSION

E. histolytica is acquired by ingestion of viable cysts from fecally contaminated water, food, or hands. Food-borne exposure is most prevalent and is particularly likely when food handlers are shedding cysts or food is being grown with feces-contaminated soil, fertilizer, or water. Less common means of transmission include contaminated water, oral and anal sexual practices, and -- in rare instances -- direct rectal inoculation through colonic irrigation devices. Motile trophozoites are released from cysts in the small intestine and, in most patients, remain as harmless commensals in the large bowel. After encystation, infectious cysts are shed in the stool and can survive for several weeks in a moist environment. In some patients, the trophozoites invade either the bowel mucosa, causing symptomatic colitis, or the bloodstream, causing distant abscesses of the liver, lungs, or brain. The trophozoites may not encyst in patients with active dysentery, and motile hematophagous trophozoites are frequently present in fresh stools. Trophozoites are rapidly killed by exposure to air or stomach acid, however, and therefore cannot cause infection.

EPIDEMIOLOGY

About 10% of the world's population is infected with *Entamoeba*, the majority with noninvasive *Entamoeba dispar*. Amebiasis results from infection with *E. histolytica* and is the third most common cause of death from parasitic disease (after schistosomiasis and malaria). Areas of highest incidence (due to inadequate sanitation and crowding) include most developing countries in the tropics, particularly Mexico, India, and nations of Central and South America, tropical Asia, and Africa. The main groups at risk in developed countries are travelers, recent immigrants, homosexual men, and inmates of institutions.

The wide spectrum of clinical disease is caused in part by infection with the two different species of *Entamoeba*. Isolates of *E. histolytica* from patients with invasive amebiasis have unique isoenzymes, surface antigens, DNA markers, and virulence properties and now are recognized as a distinct species from the noninvasive *E. dispar*.

Most asymptomatic carriers, including homosexual men and AIDS patients, harbor *E. dispar* and have self-limited infections. These observations suggest that *E. dispar* is incapable of causing invasive disease, since *Cryptosporidium* and *Isospora belli*, which also cause only self-limited illnesses in immunocompetent people, cause devastating

diarrhea in patients with AIDS. However, host factors play a role as well. In one study, 10% of asymptomatic patients who were colonized with *E. histolytica* went on to develop amebic colitis, while the rest remained asymptomatic and cleared the infection within 1 year.

PATHOGENESIS AND PATHOLOGY

Both trophozoites (Fig. 213-1) and cysts (Fig. 213-2) are found in the intestinal lumen, but only trophozoites of *E. histolytica* invade tissue. The trophozoite is 20 to 60 um in diameter and contains vacuoles and a nucleus with a characteristic central karyosome. In animals, depletion of intestinal mucus, diffuse inflammation, and disruption of the epithelial barrier occur before trophozoites actually come into contact with the colonic mucosa. Trophozoites attach to colonic mucus and epithelial cells by a galactose-inhibitable lectin. The earliest intestinal lesions are microulcerations of the mucosa of the cecum, sigmoid colon, or rectum that release erythrocytes, inflammatory cells, and epithelial cells. Proctoscopy reveals small ulcers with heaped up margins and normal intervening mucosa. Submucosal extension of ulcerations under viable-appearing surface mucosa causes the classic "flask-shaped" ulcer containing trophozoites at the margins of dead and viable tissues. Although neutrophilic infiltrates may accompany the early lesions in animals, human intestinal infection is marked by a paucity of inflammatory cells, probably in part because of the killing of neutrophils by trophozoites. Treated ulcers characteristically heal with little or no scarring. Occasionally, however, full-thickness necrosis and perforation occur.

Rarely, intestinal infection results in the formation of a mass lesion, or *ameboma*, in the bowel lumen. The overlying mucosa is usually thin and ulcerated, while other layers of the wall are thickened, edematous, and hemorrhagic; this condition results in exuberant formation of granulation tissue with little fibrous-tissue response.

A number of virulence factors have been linked to the ability of *E. histolytica* to invade through the interglandular epithelium. One is an extracellular cysteine proteinase that degrades collagen, elastin, secretory IgA, and the anaphylatoxins C3a and C5a. Other enzymes may disrupt glycoprotein bonds between mucosal epithelial cells in the gut. Amebas can lyse neutrophils, monocytes, lymphocytes, and cells of colonic and hepatic cell lines. The cytolytic effect of amebas appears to require direct contact with target cells and may be linked to the release of phospholipase A and pore-forming peptides.

Liver abscesses are always preceded by intestinal colonization, which may be asymptomatic. Blood vessels may be compromised early by lysis of the wall and thrombus formation. Trophozoites invade veins to reach the liver through the portal venous system. *E. histolytica* is resistant to complement-mediated lysis, a property critical to survival in the bloodstream. In contrast, *E. dispar* is rapidly lysed by complement and is thus restricted to the bowel lumen. Inoculation of amebas into the portal system of hamsters results in an acute cellular infiltrate consisting predominantly of neutrophils. Later, the neutrophils are lysed by contact with amebas, and the release of neutrophil toxins may contribute to necrosis of hepatocytes. The liver parenchyma is replaced by necrotic material that is surrounded by a thin rim of congested liver tissue. The necrotic contents of a liver abscess are classically described as "anchovy paste," although the fluid is variable in color and is composed of bacteriologically sterile

granular debris with few or no cells. Amebas, if seen, tend to be found near the capsule of the abscess.

Clinical infection does not induce immunity to recurrent colonization with *E. histolytica*, but repeated episodes of colitis or liver abscess are unusual. Antibody is not protective; titers correlate with the length of illness rather than with the severity of disease. Studies of animals suggest that cell-mediated immunity may be important for protection, although patients with AIDS appear not to be predisposed to more severe disease.

CLINICAL SYNDROMES

Intestinal Amebiasis The most common type of amebic infection is asymptomatic cyst passage. Even in highly endemic areas, most patients harbor *E. dispar*.

Symptomatic amebic colitis develops 2 to 6 weeks after the ingestion of infectious cysts. Lower abdominal pain and mild diarrhea develop gradually and are followed by malaise, weight loss, and diffuse lower abdominal or back pain. Cecal involvement may mimic acute appendicitis. Patients with full-blown dysentery may pass 10 to 12 stools per day. The stools contain little fecal material and consist mainly of blood and mucus. In contrast to those with bacterial diarrhea, fewer than 40% of patients with amebic dysentery are febrile. Virtually all patients have heme-positive stools.

More fulminant intestinal infection, with severe abdominal pain, high fever, and profuse diarrhea, is rare and occurs predominantly in children. Patients may develop toxic megacolon, in which there is severe bowel dilation with intramural air. Patients receiving glucocorticoids are at risk for severe amebiasis. Uncommonly, patients develop a chronic form of amebic colitis, which can be confused with inflammatory bowel disease. The association between severe amebiasis complications and glucocorticoid therapy emphasizes the importance of excluding amebiasis when inflammatory bowel disease is suspected. An occasional patient presents with only an asymptomatic or tender abdominal mass caused by an ameboma, which is easily confused with cancer on barium studies. A positive serologic test or biopsy can prevent unnecessary surgery in this setting. The syndrome of postamebic colitis -- persistent diarrhea following documented cure of amebic colitis -- is controversial; no evidence of recurrent amebic infection can be found, and re-treatment usually has no effect.

Amebic Liver Abscess Extraintestinal infection by *E. histolytica* most often involves the liver. Of travelers who develop an amebic liver abscess after leaving an endemic area, 95% do so within 5 months. Young patients with an amebic liver abscess are more likely than older patients to present in the acute phase with prominent symptoms of <10 days duration. Most patients are febrile and have right-upper-quadrant pain, which may be dull or pleuritic in nature and radiate to the shoulder. Point tenderness over the liver and right-sided pleural effusion are common. Jaundice is rare. Although the initial site of infection is the colon, fewer than one-third of patients with an amebic abscess have active diarrhea. Older patients from endemic areas are more likely to have a subacute course lasting 6 months, with weight loss and hepatomegaly. About one-third of patients with chronic presentations are febrile. Thus, the clinical diagnosis of an amebic liver abscess may be difficult to establish because the symptoms and signs are often nonspecific. Since 10 to 15% of patients present only with fever, amebic liver abscess

must be considered in the differential diagnosis of fever of unknown origin (Chap. 125).

Complications of Amebic Liver Abscess Pleuropulmonary involvement, which is reported in 20 to 30% of patients, is the most frequent complication of amebic liver abscess. Manifestations include sterile effusions, contiguous spread from the liver, and rupture into the pleural space. Sterile effusions and contiguous spread usually resolve with medical therapy, but frank rupture into the pleural space requires drainage. A hepatobronchial fistula may cause cough productive of large amounts of necrotic material that may contain amebas. This dramatic complication carries a good prognosis. Abscesses that rupture into the peritoneum may present as an indolent leak or an acute abdomen and require both percutaneous catheter drainage and medical therapy. Rupture into the pericardium, usually from abscesses of the left lobe of the liver, carries the gravest prognosis; it can occur during medical therapy and requires surgical drainage.

Other Extraintestinal Sites The genitourinary tract may become involved by direct extension of amebiasis from the colon or by hematogenous spread of the infection. Painful genital ulcers, characterized by a punched-out appearance and profuse discharge, may develop secondary to extension from either the intestine or the liver. Both these conditions respond well to medical therapy. Cerebral involvement has been reported in fewer than 0.1% of patients in large clinical series. Symptoms and prognosis depend on the size and location of the lesion.

DIAGNOSTIC TESTS

Laboratory Diagnosis Stool examinations, serologic tests, and noninvasive imaging of the liver are the most important procedures in the diagnosis of amebiasis. Fecal findings suggestive of amebic colitis include a positive test for heme, a paucity of neutrophils, and the presence of Charcot-Leyden crystal protein (double pyramid-shaped crystals normally found in the cytoplasm of eosinophils). The definitive diagnosis of amebic colitis is made by the demonstration of hematophagous trophozoites of *E. histolytica* (Fig. 213-1). Because trophozoites are killed rapidly by water, drying, or barium, it is important to examine at least three fresh stool specimens. Examination of a combination of wet mounts, iodine-stained concentrates, and trichrome-stained preparations of fresh stool and concentrates for cysts (Fig. 213-2) or trophozoites (Fig. 213-1) confirms the diagnosis in 75 to 95% of cases. Cultures of amebas are more sensitive but are not routinely available. If stool examinations are negative, sigmoidoscopy with biopsy of the edge of ulcers may increase the yield, but this procedure is dangerous during fulminant colitis because of the risk of perforation. Trophozoites in a biopsy specimen from a colonic mass confirm the diagnosis of ameboma, but trophozoites are rare in liver aspirates. Accurate diagnosis requires experience, since the trophozoites may be confused with neutrophils and the cysts must be differentiated morphologically from *Entamoeba hartmanni*, *Entamoeba coli*, and *Endolimax nana*, which do not cause clinical disease and do not warrant therapy. Unfortunately, the cysts of *E. histolytica* cannot be distinguished microscopically from those of *E. dispar*. Therefore, the microscopic diagnosis of *E. histolytica* can be made only by the detection of *Entamoeba* trophozoites that have ingested erythrocytes (Fig. 213-1). Diagnostic tests based on the detection of the galactose-inhibitable lectin of *E. histolytica* are now available and compare favorably with the polymerase chain reaction and with isolation in culture

followed by isoenzyme analysis in terms of sensitivity.

Serology is an important addition to the methods used for the parasitologic diagnosis of invasive amebiasis. Kits for the performance of agar gel diffusion assays and ELISAs are commercially available, and the results of these tests are positive in more than 90% of patients with colitis, amebomas, or liver abscess. Positive results in conjunction with the appropriate clinical syndrome suggest active disease because serologic findings usually revert to negative within 6 to 12 months. Even in highly endemic areas such as South Africa, fewer than 10% of asymptomatic individuals have a positive amebic serology. The interpretation of the indirect hemagglutination test is more difficult because titers may remain positive for as long as 10 years.

Up to 10% of patients with acute amebic liver abscess may have negative serologic findings; in suspected cases with an initially negative result, testing should be repeated in a week. In contrast to carriers of *E. dispar*, most asymptomatic carriers of *E. histolytica* develop antibodies. Thus, serologic tests are helpful in assessing the risk of invasive amebiasis in asymptomatic, cyst-passing individuals in nonendemic areas. Serologic tests also should be performed in patients with ulcerative colitis before the institution of glucocorticoid therapy to prevent the development of severe colitis or toxic megacolon owing to unsuspected amebiasis.

Routine hematology and chemistry tests are usually not very helpful in the diagnosis of invasive amebiasis. About three-fourths of patients with an amebic liver abscess have leukocytosis (>10,000 cells/uL); this condition is particularly likely if symptoms are acute or complications have developed. Invasive amebiasis does not elicit eosinophilia. Anemia, if present, is usually multifactorial. Even with large liver abscesses, liver enzyme levels are normal or minimally elevated. The alkaline phosphatase level is most often elevated and may remain so for months. Aminotransferase elevations suggest acute disease or a complication.

Radiographic Studies Radiographic barium studies are potentially dangerous in acute amebic colitis. Amebomas are usually identified first by a barium enema, but biopsy is necessary for differentiation from carcinoma.

Radiographic techniques such as ultrasonography, computed tomography (Fig. 213-3), and magnetic resonance imaging are all useful for detection of the round or oval hypoechoic cyst. More than 80% of patients who have had symptoms for >10 days have a single abscess of the right lobe of the liver. Approximately 50% of patients who have had symptoms for <10 days have multiple abscesses. Findings associated with complications include large abscesses (>10 cm) in the superior part of the right lobe, which may rupture into the pleural space; multiple lesions, which must be differentiated from pyogenic abscesses; and lesions of the left lobe, which may rupture into the pericardium. Because abscesses resolve slowly and may increase in size in patients who are responding clinically to therapy, frequent follow-up ultrasonography may prove confusing. Complete resolution of a liver abscess within 6 months can be anticipated in two-thirds of patients, but 10% may have persistent abnormalities for a year.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of intestinal amebiasis includes bacterial diarrheas caused by *Campylobacter*; enteroinvasive *Escherichia coli*; and *Shigella*, *Salmonella*, and *Vibrio* species. Although the typical patient with amebic colitis has less prominent fever than in these other conditions as well as heme-positive stools with few neutrophils, correct diagnosis requires bacterial cultures, microscopic examination of stools, and amebic serologic testing. As has already been mentioned, amebiasis must be ruled out in any patient thought to have inflammatory bowel disease.

Because of the variety of presenting signs and symptoms, amebic liver abscess can easily be confused with pulmonary or gallbladder disease or with any febrile illness with few localizing signs, such as malaria or typhoid fever. The diagnosis should be considered in members of high-risk groups who have recently traveled outside the United States and in inmates of institutions. Once radiographic studies have identified an abscess in the liver, the most important differential diagnosis is between amebic and pyogenic abscess. Patients with pyogenic abscess typically are older and have a history of underlying bowel disease or recent surgery. Amebic serology is helpful, but aspiration of the abscess, with Gram's staining and culture of the material, may be required for differentiation of the two diseases.

TREATMENT

Intestinal Disease The drugs used to treat amebiasis can be classified according to their primary site of action. Luminal amebicides are poorly absorbed and reach high concentrations in the bowel, but their activity is limited to cysts and trophozoites close to the mucosa. Only two luminal drugs are available in the United States: iodoquinol and paromomycin (Table 213-1). Indications for the use of luminal agents include eradication of cysts in patients with colitis or a liver abscess and treatment of asymptomatic carriers. The majority of asymptomatic individuals who pass cysts are colonized with *E. dispar*, which does not warrant specific therapy. However, unless the presence of *E. dispar* can be proven by specific antigen detection tests and the lack of an antibody response, it may be prudent to treat asymptomatic individuals who pass cysts.

Tissue amebicides reach high concentrations in the blood and tissue after oral or parenteral administration. The development of nitroimidazole compounds, especially metronidazole, was a major advance in the treatment of invasive amebiasis. Patients with amebic colitis should be treated with intravenous or oral metronidazole (750 mg three times daily for 5 to 10 days). Side effects include nausea, vomiting, abdominal discomfort, and a disulfiram-like reaction. Other imidazole compounds, such as tinidazole and ornidazole, are as effective but are not available in the United States. All patients should also receive a full course of therapy with a luminal agent, since metronidazole does not eradicate cysts. Resistance to metronidazole has not been identified. Relapses are not uncommon and probably represent reinfection or failure to eradicate amebas from the bowel because of an inadequate dosage or duration of therapy.

Amebic Liver Abscess Metronidazole is the drug of choice for amebic liver abscess. The usefulness of nitroimidazoles in single-dose or abbreviated regimens is important in endemic areas where access to hospitalization is limited. With early diagnosis and therapy, mortality from uncomplicated amebic liver abscess is<1%. The second-line

therapeutic agents emetine and chloroquine should be avoided if possible because of the potential cardiovascular and gastrointestinal side effects of the former and the higher relapse rates with the latter. There is no evidence that combined therapy with two drugs is more effective than the single-drug regimen. Studies of South Africans with liver abscesses demonstrated that 72% of patients without intestinal symptoms had bowel infection with *E. histolytica*; thus, all treatment regimens should include a luminal agent to eradicate cysts and prevent further transmission. Amebic liver abscess recurs rarely.

Aspiration of Liver Abscesses More than 90% of patients respond dramatically to metronidazole therapy with decreases in both pain and fever within 72 h. Indications for aspiration of liver abscesses are (1) the need to rule out a pyogenic abscess, particularly in patients with multiple lesions; (2) the failure to respond clinically in 3 to 5 days; (3) the threat of imminent rupture; and (4) the prevention of rupture of left-lobe abscesses into the pericardium. There is no evidence that aspiration, even of large abscesses (up to 10 cm), accelerates healing. Percutaneous drainage may be successful even if the liver abscess has already ruptured. Surgery should be reserved for instances of bowel perforation and rupture into the pericardium.

PREVENTION

Amebic infection is spread by ingestion of food or water contaminated with cysts. Since an asymptomatic carrier may excrete up to 15 million cysts per day, prevention of infection requires adequate sanitation and eradication of cyst carriage. In high-risk areas, infection can be minimized by the avoidance of unpeeled fruits and vegetables and the use of bottled water. Because cysts are resistant to readily attainable levels of chlorine, disinfection by iodination (tetraglycine hydroperiodide) is recommended. There is no effective prophylaxis.

INFECTION WITH FREE-LIVING AMEBAS

EPIDEMIOLOGY

Free-living amebas of the genera *Acanthamoeba*, *Naegleria*, and *Balamuthia* are distributed throughout the world and have been isolated from a wide variety of fresh and brackish water, including that from lakes, taps, hot springs, swimming pools, and heating and air-conditioning units, and even from the nasal passages of healthy children. Encystation may protect the protozoa from desiccation and food deprivation. The persistence of *Legionella pneumophila* in water supplies may be attributable in part to chronic infection of free-living amebas, particularly *Naegleria*.

NAEGLERIA INFECTIONS

Primary amebic meningoencephalitis caused by *Naegleria fowleri* follows the aspiration of water contaminated with trophozoites or cysts or the inhalation of contaminated dust, leading to invasion of the olfactory neuroepithelium. After an incubation period of 2 to 15 days, severe headache, high fever, nausea, vomiting, and meningismus develop. Photophobia and palsies of the third, fourth, and sixth cranial nerves are common. Rapid progression to seizures and coma may follow, and most patients die within a week. Infection is most common in otherwise healthy children or young adults, who

often report recent swimming in lakes or heated swimming pools.

Diagnosis depends on the detection of motile trophozoites in wet mounts of fresh spinal fluid. Other laboratory findings resemble those for fulminant bacterial meningitis, with elevated intracranial pressure, high white blood cell counts (up to 20,000 cells/uL), and elevated protein concentrations and low glucose levels in cerebrospinal fluid. The diagnosis should be considered in any patient who has purulent meningitis without evidence of bacteria on Gram's staining, antigen detection assay, and culture. The prognosis is uniformly poor. Only four survivors, treated with high-dose amphotericin B and rifampin, have been reported. Antibodies to *Naegleria* spp. have been detected in normal adults; serologic testing is not useful in the diagnosis of acute infection.

ACANTHAMOEBA INFECTIONS

Granulomatous Amebic Encephalitis Infection with *Acanthamoeba* species follows a more indolent course and occurs typically in chronically ill or debilitated patients. Risk factors include lymphoproliferative disorders, chemotherapy, glucocorticoid therapy, lupus erythematosus, and AIDS. Infection usually reaches the central nervous system hematogenously from a primary focus in the sinuses, skin, or lungs. In the central nervous system, the onset is insidious, and the syndrome often mimics a space-occupying lesion. Altered mental status, headache, and stiff neck may be accompanied by focal findings such as cranial nerve palsies, ataxia, and hemiparesis. In the United States, cutaneous ulcers or hard nodules containing amebas were detected in 8 of 13 AIDS patients with disseminated *Acanthamoeba* infection.

Examination of the cerebrospinal fluid for trophozoites may be diagnostically helpful, but lumbar puncture may be contraindicated because of increased intracerebral pressure. Computed tomography frequently reveals cortical and subcortical lesions of decreased density consistent with embolic infarcts. In other patients, multiple enhancing lesions with edema may mimic the computed tomographic appearance of toxoplasmosis. Demonstration of the trophozoites and cysts of *Acanthamoeba* on wet mounts or in biopsy specimens establishes the diagnosis. Culture on nonnutrient agar plates seeded with *Escherichia coli* may also be helpful. Fluorescein-labeled antiserum is available from the Centers for Disease Control and Prevention (CDC) for the detection of protozoa in biopsy specimens. At least nine cases of granulomatous amebic encephalitis have been reported in patients with AIDS, in whom the disease may have an accelerated course (with survival for only 3 to 40 days) because of their difficulty in forming granulomas. Although studies in animals suggest that rifampin may be useful, the infection is almost uniformly fatal.

Keratitis The incidence of keratitis caused by *Acanthamoeba* has increased in the past 20 years, in part as a result of improved diagnosis. The first of these infections to be recognized were associated with trauma to the eye and exposure to contaminated water. At present, most infections are linked to extended-wear contact lenses. Risk factors include the use of homemade saline, the wearing of lenses while swimming, and inadequate disinfection. Since contact lenses presumably cause microscopic trauma, the early corneal findings may be nonspecific. The first symptoms usually include tearing and the painful sensation of a foreign body. Once infection is established, progression is rapid; the characteristic clinical sign is an annular, paracentral corneal

ring representing a corneal abscess. Deeper corneal invasion and loss of vision may follow.

The differential diagnosis includes bacterial, mycobacterial, and herpetic infection. The irregular polygonal cysts of *Acanthamoeba* (Fig. 213-4) may be identified in corneal scrapings or biopsy material, and trophozoites can be grown on special media. Cysts are resistant to available drugs, and the results of medical therapy have been disappointing. Some reports have suggested partial responses to propamidine isethionate eyedrops. Severe infections usually require keratoplasty.

BALAMUTHIA INFECTIONS

Balamuthia mandrillaris, a free-living ameba previously referred to as a leptomyxid ameba, is an important etiologic agent of amebic meningoencephalitis in immunocompetent hosts. The course is typically subacute, with focal neurologic signs, fever, seizures, and headaches leading to death within 1 week to several months after onset. Examination of cerebrospinal fluid reveals mononuclear pleocytosis, elevated protein levels, and normal to low glucose concentrations. Multiple hypodense lesions are usually detected with imaging studies. The diagnosis is almost always made post-mortem, and specific identification may require immunofluorescence with antibodies from theCDC to differentiate the trophozoites from *Acanthamoeba*.

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214. MALARIA AND BABESIOSIS: DISEASES CAUSED BY RED BLOOD CELL PARASITES - *Nicholas J. White, Joel G. Breman*

"Humanity has but three great enemies: Fever, famine and war; of these by far the greatest, by far the most terrible, is fever."

William Osler

MALARIA

Malaria is a protozoan disease transmitted by the bite of infected *Anopheles* mosquitoes. It is the most important of the parasitic diseases of humans, with transmission in 103 countries affecting more than 1 billion people and causing between 1 and 3 million deaths each year. Malaria has now been eradicated from North America, Europe, and Russia but, despite enormous control efforts, has resurged in many parts of the tropics. Added to this resurgence are the increasing problems of drug resistance of the parasite and insecticide resistance of the vectors. Occasional local transmission following importation of malaria has occurred recently in several southern and eastern areas of the United States and in Europe, indicating the continual danger to nonmalarious countries. Malaria remains today, as it has been for centuries, a heavy burden on tropical communities, a threat to nonendemic countries, and a danger to travelers.

ETIOLOGY AND PATHOGENESIS

Four species of the genus *Plasmodium* cause nearly all malarial infections in humans (although rare infections involve species normally affecting other primates). These are *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* (Table 214-1). Almost all deaths are caused by falciparum malaria. Human infection begins when a female anopheline mosquito inoculates plasmodial sporozoites from its salivary gland during a blood meal (Fig. 214-1). These microscopic motile forms of the malarial parasite are carried rapidly via the bloodstream to the liver, where they invade hepatic parenchymal cells and begin a period of asexual reproduction. By this amplification process (known as intrahepatic or preerythrocytic schizogony or merogony), a single sporozoite eventually may produce 10,000 to more than 30,000 daughter merozoites. The swollen liver cell eventually bursts, discharging motile merozoites into the bloodstream; at this point the symptomatic stage of the infection begins. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain dormant for months to years before reproduction begins. These dormant forms, or hypnozoites, are the cause of the relapses that characterize infection with these two species.

After entry into the bloodstream, merozoites rapidly invade erythrocytes and become trophozoites. Attachment is mediated via a specific erythrocyte surface receptor. In the case of *P. vivax*, this receptor is related to the Duffy blood-group antigen Fy^a or Fy^b. Most West Africans and people with origins in that region carry the Duffy-negative FyFy phenotype and are therefore resistant to *P. vivax* malaria. During the early stage of intraerythrocytic development, the small "ring forms" of the four parasitic species appear similar under light microscopy. As the trophozoites enlarge, species-specific characteristics become evident, pigment becomes visible, and the parasite assumes an

irregular or ameboid shape. By the end of the 48-h intraerythrocytic life cycle (72 h for *P. malariae*), the parasite has consumed nearly all the hemoglobin and grown to occupy most of the red cell. Multiple nuclear divisions take place (merogony), and the red cell ruptures to release 6 to 30 daughter merozoites, each capable of invading a new red cell and repeating the cycle. The disease in human beings is caused by the direct effects of red cell invasion and destruction by the asexual parasite and the host's reaction. After a series of asexual cycles (*P. falciparum*) or immediately (*P. vivax*, *P. ovale*, *P. malariae*), some of the parasites develop into morphologically distinct long-lived sexual forms (gametocytes) that can transmit malaria.

After being ingested in the blood meal of a biting female anopheline mosquito, the male and female gametocytes form a zygote in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which then migrate in the hemolymph to the salivary gland of the mosquito to await inoculation into another human at the next feeding.

EPIDEMIOLOGY

Malaria occurs throughout most of the tropical regions of the world (Fig. 214-2). *P. falciparum* predominates in Africa, New Guinea, and Haiti; *P. vivax* is more common in Central America and the Indian subcontinent. The prevalence of these two species is approximately equal in South America, eastern Asia, and Oceania. *P. malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less common than the other species mentioned. *P. ovale* is relatively unusual outside of Africa and, where it is found, comprises <1% of isolates.

The epidemiology of malaria is complex and may vary considerably even within relatively small geographic areas. Endemicity traditionally has been defined in terms of parasitemia rates or palpable-spleen rates in children 2 to 9 years of age as hypoendemic (<10%), mesoendemic (11 to 50%), hyperendemic (51 to 75%), and holoendemic (>75%). In holo- and hyperendemic areas -- e.g., certain regions of tropical Africa or coastal New Guinea, where there is intense *P. falciparum* transmission and there can be more than one human bite per infected mosquito per day -- people are infected repeatedly throughout their lives. Here, morbidity and mortality during childhood are considerable. Immunity against disease is hard won in these areas, and the young-childhood burden of disease is high; by adulthood, however, most malarial infections are asymptomatic. This situation, with frequent year-round infection, is termed *stable transmission* and generally occurs where there is holo- and hyperendemicity. In areas where transmission is low, erratic, or focal, full protective immunity is not acquired, and symptomatic disease may occur at all ages. This situation usually exists in hypoendemic areas and is termed *unstable transmission*. Even in areas with stable transmission, there is often an increased incidence coinciding with increased mosquito breeding during the rainy season. Malaria behaves like an epidemic disease in some areas, particularly those with unstable malaria, such as northern India, Sri Lanka, Southeast Asia, Ethiopia, southern Africa, and Madagascar. An epidemic can develop when there are changes in environmental, economic, or social conditions, such as heavy rains following drought or migrations (usually of refugees or workers) from a nonmalarious region to an area of high transmission; a breakdown in malaria control

and prevention services can intensify epidemic conditions. This situation usually results in considerable mortality among all age groups.

The principal determinants of the epidemiology of malaria are the number (density), the human-biting habits, and the longevity of the anopheline mosquito vectors. Not all anophelines can transmit malaria, and those that do vary considerably in their efficiency as malaria vectors. More specifically, the transmission of malaria is directly proportional to the density of the vector, the square of the number of human bites per day per mosquito, and the tenth power of the probability of the mosquito's surviving for 1 day. Mosquito longevity is particularly important, because the portion of the parasite's life cycle that takes place within the mosquito -- from gametocyte ingestion to subsequent inoculation (sporogony) -- lasts for 8 to 30 days, depending on ambient temperature; thus, to transmit malaria, the mosquito must survive for longer than 7 days. In general, at temperatures below 16 to 18°C, sporogony is not completed and transmission does not occur. Therefore, the most effective mosquito vectors of malaria are those such as *A. gambiae*, which are long-lived, occur in high densities in tropical climates, breed readily, and bite humans in preference to other animals. The entomologic inoculation rate -- the number of sporozoite-positive mosquito bites per year -- is the most common measure of malarial transmission and varies from <1 in some parts of Latin America and Southeast Asia to >300 in parts of tropical Africa.

ERYTHROCYTE CHANGES IN MALARIA

After invading an erythrocyte, the growing parasite progressively consumes and degrades intracellular proteins, principally hemoglobin. The potentially toxic heme is polymerized to biologically inert hemozoin, or malaria pigment. The parasite also alters the red cell membrane by changing its transport properties, exposing cryptic surface antigens, and inserting new parasite-derived proteins. The red cell becomes more irregular in shape, more antigenic, and less deformable.

In *P. falciparum* infections, membrane protuberances appear on the erythrocyte's surface in the second 24 h of the asexual cycle. These "knobs" extrude a high-molecular-weight, antigenically variant, strain-specific, adhesive protein (PfEMP1) that mediates attachment to receptors on venular and capillary endothelium -- an event termed *cytoadherence*. Several receptors have been identified, of which intercellular adhesion molecule 1 is probably the most important in the brain, chondroitin sulfate B in the placenta, and CD36 in most other organs. Thus the infected erythrocytes stick inside the small blood vessels. At the same stage, these *P. falciparum*-infected red cells may also adhere to uninfected red cells to form rosettes. The processes of cytoadherence and rosetting are central to the pathogenesis of falciparum malaria. They result in the sequestration of red cells containing mature forms of the parasite in vital organs (particularly the brain), where they interfere with microcirculatory flow and metabolism. Sequestered parasites continue to develop out of reach of the principal host defense mechanism: splenic processing and filtration. As a consequence, only the younger ring forms of the asexual parasites are seen in the peripheral blood in falciparum malaria, and the level of peripheral parasitemia underestimates the true number of parasites within the body. Severe malaria is also associated with reduced deformability of the uninfected erythrocytes, which compromises their passage through the partially obstructed capillaries and venules and shortens red cell survival.

In the other three "benign" malarias, sequestration does not occur, and all stages of the parasite's development are evident on peripheral blood smears. Whereas *P. vivax*, *P. ovale*, and *P. malariae* show a marked predilection for either old red cells or reticulocytes and produce a level of parasitemia seldom exceeding 2%, *P. falciparum* can invade erythrocytes of all ages and may be associated with very high levels of parasitemia.

HOST RESPONSE

Initially, the host responds to plasmodial infection by activating nonspecific defense mechanisms. Splenic immunologic and filtrative clearance functions are augmented in malaria, and the removal of both parasitized and uninfected erythrocytes is accelerated. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures. The material released induces the activation of macrophages and the release of proinflammatory mononuclear cell-derived cytokines, which cause fever and exert other pathologic effects. Temperatures of³40°C damage mature parasites; in untreated infections, the effect of such temperatures is to synchronize further the parasitic cycle with eventual production of the regular fever spikes and rigors that originally served to characterize the different malarias. These regular fever patterns (tertian, every 2 days; quartan, every 3 days) are seldom seen in patients who receive prompt and effective antimalarial treatment.

The geographic distributions of sickle cell disease, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency closely resemble that of malaria before the introduction of control measures. This observation suggests that these genetic disorders confer protection against death from falciparum malaria. For example, HbA/S heterozygotes (sickle cell trait) have a sixfold reduction in the risk of dying from severe falciparum malaria. This decrease in risk appears to be related to impaired parasite growth at low oxygen tensions. In Melanesia, children witha-thalessemia appear to have more frequent malaria (both vivax and falciparum) in the early years of life, and this pattern of infection appears to protect against severe disease. In Melanesian ovalocytosis, rigid erythrocytes resist merozoite invasion and the intraerythrocytic milieu is hostile.

The specific immune response to malaria eventually controls the infection and, with exposure to sufficient strains, confers protection from high-level parasitemia and disease but not from infection. As a result of this state of infection without illness (premunition), asymptomatic parasitemia is common among adults and older children living in regions with stable and intense transmission (i.e., holo- or hyperendemic areas). Immunity is specific for both the species and the strain of infecting malarial parasite. Both humoral immunity and cellular immunity are necessary for protection, but the mechanisms of each are incompletely understood (Fig. 214-1). Immune individuals have a polyclonal increase in serum levels of IgM, IgG, and IgA, although much of this antibody is unrelated to protection. Antibodies to a variety of parasitic antigens presumably act in concert to limit in vivo replication of the parasite. In the case of falciparum malaria, the most important of these is the antigenically variant protein PfEMP1 mentioned above. Passively transferred IgG from immune adults has been shown to reduce levels of parasitemia in children, and passive transfer of maternal

antibody contributes to the relative protection of infants from severe malaria in the first months of life. This complex immunity to disease is lost when a person lives outside an endemic area for several months or longer.

Several factors retard the development of cellular immunity to malaria. These factors include the absence of major histocompatibility antigens on the surface of infected red cells, which precludes direct T cell recognition; malaria antigen-specific immune unresponsiveness; and the enormous strain diversity of malarial parasites along with the ability of the parasites to express immunodominant variant antigens on the erythrocyte surface that change during the period of infection. Strain diversity also has an impact on the heterogeneity of the humoral antibody response. Immunity to all strains is never achieved. Parasites may persist in the blood for months (or, in the case of *P. malariae*, for many years) if treatment is not given. The complexity of the immune response in malaria, the sophistication of the parasites' evasion mechanisms, and the lack of a good in vitro correlate with clinical immunity have all slowed progress toward an effective vaccine.

CLINICAL FEATURES

The first symptoms of malaria are nonspecific; the lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. In some instances, a prominence of headache, chest pain, abdominal pain, arthralgia, myalgia, or diarrhea may suggest another diagnosis. Although headache may be severe in malaria, there is no neck stiffness or photophobia resembling that in meningitis. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, suggest infection with *P. vivax* or *P. ovale*. The fever is irregular at first (that of falciparum malaria may never become regular); the temperature of nonimmune individuals and children often rises above 40°C in conjunction with tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are specifically associated with falciparum malaria and may herald the development of cerebral disease. Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise, mild anemia, and (in some cases) a palpable spleen. Anemia may be quite common among young children living in areas with stable transmission, particularly where there is parasite resistance to chloroquine or other drugs. Splenic enlargement is very common among otherwise-healthy individuals in malaria-endemic areas and reflects repeated infections; however, in nonimmune individuals with malaria, the spleen takes several days to become palpable. Slight enlargement of the liver is also common, particularly in young children. Mild jaundice is common in adults; it may develop in patients with otherwise uncomplicated falciparum malaria and usually resolves over 1 to 3 weeks. Malaria is not associated with a rash like those seen in meningococcal septicemia, typhus, enteric fever, viral exanthems, and drug reactions. Petechial hemorrhages in the skin or mucous membranes -- features of viral hemorrhagic fevers and leptospirosis -- develop only rarely in severe falciparum malaria.

Severe Falciparum Malaria Appropriately treated, uncomplicated falciparum malaria carries a mortality rate of ~0.1%. However, once vital organ dysfunction occurs or the proportion of erythrocytes infected increases to>3%, mortality rises steeply. The major manifestations of severe falciparum malaria are shown inTable 214-2.

Cerebral Malaria Coma is a characteristic and ominous feature of falciparum malaria and, despite treatment, is associated with death rates of ~20% among adults and 15% among children. Lesser degrees of obtundation, delirium, and abnormal behavior should also be taken very seriously. The onset may be gradual or sudden following a convulsion.

Cerebral malaria manifests as diffuse symmetric encephalopathy; focal neurologic signs are unusual. Although some passive resistance to head flexion may be detected, signs of meningeal irritation are lacking. The eyes may be divergent and a pout reflex is common, but other primitive reflexes are usually absent. The corneal reflexes are preserved except in deep coma. Muscle tone may be either increased or decreased. The tendon reflexes are variable, and the plantar reflexes may be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing may be documented. Approximately 15% of patients have retinal hemorrhages; with pupillary dilatation and indirect ophthalmoscopy, this figure increases to 30 to 40%. Other abnormalities include discrete spots of retinal opacification (30 to 60%), papilledema (8% of children, rare in adults), cotton wool spots (<5%), and decolorization of a retinal vessel or segment of vessel (occasional cases). Convulsions, usually generalized and often repeated, occur in up to 50% of children with cerebral malaria. More covert seizure activity is common, particularly in children, and may manifest as repetitive tonic-clonic eye movements. Whereas adults rarely suffer neurologic sequelae, ~10% of children surviving cerebral malaria -- especially those with hypoglycemia, severe anemia, repeated seizures, and deep coma -- have some residual neurologic deficit when they regain consciousness; hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition and learning -- all of varying duration -- have been reported.

Hypoglycemia An important and common complication of severe malaria, hypoglycemia is associated with a poor prognosis and is particularly problematic in children and pregnant women. Hypoglycemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose by both host and parasite. To compound the situation, quinine and quinidine -- drugs used commonly for the treatment of severe chloroquine-resistant malaria -- are powerful stimulants of pancreatic insulin secretion. Hyperinsulinemic hypoglycemia is especially troublesome in pregnant women receiving quinine treatment. In severe disease, the clinical diagnosis of hypoglycemia is difficult: the usual physical signs (sweating, gooseflesh, tachycardia) are absent, and the neurologic impairment caused by hypoglycemia cannot be distinguished from that caused by malaria.

Lactic Acidosis Lactic acidosis commonly coexists with hypoglycemia in patients with malaria and is an important contributor to death from severe malaria. In adults, coexisting renal impairment often compounds the acidosis. Acidotic breathing, sometimes called respiratory distress, is a sign of poor prognosis. It is often followed by circulatory failure refractory to volume expansion or inotropic drugs or by respiratory arrest. The plasma concentrations of bicarbonate or lactate are the best biochemical

prognosticators in severe malaria. Lactic acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory flow, lactate production by the parasites, and a failure of hepatic and renal lactate clearance. The prognosis of lactic acidosis is poor.

Noncardiogenic Pulmonary Edema Adults with severe falciparum malaria may develop noncardiogenic pulmonary edema even after several days of antimalarial therapy. This manifestation may also develop in otherwise-uncomplicated vivax malaria, where recovery is usual. The pathogenesis of this variant of the adult respiratory distress syndrome is unclear. The mortality rate is >80%. This condition can be aggravated by overly vigorous administration of intravenous fluid.

Renal Impairment Renal impairment is common among adults with severe falciparum malaria but rare among children. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration interfering with renal microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis; renal cortical necrosis never develops. Mortality in the initial phase of hypercatabolic acute renal failure is high; in survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days (Chap. 269). Dialysis or hemofiltration considerably enhances the likelihood of a patient's survival.

Hematologic Abnormalities Anemia results from accelerated red cell destruction and removal by the spleen in conjunction with ineffective erythropoiesis. In severe malaria, both infected and uninfected red cells show reduced deformability, which correlates with prognosis and development of anemia. Splenic clearance of cells is also increased. In nonimmune individuals and in areas with unstable transmission, anemia can develop rapidly and transfusion is often required. In many areas of Africa, children may develop severe anemia as a result of repeated malarial infections. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection.

Slight coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual. As mentioned above, fewer than 5% of patients with severe malaria have significant bleeding with evidence of disseminated intravascular coagulation. Hematemesis, presumably from stress ulceration or acute gastric erosions, may also occur.

Liver Dysfunction Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with *P. falciparum* infections, is more common among adults than among children, and results from hemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis, and impaired drug metabolism.

Other Complications Aspiration pneumonia following convulsions is an important cause of death in cerebral malaria. Chest infections and catheter-induced urinary tract infections are common among patients who are unconscious for>3 days. Septicemia may complicate severe malaria; in endemic areas *Salmonella* bacteremia has been associated specifically with *P. falciparum* infections.

Malaria in Pregnancy In hyper- and holoendemic areas, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, ~170 g) and consequently increased infant and childhood mortality. In general, infected mothers in areas of stable transmission remain asymptomatic despite intense parasitization of the placenta due to sequestration of parasitized erythrocytes in the placental microcirculation. Maternal HIV infection predisposes pregnant women to a higher prevalence of malaria and parasite density and predisposes their newborns to congenital malaria infection and low birth weight.

In areas with unstable transmission of malaria, pregnant women are prone to severe infections and are particularly vulnerable to high-level parasitemia with anemia, hypoglycemia, and acute pulmonary edema. Fetal distress, premature labor, and stillbirth or low birth weight are common results. Congenital malaria occurs in fewer than 5% of newborns whose mothers are infected and is related directly to the parasite density in maternal blood and in the placenta. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight (average, 100 g), but, in contrast with the situation in falciparum malaria, this effect is greater in multigravid than in primigravid women.

Malaria in Children Most of the estimated 1 to 3 million persons who die of falciparum malaria each year are young African children. Convulsions, coma, hypoglycemia, metabolic acidosis, and severe anemia are relatively common among children with severe malaria, whereas deep jaundice, acute renal failure, and acute pulmonary edema are unusual. Severely anemic children may present with labored deep breathing, which in the past has been attributed incorrectly to "anemic congestive cardiac failure" but is in fact usually caused by metabolic acidosis, often compounded by hypovolemia. In general, children tolerate antimalarial drugs well and respond rapidly to treatment.

Transfusion Malaria Malaria can be transmitted by blood transfusion, needle-stick injury, sharing of needles by infected drug addicts, or organ transplantation. The incubation period in these settings is often short because there is no preerythrocytic stage of development. The clinical features and management of these cases are the same as for naturally acquired infections, although falciparum malaria tends to be especially severe in drug addicts. Radical chemotherapy with primaquine is unnecessary for *P. vivax* and *P. ovale* infections.

CHRONIC COMPLICATIONS OF MALARIA

Tropical Splenomegaly (Hyperreactive Malarial Splenomegaly) Chronic or repeated malarial infections produce hypergammaglobulinemia; normochromic, normocytic anemia; and, in certain situations, splenomegaly. Some residents of malaria-endemic areas in tropical Africa and Asia exhibit an abnormal immunologic response to repeated infections that is characterized by massive splenomegaly, hepatomegaly, marked elevations in serum titers of IgM and malarial antibody, hepatic sinusoidal lymphocytosis, and (in Africa) peripheral B cell lymphocytosis. This syndrome has been associated with the production of cytotoxic IgM antibodies to suppressor (CD8+) lymphocytes, antibodies to CD5+ T cells, and an increase in the ratio of CD4+ T cells to CD8+ T cells. It is believed that these events lead to uninhibited B cell production of IgM

and the formation of cryoglobulins (IgM aggregates and immune complexes). This immunologic process stimulates reticuloendothelial hyperplasia and clearance activity and eventually produces splenomegaly. Patients with hyperreactive malarial splenomegaly (HMS) present with an abdominal mass or a dragging sensation in the abdomen and occasional sharp abdominal pains suggesting perisplenitis. Anemia and some degree of pancytopenia are usually evident, but in many cases malarial parasites cannot be found in peripheral blood smears. Vulnerability to respiratory and skin infections is increased; many patients die of overwhelming sepsis. Persons with HMS who are living in endemic areas should receive antimalarial chemoprophylaxis: the results are usually good. In nonendemic areas, treatment is advised. In some cases refractory to therapy, clonal lymphoproliferation may develop and then evolve into a malignant lymphoproliferative disorder.

Quartan Malarial Nephropathy Chronic or repeated infections with *P. malariae*, and possibly other malarial species, may cause soluble immune-complex injury to the renal glomeruli, resulting in the nephrotic syndrome. Other, unidentified factors must contribute to this process since only a very small proportion of infected patients develop renal disease. The histologic appearance is that of focal or segmental glomerulonephritis with splitting of the capillary basement membrane. Subendothelial dense deposits are seen on electron microscopy, and immunofluorescence reveals deposits of complement and immunoglobulins; in samples of renal tissue from children, *P. malariae* antigens are often visible. A coarse-granular pattern of basement membrane immunofluorescent deposits (predominantly IgG3) with selective proteinuria carries a better prognosis than a fine-granular, predominantly IgG2 pattern with nonselective proteinuria. Quartan nephropathy usually responds poorly to treatment with either antimalarial agents or glucocorticoids and cytotoxic drugs.

Burkitt's Lymphoma and Epstein-Barr Virus Infection It is possible that malaria-related immunosuppression provokes infection with lymphoma viruses. Burkitt's lymphoma is strongly associated with Epstein-Barr virus. The prevalence of this childhood tumor is high in malarious areas of Africa.

DIAGNOSIS

Demonstration of the Parasite The diagnosis of malaria rests on the demonstration of asexual forms of the parasite in peripheral blood smears subjected to Romanovsky staining. Following a negative blood smear, repeat smears should be made if there is a high degree of suspicion. Giemsa at pH 7.2 is preferred; Wright's, Field's, or Leishman's stain can also be used. Both thin and thick blood smears should be examined (See Plates VI-3,VI-4,VI-5,VI-6,VI-7,VI-8,VI-9,VI-10,VI-11,VI-12,VI-13,VI-14,VI-15,VI-16,VI-17,VI-18, VI-19,VI-20, andVI-21and Plates VI-23,VI-24,VI-25,VI-26,VI-27,VI-28,VI-29,VI-30,VI-31,VI-32, andVI-33).

The thin blood smear should be rapidly air-dried, fixed in anhydrous methanol, and stained, and the red cells in the tail of the film should then be examined under oil immersion. The level of parasitemia is expressed as the number of parasitized erythrocytes among 1000 cells, and this figure is converted to the number of parasitized erythrocytes per microliter. Simple, sensitive, and specific antibody-based diagnostic

stick or card tests that detect *P. falciparum*-specific, histidine-rich protein (HRP) 2 or lactate dehydrogenase antigens in finger-prick blood samples have been introduced. Some of these tests carry a second antibody, which allows falciparum malaria to be distinguished from the less dangerous malarias. The relationship between parasitemia and prognosis is complex; in general, patients with>10_5parasites per microliter are at increased risk of dying, but nonimmune patients may die with much lower counts and semi-immune persons may tolerate parasitemia levels many times higher with only minor symptoms. In severe malaria, a poor prognosis is indicated by a predominance of more mature *P. falciparum* parasites (i.e., >20% of parasites with visible pigment), by the presence of circulating schizonts in the peripheral blood film, or by the presence of phagocytosed malarial pigment in>5% of neutrophils. Gametocytes may remain evident for several days after treatment has begun; unless trophozoites are also visible on the blood film, their presence does not constitute evidence of drug resistance.

The thick blood film should be of uneven thickness. The smear should be dried thoroughly and stained without fixing. As many layers of erythrocytes overlie one another and are lysed during the staining procedure, the thick film has the advantage of concentrating the parasites (by 20- to 40-fold compared with a thin blood film) and thus increasing diagnostic sensitivity. Both parasites and white cells are counted, and the number of parasites per unit volume is calculated from the total leukocyte count. Alternatively, a white count of 8000/uL is assumed. A minimum of 200 white cells should be counted. Interpretation of thick films requires some experience because artifacts are common. Before a thick smear is judged to be negative, 100 to 200 fields should be examined under oil immersion. Phagocytosed malarial pigment is sometimes seen inside peripheral blood monocytes or polymorphonuclear leukocytes and may provide a clue to recent infection if malarial parasites are not detectable. After the clearance of the parasites, malarial pigment is often evident for several days in peripheral blood phagocytes, bone marrow aspirates, or smears of fluid expressed after intradermal puncture. Staining of parasites with the fluorescent dye acridine orange allows more rapid diagnosis of cases in which the level of parasitemia is low.

Laboratory Findings Normochromic, normocytic anemia is usually documented. The leukocyte count is generally low to normal, although it may be raised in very severe infections. The erythrocyte sedimentation rate, degree of plasma viscosity, and level of C-reactive protein are high. The platelet count is usually reduced to ~10_5/uL. Severe infections may be accompanied by prolonged prothrombin and partial thromboplastin times and by severe thrombocytopenia. Levels of antithrombin III are reduced even in mild infection. In uncomplicated malaria, plasma concentrations of electrolytes, blood urea nitrogen, and creatinine are usually normal. Findings in severe malaria may include metabolic acidosis, with low plasma concentrations of glucose, sodium, bicarbonate, calcium, phosphate, and albumin together with elevations in lactate, blood urea nitrogen, creatinine, urate, muscle and liver enzymes, and conjugated and unconjugated bilirubin. Hypergammaglobulinemia is usual in immune and semi-immune subjects, and urinalysis generally gives normal results. In adults and children with cerebral malaria, the mean opening pressure at lumbar puncture is ~160 mm of cerebrospinal fluid (CSF); the CSF is usually normal or has a slightly elevated total protein level [<1.0 g/L (100 mg/dL)] and cell count (<20/uL).

PREVENTION

In most of the tropics, the eradication of malaria is not yet feasible because of the widespread distribution of *Anopheles* breeding sites; the great number of infected persons; and inadequacies in resources, infrastructure, and control programs. Where possible, the disease is contained by judicious use of insecticides to kill the mosquito vector, rapid diagnosis and appropriate patient management, and administration of chemoprophylaxis to high-risk groups. Malaria researchers are intensifying their efforts to better understand parasite-human-mosquito-environmental interactions and develop more effective control and prevention interventions. Despite the enormous investment in efforts to develop a malaria vaccine, no safe, effective, long-lasting vaccine is likely to be available for general use in the near future (Chap. 122). While there is promise for one or more malaria vaccines on the more distant horizon, prevention and control measures continue to rely on antivector and drug use strategies.

Personal Protection Against Malaria Simple measures to reduce the frequency of mosquito bites in malarious areas are very important. These measures include the avoidance of exposure to mosquitoes at their peak feeding times (usually dusk and dawn, but also throughout the night) and the use of insect repellents, suitable clothing, and insecticide-impregnated bed nets. Widespread use of bed nets, particularly those treated with residual pyrethroids, reduces the incidence of malaria and has been shown to reduce mortality in western and eastern Africa.

Chemoprophylaxis (Table 214-3) Few areas of therapeutics are as controversial as antimalarial drug prophylaxis. Recommendations for prophylaxis depend on knowledge of local patterns of plasmodial drug sensitivity and the likelihood of acquiring malarial infection. Chemoprophylaxis is never entirely reliable, and malaria should always be considered in the differential diagnosis of fever in patients who have traveled to endemic areas, even if they are taking prophylactic antimalarial drugs.

Pregnant women traveling to malarious areas should be warned about the potential risks. All pregnant women at risk in endemic areas should be encouraged to attend regular antenatal clinics and should receive either prophylaxis with chloroquine or proguanil (chloroguanide) or intermittent treatment with pyrimethamine-sulfadoxine, provided there is not high-level resistance to these drugs. In addition, antimalarial prophylaxis should be considered for children between the ages of 3 months and 4 years in areas where malaria causes high childhood mortality; such prophylaxis may not be logistically or economically feasible in many countries. Children born to nonimmune mothers in endemic areas (usually expatriates moving to these areas) should receive prophylaxis from birth.

Travelers should start taking antimalarial drugs at least 1 week before departure so that any untoward reactions can be detected and therapeutic antimalarial blood concentrations will be present when needed. Antimalarial prophylaxis should continue for 4 weeks after the traveler has left the endemic area.

Mefloquine has become the antimalarial prophylactic agent of choice for much of the tropics because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well tolerated. Mild nausea, dizziness, fuzzy thinking, disturbed sleep patterns, and malaise are relatively common. Approximately 1 in every 10,000 recipients

develops an acute reversible neuropsychiatric reaction manifested by confusion, psychosis, convulsions, or encephalopathy. The role of mefloquine prophylaxis in pregnancy remains uncertain; in studies in Africa, mefloquine prophylaxis was found to be effective and safe during pregnancy. However, in one study from Thailand, treatment of malaria with mefloquine was associated with an increased risk of stillbirth.

Daily administration of doxycycline is an effective alternative to mefloquine that also exhibits some causal (preerythrocytic) prophylactic activity. Doxycycline is generally well tolerated but may cause vulvovaginal thrush, diarrhea, and photosensitivity and cannot be used by children <8 years old or by pregnant women. The combination drug atovaquone-proguanil hydrochloride (3.75/1.5 mg/kg, or 250/100 mg daily, adult dose) has recently been shown to be a very effective alternate to mefloquine chemoprophylaxis in drug-resistant areas. This drug must be taken with food or a milky drink because it is highly lipophilic: it is well-tolerated by adults and children.

Chloroquine remains the drug of choice for the prevention of infection with drug-sensitive *P. falciparum* and with the other human malarial species (although chloroquine-resistant *P. vivax* has been reported from parts of eastern Asia, Oceania, and South America). Unfortunately, there are few areas of the world with chloroquine-sensitive *P. falciparum*. Chloroquine is generally well tolerated, although some patients are unable to take the drug because of malaise, headache, or (in dark-skinned patients) pruritus. A concomitant filarial infection may provoke or aggravate chloroquine-induced pruritus. Chloroquine is considered safe in pregnancy. With chronic administration for>5 years, a characteristic dose-related retinopathy may develop, but this condition is rare at the doses used for antimalarial prophylaxis. Idiosyncratic or allergic reactions are also rare. Skeletal and cardiac myopathy are potential problems with protracted prophylactic use; they occur most often at the high doses used in the treatment of rheumatoid arthritis. Neuropsychiatric reactions and skin rashes are unusual. Amodiaquine, a related aminoquinoline, is associated with a high risk of agranulocytosis (~1 person in 2000 with continuous use) and should not be used for prophylaxis.

In the past, the dihydrofolate reductase inhibitors pyrimethamine and proguanil (chloroguanide) have been administered widely, but resistant strains of both *P. falciparum* and *P. vivax* have limited their use. Whereas antimalarial quinolines such as chloroquine act on the erythrocyte stage of parasitic development, the dihydrofolate reductase inhibitors also inhibit preerythrocytic growth in the liver (causal prophylaxis) and development in the mosquito (sporonticidal activity). Proguanil is safe and well tolerated, although mouth ulceration occurs in ~8% of persons using this drug; it is considered safe for antimalarial prophylaxis in pregnancy. The prophylactic use of the combination of pyrimethamine and sulfadoxine is not recommended because of an unacceptable incidence of severe toxicity, principally exfoliative dermatitis and other skin rashes, agranulocytosis, hepatitis, and pulmonary eosinophilia. The combination of pyrimethamine with dapsone (0.2/1.5 mg/kg weekly; 25/200 mg maximum) is a second-line alternative available in some countries and can be used in areas with chloroquine-resistant *P. falciparum*. This combination is generally well tolerated; however, resistance is increasing, and dapsone may cause methemoglobinemia and allergic reactions and (at higher doses) may pose a significant risk of agranulocytosis. Primaquine (0.5 mg/kg, or 30 mg daily) has also proved safe and effective in clinical

trials in drug-resistant areas and can be considered when all other options are containdicated. Proguanil and the pyrimethamine-dapsone combination are not available in the United States.

Because of the increasing spread and intensity of plasmodial resistance to chloroquine in Africa and other areas of the world (Fig. 214-2), the Centers for Disease Control and Prevention (CDC;http://www.cdc.gov/travel/index.htm), which recommends a weekly dose of mefloquine for all travelers, maintains an updated 24-h travel and malaria information audiotape that can be accessed by touch-tone telephone (888-232-3228). Regional and disease-specific documents may be requested from the CDC Fax Information Service (888-232-3299). Consultation for the evaluation of prophylaxis failures or treatment of malaria can be obtained from state and local health departments and the CDC (770-488-7788).

TREATMENT

When a patient in or from a malarious area presents with fever, thick and thin blood smears should be prepared and examined immediately to confirm the diagnosis and identify the species of infecting parasite. Repeat blood smears should be performed at least every 12 h for 2 days if the first smears are negative. Patients with severe malaria or those unable to take oral drugs should receive parenteral antimalarial therapy. If there is any doubt about the resistance status of the infecting organism, then quinine or quinidine should be given. Several drugs are available for oral treatment, and the choice of drug depends on the likely sensitivity of the infecting parasites. Despite recent evidence of chloroquine resistance in *P. vivax* (from parts of Indonesia, Oceania, and Brazil), chloroquine remains the treatment of choice for the "benign" human malarias (*P. vivax*, *P. ovale*, *P. malariae*). Characteristics of various antimalarial agents are shown inTable 214-4, and drug regimens approved by the U.S. Food and Drug Administration are detailed inTable 214-5. The availability of antimalarial drugs varies considerably between countries. Many of the drugs used to treat malaria in endemic areas are not available in temperate countries such as the United States.

Severe Malaria Because of resistance, chloroquine can no longer be relied upon in most countries for the treatment of severe malaria. The antiarrhythmic quinidine gluconate is as effective as quinine and, as it is more readily available, has replaced quinine for the treatment of malaria in the United States. The administration of quinidine must be closely monitored if dysrrhythmias and hypotension are to be avoided. Total plasma levels in excess of 8 ug/mL, a QT_cinterval of >0.6 s, or QRS widening beyond 25% of baseline are indications for slowing infusion rates. If arrhythmia or saline-unresponsive hypotension develops, treatment with this drug should be discontinued. Quinine is safer than quinidine; cardiovascular monitoring is not required except when the recipient has cardiac disease. In some areas of Asia, the Chinese drugs derived from artemisinin (artemether and artesunate) have become first-line treatments for severe malaria. These agents are rapidly effective against multidrug-resistant falciparum malaria and are at least as effective as and safer than quinine or quinidine. They are not available in the United States.

Severe falciparum malaria constitutes a medical emergency requiring intensive nursing care and careful management. The patient should be weighed and, if comatose, placed

on his or her side. Frequent evaluation of the patient's condition is essential. Ancillary drugs such as high-dose glucocorticoids, urea, heparin, and dextran are of no value.

Parenteral antimalarial treatment should be started as soon as possible. An initial loading dose should be given so that therapeutic concentrations are reached as soon as possible. Both quinine and quinidine will cause dangerous hypotension if injected rapidly; when given intravenously, they must be administered carefully by rate-controlled infusion only. The optimal therapeutic range for quinine and quinidine in severe malaria is not known with certainty, but total plasma concentrations of 8 to 15 mg/mL for quinine and 3.5 to 8.0 mg/mL for quinidine are effective and do not cause serious toxicity. The systemic clearance and apparent volume of distribution of these alkaloids are markedly reduced and plasma protein binding is increased in severe malaria, so that the blood concentrations attained with a given dose are higher. If the patient remains seriously ill or in acute renal failure for>2 days, the maintenance doses of quinine or quinidine should be reduced by 30 to 50% to prevent toxic accumulation of the drugs. The initial doses should never be reduced. If one of the artemisinin derivatives or chloroquine is given, dose reductions are unnecessary, even in renal failure. Exchange transfusion should be considered for severely ill patients, although the precise indications for this procedure have not been agreed upon. It has been recommended that -- if safe and feasible -- exchange should be considered for parasitemia levels of 5 to 15% and is indicated for parasitemia levels of>15%. The role of prophylactic intramuscular phenobarbital in preventing convulsions in cerebral malaria also remains uncertain.

When the patient is unconscious, the blood glucose level should be measured every 4 to 6 h, and values below 2.2 mmol/L (40 mg/dL) should prompt treatment with intravenous dextrose. All patients treated with intravenous quinine or quinidine should receive a continuous infusion of 5 to 10% dextrose. The parasite count and hematocrit level should be measured every 6 to 12 h. Anemia develops rapidly; if the hematocrit falls below 20%, then whole blood (preferably fresh) or packed cells should be transfused slowly, with careful attention to circulatory status. Renal function should be checked daily. Judicious use of small doses of a diuretic to prevent fluid overload may be needed, particularly in the elderly. Children presenting with severe anemia and acidotic breathing are often hypovolemic; in this situation, resuscitation with crystalloids or blood is indicated. Accurate assessment is vital. Management of fluid balance is difficult in severe malaria, particularly in adults, because of the thin dividing line between overhydration (leading to pulmonary edema) and underhydration (contributing to renal impairment). If necessary, pulmonary artery occlusion pressures should be measured and maintained in the low-normal range. As soon as the patient can take fluids, oral therapy should be substituted for parenteral treatment.

Uncomplicated Malaria Infections due to *P. vivax*, *P. malariae*, *P. ovale*, and known sensitive strains of *P. falciparum* should be treated with oral chloroquine (total dose, 25 mg of base/kg). In Africa, chloroquine-resistant strains are usually sensitive to sulfadoxine/pyrimethamine. Where there is resistance to the latter combination, either (1) quinine plus tetracycline or doxycycline (or clindamycin) or (2) mefloquine should be used; tetracycline and doxycycline cannot be given to pregnant women or to children<8 years of age. Oral quinine is extremely bitter and regularly produces cinchonism comprising tinnitus, high-tone deafness, nausea, vomiting, and dysphoria. Compliance is poor with the required 5- to 7-day regimens of this drug. Mefloquine should be given

at a total dosage of 25 mg/kg (15 mg/kg followed 8 to 12 h later by 10 mg/kg) and, where available and approved for use, combined with artesunate or artemether (4 mg/kg per day for 3 days). Although significant resistance to mefloquine has been documented in Thailand, Burma, Vietnam, and Cambodia, this agent is usually effective against multidrug-resistant strains of *P. falciparum* outside these areas. Artemether-lumefantrine and atovaquone-proguanil are recently introduced, well-tolerated antimalarial drugs used in 3-day regimens. They are both effective against multidrug-resistant falciparum malaria.

Patients should be monitored for vomiting for 1 h after the administration of any oral antimalarial drug. Symptom-based treatment, with tepid sponging and acetaminophen administration, lowers fever and thereby reduces the patient's propensity to vomit these drugs. Minor central nervous system reactions (nausea, dizziness, sleep disturbances) are common. The incidence of serious adverse neuropsychiatric reactions to mefloquine treatment is ~1 in 1000 in Asia but may be as high as 1 in 200 among Africans and Caucasians. All the antimalarial quinolines (chloroquine, mefloquine, and quinine) exacerbate the orthostatic hypotension associated with malaria, and all are tolerated better by children than by adults. Pregnant women, young children, patients unable to tolerate oral therapy, and nonimmune subjects (e.g., travelers) with suspected malaria should be evaluated carefully and hospitalization considered. If there is any doubt as to the identity of the infecting malarial species, treatment for falciparum malaria should be given. A negative blood smear does not rule out malaria; thick blood films should be checked 1 and 2 days later to exclude the diagnosis. Nonimmune subjects receiving treatment for malaria should have daily parasite counts performed until negative thick films indicate clearance of the parasite. If the level of parasitemia does not fall below 25% of the admission value in 48 h or if parasitemia has not cleared by 7 days (and compliance is assured), drug resistance is likely and the regimen should be changed. Quinine (or quinidine) and tetracycline should be reserved for multidrug-resistant infections, but if falciparum malaria has been contracted in an area of known drug sensitivity, then treatment with chloroquine, sulfadoxine/pyrimethamine, or mefloquine is preferable because these agents are better tolerated and simpler to administer.

Primaquine (0.3 mg of base/kg; 15 mg of base, adult dose) should be given daily for 14 days to patients with *P. vivax* or *P. ovale* infections after laboratory tests forG6PDdeficiency have proved negative. A dose of 22.5 to 30 mg for an adult is recommended for infections acquired in Southeast Asia and Oceania. If the patient has a mild variant of G6PD deficiency, primaquine can be given in a dose of 0.6 mg of base/kg (45 mg maximum) once weekly for 8 weeks.

PREVENTING DRUG RESISTANCE

In much of the tropics, drug-resistant *P. falciparum* is increasing in distribution, frequency, and intensity. There is a growing belief among malariologists that, to prevent resistance, falciparum malaria should no longer be treated with single drugs in endemic areas; the same rationale has been applied in the treatment of tuberculosis and HIV/AIDS. This strategy is based upon simultaneous use of two or more drugs with different modes of action: one, an artemisinin derivative (artesunate, artemether, or dihydroartemisinin), given for 3 days; and the other, a slower-acting antimalarial. In areas where *P. falciparum* is still sensitive, chloroquine is used as the second drug;

where there is low-grade chloroquine resistance (e.g., many areas of Africa), either amodiaquine or sulfadoxine/pyrimethamine can be used in combination with the artemisinin derivative. Where there is also resistance to sulfadoxine/pyrimethamine, the combinations artesunate plus mefloquine, artemether plus lumefantrine, or quinine plus tetracycline or clindamycin can be considered (although tetracycline cannot be given to pregnant women or to children <8 years of age). Atovaquone/proguanil, which is also effective against drug-resistant malaria, can also be combined with artesunate to prevent the emergence of resistance. While significant resistance to mefloquine occurs in Thailand, Burma, and Cambodia, the mefloquine/artesunate combinations are still reliably effective in these areas. The artemisinin derivatives and lumefantrine (all unlicensed in the United States) and atovaquone-proguanil are tolerated well with no significant adverse effects.

COMPLICATIONS

Acute Renal Failure If the level of blood urea nitrogen or creatinine rises despite adequate rehydration, fluid administration should be restricted to prevent volume overload. The indications for dialysis are the same as those in other forms of hypercatabolic acute renal failure (Chap. 269). Even with adequate peritoneal dialysis, secondary bacterial infections are common in the tropics, and hemodialysis or hemofiltration is preferable. Some patients pass small volumes of urine sufficient to allow control of fluid balance; these cases can be managed conservatively if other indications for dialysis do not arise. Renal function usually improves within days, but full recovery may take weeks.

Acute Pulmonary Edema Patients should be positioned at 45° and given oxygen and intravenous diuretics. Pulmonary artery occlusion pressures may be normal, indicating increased pulmonary capillary permeability. Positive pressure ventilation should be started early if the immediate measures fail (Chap. 233).

Hypoglycemia An initial slow injection of 50% dextrose (0.5 g/kg) should be followed by an infusion of 10% dextrose (0.10 g/kg per hour). The blood glucose level should be checked regularly thereafter, as recurrent hypoglycemia is common, particularly in patients receiving quinine or quinidine. In severely ill patients, hypoglycemia commonly occurs together with metabolic (lactic) acidosis and carries a poor prognosis.

Other Complications Patients who develop spontaneous bleeding should be given fresh blood and intravenous vitamin K. Convulsions should be treated with intravenous or rectal benzodiazepines and, if necessary, respiratory support. Aspiration pneumonia should be suspected in any unconscious patient with convulsions, particularly with persistent hyperventilation; intravenous antimicrobial agents and oxygen should be administered, and pulmonary toilet should be undertaken. Treatment for systemic *Salmonella* and other infections common in African children with falciparum malaria should be considered. Hypoglycemia or gram-negative septicemia should be suspected when the condition of any patient suddenly deteriorates for no obvious reason during antimalarial treatment.

BABESIOSIS

Babesiosis is a protozoan disease of animals that is transmitted by ticks; humans are infected incidentally and initially develop a nonspecific febrile illness. *Babesia* organisms enter red blood cells and resemble malarial parasites morphologically, thus posing a diagnostic problem.

ETIOLOGY AND NATURAL CYCLE

Of the more than 100 species of *Babesia*, *B. microti* and *B. divergens* are the two that cause most human infections. Ixodid (hard-bodied) ticks, in particular *Ixodes scapularis* (*I. dammini*) and *I. ricinus*, are the vectors of the parasite. Ticks ingest *Babesia* while feeding, and the parasite multiplies within the tick's gut wall. The organisms then spread to the salivary glands; their inoculation into a vertebrate host by a tick larva, nymph, or adult completes the cycle of transmission. Asexual reproduction of *Babesia* within red blood cells produces two or four parasites.

EPIDEMIOLOGY

While *Babesia* infections in wild and domestic animals are distributed globally, almost all *B. microti* infections in the United States occur along the northeastern coast, including Nantucket Island, Martha's Vineyard, and Cape Cod in Massachusetts; Block Island in Rhode Island; Long Island, Shelter Island, and Fire Island in New York; and the nearby mainland, including Connecticut. Cases also have been reported from Wisconsin, Minnesota, Virginia, Maryland, Georgia, and Mexico. *Babesia* isolates from patients in Washington and California have been characterized as WA-1-type parasites, a category that is genetically and antigenically distinct from *B. microti*. A strain isolated in Missouri differs from these isolates, suggesting that babesiosis may be an "emerging infection." The deer tick, *I. scapularis*, is the vector associated with *B. microti*. In Europe, *B. divergens* has been responsible for the majority of the 22 reported cases of babesiosis; Yugoslavia, Russia, France, the United Kingdom, and Ireland have accounted for most of these infections.

Transfusions are another source of babesiosis. In the more than 20 transfusion-associated cases reported, parasites were uncommonly detected in blood donors, but serologic testing of their blood for *Babesia* gave positive results.

Infections with *B. divergens* have occurred sporadically in previously splenectomized patients in several countries in Europe. *I. ricinus* is probably the vector in these cases, as it is for the transmission of this organism among cattle. The infected persons were predisposed to illness by their asplenic status.

I. scapularis feeds on rodents as a larva and a nymph and on deer as an adult; nymphs are abundant during the spring and summer and feed on humans readily. In some endemic areas, the seroprevalence in the human population may be >2%. This figure indicates that asymptomatic infection is more frequent than is generally thought.

CLINICAL PRESENTATION

The incubation period for *B. microti* infection is about 1 to 4 weeks. Immunosuppressed patients, splenectomized individuals, and the elderly have the most severe illness. The

clinical presentation varies widely; symptoms and signs include a gradual onset of irregular fever, chills, sweating, muscle pain, and fatigue. Mild hepatosplenomegaly and mild hemolytic anemia may develop. The level of parasitemia may exceed 10%. The illness may continue for weeks or months.

Patients infected with *B. divergens* have a more severe illness, with a rapid onset of chills, fever, nausea, vomiting, and hemolytic anemia progressing to jaundice, hemoglobinemia, and renal failure. *B. divergens* infections are often fatal.

DIAGNOSIS

Whether or not they have a history of exposure to ticks or tick bites, febrile persons living in endemic areas should have Giemsa-stained thick and thin blood films (see Plate VI-22) examined for small intraerythrocytic parasites. *B. microti* appears as a small ring form resembling *P. falciparum*. Unlike infection with *Plasmodium*, however, that with *Babesia* does not cause the production of pigment in parasites, nor are schizonts or gametocytes formed. Dividing within red blood cells, *B. microti* can form four daughter parasites attached by strands of cytoplasm; these "tetrad" forms are seen infrequently in human blood films but are a distinguishing feature. An indirect immunofluorescence antibody test is useful for the diagnosis of infection with *B. microti* but does not replace the blood smear. The serum antibody titer rises 2 to 4 weeks after the onset of illness and then wanes over 6 to 12 months; cross-reactions can occur with other species of *Babesia* and with *Plasmodium*.

About 50% of patients infected with *B. microti* have antibody to *Borrelia burgdorferi*, the agent of Lyme disease (Chap. 176); this figure varies with the geographic area. The occurrence of mixed infections is not surprising since both organisms are transmitted by *I. scapularis*. This tick species is also a potential vector of human granulocytic ehrlichiosis; the same tick may carry more than one tick-borne disease. Intraperitoneal inoculation of blood from patients with babesiosis into hamsters or gerbils results in detectable parasitemia within 2 to 4 weeks.

TREATMENT

B. microti infections in patients with intact spleens are often self-limiting without treatment, although symptoms may persist for months with or without treatment. Because silent parasitemia may have prolonged symptoms and signs, treatment is advised for all patients infected with *Babesia*. Treatment with the combination of quinine sulfate (650 mg of salt orally tid) plus clindamycin (600 mg orally tid or 1.2 g parenterally bid) for 7 to 10 days is usually effective but may not always eliminate parasites. The pediatric dose is 20 to 40 mg/kg per day for quinine sulfate and 25 mg/kg per day for clindamycin, both given in three divided doses over 7 to 10 days. Atovaquone suspension (750 mg bid) plus azithromycin (500 to 1000 mg/d) may be effective when quinine and clindamycin fail. Especially severe infections with high-level *B. microti* parasitemia in asplenic patients have been successfully treated with exchange transfusions in addition to quinine and clindamycin.

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215. LEISHMANIASIS - *Barbara L. Herwaldt*

OVERVIEW

DEFINITION

The term *leishmaniases* refers collectively to various clinical syndromes caused by obligate intracellular protozoa of the genus *Leishmania* (order Kinetoplastida). Leishmaniasis is endemic in diverse ecologic settings in the tropics, the subtropics, and southern Europe that range from deserts to rain forests and from rural to periurban areas. It typically is a vector-borne zoonosis, with rodents and canids as common reservoir hosts and humans as incidental hosts. In humans, visceral, cutaneous, and mucosal leishmaniasis result from infection of macrophages throughout the mononuclear-phagocyte system, in the skin, and in the naso-oropharyngeal mucosa, respectively. Current challenges include the emergence of leishmaniasis in new geographic areas and host populations (e.g., visceral leishmaniasis in persons infected with HIV) as well as the need for field-applicable, rapid diagnostic tests and for effective, safe, and affordable oral therapies, control measures, and immunoprophylactic agents.

ETIOLOGY

The organisms that cause the various forms of leishmaniasis in humans are listed inTable 215-1. Visceral leishmaniasis is typically but not exclusively caused by organisms of the *Leishmania donovani* complex; Old World cutaneous leishmaniasis by *L. tropica*, *L. major*, and *L. aethiopica*; New World (or American) cutaneous leishmaniasis by organisms of the *L. mexicana* complex and the *Viannia* subgenus; and mucosal leishmaniasis by some organisms in the *Viannia* subgenus.

LIFE CYCLE

Leishmania parasites are transmitted by the bite of female phlebotomine sandflies [genus *Phlebotomus* (Old World) or *Lutzomyia* (New World)]. As the flies attempt to feed, they regurgitate the parasite's flagellated promastigote stage into the skin of mammalian hosts. Promastigotes attach to receptors on macrophages, are phagocytized, and transform within phagolysosomes into the nonflagellated amastigote stage, which multiplies by binary fission. After rupture of infected macrophages, amastigotes are phagocytized by other macrophages. If ingested by feeding sandflies, amastigotes transform back into promastigotes, which require at least 7 days to become infective.

IMMUNOLOGY

Advances in the understanding of the immunology of leishmaniasis have made this parasitic disease the paradigm for studies of the T cell subsets and cytokines that govern resistance and susceptibility to intracellular pathogens. The paradigm is best demonstrated in murine *L. major* infection. In inbred mice, production of interferon g (IFN-g) by T_H1 and natural killer cells confers resistance. Interleukin (IL)12 induces naive T cells to differentiate into T_H1 cells and induces T cells and natural killer cells to produce IFN-g. In contrast, expansion of IL-4-producing T_H2 cells mediates

susceptibility.

Not all aspects of leishmaniasis in mice, whose susceptibility to leishmanial infection is genetically determined, apply to human infection, for which the genetic determinants are being investigated. However, a consistent principle is that healing and resistance to reinfection are associated with expanding numbers of *Leishmania*-specific T_H1 cells, production ofIFN-g, and activation of macrophages to kill intracellular amastigotes. In human visceral leishmaniasis,IL-10 appears to be associated with pathology; in addition, IL-4 may contribute to progression of disease.

GENERAL DIAGNOSTIC PRINCIPLES

Definitive diagnosis of leishmaniasis requires demonstration of the parasite. To identify amastigotes by light-microscopic examination, the specimen obtained from an infected site (e.g., thin smear, histologic section) should be stained with Giemsa or another Romanovsky stain and presumptive amastigotes (2 to 4 um in diameter) examined under oil immersion for the presence of a nucleus and a rod-shaped kinetoplast (Fig. 215-1); the latter is a specialized mitochondrial structure that contains extranuclear DNA. Other means of parasitologic confirmation include in vitro culture (e.g., on Novy-MacNeal-Nicolle medium), animal inoculation, and use of molecular techniques that are under investigation (e.g., polymerase chain reaction).

The *Leishmania* species that infect humans are morphologically similar. They can be distinguished by isoenzyme analysis of cultured promastigotes, determination of monoclonal antibody specificity, or various molecular methods.

Indirect immunologic methods for diagnosis include serologic assays and tests for *Leishmania*-specific cell-mediated immunity (e.g., skin testing for delayed-type hypersensitivity reactions). The usefulness of such methods depends in part on the clinical syndrome (see below). Traditional serologic assays (e.g., indirect immunofluorescent antibody testing) do not reliably distinguish past from current infection, and no leishmanin skin-test preparation has been approved for use in the United States. Advances in molecular methods (e.g., production of recombinant/synthetic antigens) may lead to the development of better diagnostic techniques.

GENERAL THERAPEUTIC PRINCIPLES

For a given case of leishmaniasis, it is important to consider whether the patient's illness could result in substantial morbidity or in death and therefore requires expeditious treatment with a regimen that generally is highly effective. For decades, the pentavalent antimonial (Sb^V) compounds sodium stibogluconate and meglumine antimonate have been the mainstays of antileishmanial therapy (Table 215-2). Toxicity (with such manifestations as myalgia, arthralgia, fatigue, elevated aminotransferase levels, chemical pancreatitis, and electrocardiographic abnormalities) becomes increasingly common as the course of treatment progresses but usually does not limit therapy and is reversible.

The traditional parenteral alternatives to Sb^V -- amphotericin B and pentamidine

isethionate -- are generally considered more apt to induce serious or irreversible toxicity (e.g., nephrotoxicity). However, these agents are being advocated for use in some situations (see below; Table 215-2), in part because of the benefits of new formulations (e.g., lipid formulations of amphotericin B) or dosage regimens of these drugs and the decreasing effectiveness of Sb^{V} in some settings. Many other agents have been touted as alternatives or adjuncts to Sb^{V}, often on the basis of suboptimal data. Some of these agents may be useful in certain situations, with one caveat: even the results of well-conducted clinical trials are not always generalizable to the treatment of patients in other settings. Most of the nonparenteral agents evaluated to date have at best modest activity against some of the *Leishmania* species.

PREVENTION AND CONTROL

The transmission of *Leishmania* species typically is focal, with local "hot spots," in part because of the limited flight range of sandflies; these insects have a short, hopping flight style and usually remain within a few hundred meters of their breeding site. They rest in dark, moist places in habitats ranging from deserts to rain forests; peridomestic sandflies rest in debris or rubble near buildings.

Personal protective measures include the avoidance of outdoor activities when sandflies are most active (dusk to dawn); the use of mechanical barriers such as screens and bed-nets that keep out sandflies, which are about one-third the size of mosquitoes; the wearing of protective clothing; and the application of insect repellent to exposed skin. Impregnation of clothing, bed-nets, and screens with permethrin may also be useful, as may spraying of dwellings with residual-action insecticide. Vaccine strategies are being investigated. Treatment of human cases is an effective control measure only where humans are the primary reservoirs of infection. Vector control and elimination of reservoir hosts may be useful in select settings -- for example, where transmission is intra- or peridomiciliary.

VISCERAL LEISHMANIASIS

More than 90% of the world's cases of visceral leishmaniasis occur in Bangladesh, northeastern India (particularly Bihar State), Nepal, Sudan, and northeastern Brazil. The causative species typically are those of the *L. donovani* complex (Table 215-1). The organisms can be transmitted not only by sandflies but also congenitally and parenterally (e.g., through blood transfusions or sharing of needles). Infection begins in macrophages at the inoculation site (e.g., in dermal macrophages at the site of a sandfly bite) and disseminates throughout the mononuclear-phagocyte system in the context of both specific (i.e., to leishmanial antigens) and nonspecific (e.g., to tuberculin) anergy.

CLINICAL MANIFESTATIONS

Visceral infection can remain subclinical or become symptomatic, with an acute, subacute, or chronic course. In some settings, inapparent infections far outnumber clinically apparent ones; malnutrition is among the risk factors for the development of disease. The incubation period usually ranges from weeks to months but can be as long as years. Whereas the general term *visceral leishmaniasis* covers a broad spectrum of severity and manifestations, the term *kala-azar* (Hindi for "black fever," indicating that

the skin of some patients turns gray) generally conjures up the classic image of profoundly cachectic, febrile patients who are heavily infected with parasites and have life-threatening disease. Splenomegaly (with the spleen most often soft and nontender) typically is more impressive than hepatomegaly, and the spleen can in fact be massive; both splenomegaly and hepatomegaly result from reticuloendothelial cell hyperplasia. Peripheral lymphadenopathy is common in some settings, including Sudan.

The abnormal laboratory findings associated with advanced disease include pancytopenia -- anemia, leukopenia (neutropenia, marked eosinopenia, relative lymphocytosis and monocytosis), and thrombocytopenia -- as well as hypergammaglobulinemia (chiefly involving IgG, from polyclonal B cell activation) and hypoalbuminemia. Causes of anemia can include bone-marrow infiltration, hypersplenism, autoimmune hemolysis, and bleeding.

Some patients develop post-kala-azar dermal leishmaniasis. This syndrome is manifested by skin lesions (including macules, papules, nodules, and patches) that typically are most prominent on the face. These lesions can develop during therapy or within a few months thereafter (e.g., in East Africa) or can develop years later (e.g., in India); relapse of visceral infection can occur. Persons with persistent skin lesions can serve as reservoir hosts of infection.

Viscerotropic leishmaniasis caused by *L. tropica*, which typically is dermotropic, was recognized among U.S. soldiers who participated in Operation Desert Storm in the Persian Gulf. The affected persons had light parasite burdens and nonspecific manifestations of visceral infection (e.g., fatigue, fever, and gastrointestinal symptoms).

DIAGNOSIS

Although molecular techniques are under investigation, parasitologic diagnosis of visceral leishmaniasis has traditionally been accomplished by demonstration of the parasite on stained slides or in cultures of a tissue aspirate or a biopsy specimen (e.g., of spleen, liver, bone marrow, or lymph node). The diagnostic yield is highest for splenic aspiration (specifically, as high as 98% vs.<90% for other specimens), but this procedure can cause hemorrhage.

Patients with florid kala-azar commonly have relatively heavy parasite burdens, develop high titers of antibody to *Leishmania* (diagnostically useful but not protective), and have undetectable *Leishmania*-specific cell-mediated immunity (with leishmanin skin-test reactivity as well as lymphocyte proliferation andIFN-gresponses to leishmanial antigens typically noted only after recovery). In contrast, viscerotropic leishmaniasis can be difficult to diagnose because of a light parasite burden and a minimal antibody response. A promising noninvasive serologic method for diagnosing kala-azar uses nitrocellulose paper strips impregnated with K39, a recombinant leishmanial polypeptide; this technique is being field-tested.

The differential diagnosis of visceral leishmaniasis includes other tropical infectious diseases that cause fever or organomegaly (e.g., typhoid fever, miliary tuberculosis, brucellosis, malaria, tropical splenomegaly syndrome, and schistosomiasis) as well as diseases such as leukemia and lymphoma. Post-kala-azar dermal leishmaniasis should

be differentiated from syphilis, yaws, and leprosy.

TREATMENT

Because persons who have kala-azar generally die if not appropriately treated, highly effective therapy is essential, as is close monitoring for bleeding and intercurrent infectious conditions such as pneumonia and diarrhea. Outside of India, treatment with a pentavalent antimonial compound still is common (Table 215-2). The use of an alternative parenteral agent (Table 215-2) should be considered even for first-line therapy if unresponsiveness to Sb^{V}therapy is prevalent, as it is in India, or if nonantimonial therapy would be advantageous for other reasons (e.g., toxicity profile or duration of therapy).

A major advance has been the advent of lipid formulations of amphotericin B, in which various lipids have replaced deoxycholate. These formulations, which passively target amphotericin to macrophage-rich organs, are more costly than conventional amphotericin B but are associated with less nephrotoxicity and can be given in shorter courses. Other parenteral alternatives that have merit in some settings include the aminoglycoside paromomycin (the chemical equivalent of aminosidine; not commercially available as of this writing), which has been used as monotherapy (in India) or as an adjunct to Sb^{V}, and pentamidine. The oral agent miltefosine is being evaluated in clinical trials and preliminarily appears to be highly effective and acceptably tolerated.

Typically, patients feel better and become afebrile during the first week of treatment. Abnormal laboratory findings and splenomegaly may take weeks or months to resolve. The best indicator of permanent cure is freedom from clinical relapse during at least 6 months of follow-up. Repeat tissue sampling is indicated if the patient's status is in question. The persistence of some parasites is not necessarily a poor prognostic indicator, whereas the apparent absence of parasites does not ensure that the patient will not have a relapse.

VISCERAL LEISHMANIASIS IN PERSONS INFECTED WITH HIV

Visceral leishmaniasis has become an important opportunistic infection among persons infected with HIV-1 in geographic areas in which both infections are endemic. To date, most dual infections have been reported from southern Europe, where *L. infantum* (of the *L. donovani* complex) is endemic. In patients infected with HIV, even relatively avirulent *Leishmania* strains can disseminate to the viscera. Clinical leishmaniasis in coinfected patients can represent newly acquired or reactivated infection; most coinfected patients with clinically evident leishmaniasis have fewer than 200 CD4+ lymphocytes per microliter. Recent data suggest that leishmaniasis is a cofactor in the pathogenesis of HIV infection; the lipophosphoglycan (a major surface molecule) of *L. donovani* induces transcription of HIV in CD4+ cells.

A diagnosis of visceral leishmaniasis should be considered for patients infected with HIV who have ever been in leishmaniasis-endemic areas and who have manifestations such as unexplained fever, organomegaly, anemia, or pancytopenia. Coinfected patients can develop unusual manifestations of visceral leishmaniasis, in part because of atypical localization of the parasite (e.g., in the gastrointestinal tract).

The diagnostic sensitivity of classic serologic methods is lower in coinfected than in immunocompetent patients (~50% vs. >90%). However, parasitologic diagnosis by noninvasive means is easier in coinfected patients. Parasites are more commonly found in the circulating blood monocytes of these patients; the sensitivities are ~50% for a Giemsa-stained peripheral-blood smear and ~70% for culture of a buffy-coat preparation. Invasive methods of parasitologic diagnosis (e.g., microscopic examination or culture of a bone marrow aspirate) typically are highly sensitive, especially for previously untreated patients, who commonly have heavy parasite burdens.

Coinfected patients may initially respond well to standard antileishmanial therapy, albeit with more drug toxicity than is experienced by most immunocompetent persons. However, coinfected patients commonly have a chronic or relapsing course, seemingly irrespective of the drug regimens used for induction and suppression therapy.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis has traditionally been classified as New World (American) or Old World disease. Local names for New World disease include *chiclero ulcer* (Fig. 215-CD1), *pian bois* (bush yaws), and *uta*; those for Old World disease include *oriental sore*, *bouton d'orient*, *Aleppo evil,* and *Baghdad boil*. More than 90% of the world's cases of cutaneous leishmaniasis occur in Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, Syria, Brazil, and Peru. In the Americas, the leishmaniasis-endemic area extends from southern Texas to northern Argentina; the etiologic agents typically are those of the *L. mexicana* complex and the *Viannia* subgenus (Table 215-1) but also include *L. major*-like organisms and *L. chagasi*. Old World cutaneous leishmaniasis is caused by *L. tropica*, *L. major*, and *L. aethiopica* as well as by *L. infantum* and *L. donovani*.

CLINICAL MANIFESTATIONS

The incubation period for clinically evident disease typically ranges from weeks to months. The first manifestation is usually a papule at the site of the sandfly bite but can be regional lymphadenopathy (sometimes bubonic) in *L. (V.) braziliensis* infection. Most skin lesions evolve from papular to nodular to ulcerative (Fig. 215-CD2), with a central depression (which can be several centimeters in diameter) surrounded by a raised indurated border (Fig. 215-2). Some lesions persist as nodules or plaques. Multiple primary lesions, satellite lesions, regional adenopathy, sporotrichoid subcutaneous nodules, lesion pain or pruritus, and secondary bacterial infection are variably present. The infecting species, the location of the lesion, and the host's immune response are among the determinants of the clinical manifestations and chronicity of untreated lesions. For example, in the New World, lesions caused by *L. mexicana* tend to be smaller and less chronic than those caused by *L. (V.) braziliensis*; in the Old World, *L. major* tends to cause "wet" exudative lesions that are less chronic than the "dry" lesions with central crusting that are caused by *L. tropica*. The spontaneous resolution of lesions does not preclude reactivation or reinfection.

The polyparasitic and oligoparasitic ends of the spectrum of cutaneous leishmaniasis are respectively represented by the rare syndromes of diffuse cutaneous leishmaniasis (DCL) and leishmaniasis recidivans, both of which are notoriously difficult to treat. DCL,

caused by *L. aethiopica* (Old World) or by the *L. mexicana* complex (New World), develops in the context of *Leishmania*-specific anergy and is manifested by chronic, disseminated, nonulcerative skin lesions; on histopathologic examination of specimens from these lesions, abundant parasites but few lymphocytes are noted. Leishmaniasis recidivans, a hyperergic variant with scarce parasites, is usually caused by *L. tropica* and manifested by a chronic solitary lesion on the cheek that expands slowly despite central healing.

DIAGNOSIS

Dermal scrapings of debrided ulcerative lesions are useful for histologic examination, aspirates of skin lesions and lymph nodes for in vitro culture, and biopsy specimens for both examination and culture. Although examination of histologic sections of biopsy specimens can help exclude other diagnoses, amastigotes appear larger and are more easily recognizable on Giemsa-stained thin smears (e.g., smears of dermal scrapings, touch preparations of biopsy specimens). As lesions age, amastigotes become scarcer, and parasitologic confirmation becomes more difficult.

Serologic testing is an insensitive means for diagnosing cutaneous leishmaniasis; antibody titers usually are at most minimally elevated except in patients who haveDCL. In contrast, leishmanin skin-test reactivity usually develops during active infection in persons who have simple cutaneous or recidivans leishmaniasis but not in those who have DCL.

Cutaneous leishmaniasis is frequently confused with tropical, traumatic, and venous-stasis ulcers; foreign-body reactions; superinfected insect bites; myiasis; impetigo; fungal infections (e.g., sporotrichosis); mycobacterial infections; and other diseases (e.g., sarcoidosis, neoplasms).DCL and leishmaniasis recidivans should be differentiated from lepromatous leprosy and lupus vulgaris, respectively.

TREATMENT

Decisions about whether and how to treat cutaneous leishmaniasis should take into account whether mucosal dissemination is possible (as it is in the Americas with some organisms in the *Viannia* subgenus;Table 215-1) as well as the location (e.g., on the face), number, size, evolution, and chronicity of the cutaneous lesions. When optimal effectiveness is important, intravenous or intramuscular Sb^{v}therapy is recommended (Table 215-2). In studies in Colombia (predominantly with the *Viannia* subgenus), relatively short courses of treatment with pentamidine (Table 215-2) were effective (cure rate, 96%) and quite well tolerated. Thus pentamidine may be a good parenteral alternative to Sb^{v}. The clinical response to antileishmanial therapy begins with lessening induration; healing often continues after the end of therapy. Relapse typically is manifested by clinical reactivation at the margin of the lesion.

Although many oral agents have been touted for treatment of leishmaniasis, even those that are the most effective typically are moderately active at best and are effective only against some *Leishmania* species or strains. The oral agent miltefosine is being evaluated. In the New World, ketoconazole has some activity against *L. mexicana* and *L. (V.) panamensis* and may be more active than itraconazole (at least against the

Viannia subgenus), which is better tolerated (Table 215-2). Dapsone has looked promising in India but not in Colombia. Adjunctive immunotherapy remains highly experimental but may be useful inDCL. Local or topical therapy can be considered for some cases of infection in which there is no risk of mucosal dissemination (e.g., for relatively benign lesions caused by *L. mexicana* or *L. major*). Examples of local approaches include the application of an ointment containing paromomycin and methylbenzethonium chloride (not licensed in the United States), the intralesional administration of Sb^{V}, heat therapy, and cryotherapy.

MUCOSAL LEISHMANIASIS

Leishmanial infection of the naso-oropharyngeal mucosa is a relatively rare but potentially disfiguring metastatic complication of cutaneous leishmaniasis. Mucosal disease develops despite antileishmanial cell-mediated immunity and most commonly is caused by organisms of the *Viannia* subgenus, typically *L. (V.) braziliensis* but also *L. (V.) panamensis* and *L. (V.) guyanensis*. Although mucosal disease usually becomes clinically evident within several years after the healing of the original cutaneous lesions, cutaneous and mucosal lesions can coexist or appear decades apart. Typically, the original cutaneous lesions of patients who develop mucosal disease were not treated or were suboptimally treated.

Mucosal involvement generally is manifested first by persistent unusual nasal symptoms (e.g., epistaxis), with erythema and edema of the nasal mucosa, and then by progressive, ulcerative, naso-oropharyngeal destruction (Fig. 215-CD3). Supportive laboratory data (e.g., a positive serologic test) are useful, but the scarcity of amastigotes makes parasitologic confirmation difficult. The differential diagnosis includes sarcoidosis, neoplasms, midline granuloma, rhinoscleroma, paracoccidioidomycosis, histoplasmosis, leprosy, syphilis, and tertiary yaws.

Treatment with a pentavalent antimonial compound is moderately effective for mild mucosal disease, whereas advanced disease may not respond to such treatment or may relapse repeatedly (Table 215-2). Amphotericin B (deoxycholate) is the best alternative drug currently available. Patients who develop signs of respiratory compromise during therapy may benefit from the concomitant administration of glucocorticoids.

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216. TRYPANOSOMIASIS - *Louis V. Kirchhoff*

CHAGAS' DISEASE

DEFINITION

Chagas' disease, or American trypanosomiasis, is a zoonosis caused by the protozoan parasite *Trypanosoma cruzi*. Acute Chagas' disease is usually a mild febrile illness that results from initial infection with the organism. After spontaneous resolution of the acute illness, most infected persons remain for life in the indeterminate phase of chronic Chagas' disease, which is characterized by subpatent parasitemia, easily detectable antibodies to *T. cruzi*, and an absence of symptoms. In a minority of chronically infected patients, cardiac and gastrointestinal lesions develop that can result in serious morbidity and even death.

LIFE CYCLE AND TRANSMISSION

T. cruzi is transmitted among its mammalian hosts by hematophagous triatomine insects, often called reduviid bugs. The insects become infected by sucking blood from animals or humans who have circulating parasites. Ingested organisms multiply in the gut of the triatomines, and infective forms are discharged with the feces at the time of subsequent blood meals. Transmission to a second vertebrate host occurs when breaks in the skin, mucous membranes, or conjunctivae become contaminated with bug feces that contain infective parasites. *T. cruzi* also can be transmitted by the transfusion of blood donated by infected persons, from mother to fetus, and in laboratory accidents.

PATHOLOGY

An indurated inflammatory lesion called a *chagoma* often appears at the site of the parasite's entry. Local histologic changes include the presence of parasites within leukocytes and cells of subcutaneous tissues and the development of interstitial edema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. After dissemination of the organisms through the lymphatics and the bloodstream, muscles (including the myocardium) may become heavily parasitized. The characteristic pseudocysts present in sections of infected tissues are intracellular aggregates of multiplying parasites.

The pathogenesis of chronic Chagas' disease is poorly understood. The heart is the organ most commonly affected, and changes include biventricular enlargement, thinning of the ventricular walls, apical aneurysms, and mural thrombi. Widespread lymphocytic infiltration, diffuse interstitial fibrosis, and atrophy of myocardial cells are often demonstrated, but parasites are rarely seen in myocardial tissue. Conduction-system involvement often affects the right branch and the left anterior branch of the bundle of His. In chronic Chagas' disease of the gastrointestinal tract (megadisease), the esophagus and colon may exhibit varying degrees of dilatation. On microscopic examination, focal inflammatory lesions with lymphocytic infiltration are seen, and the number of neurons in the myenteric plexus may be markedly reduced.

EPIDEMIOLOGY

T. cruzi is found only in the Americas. Wild and domestic mammals harboring *T. cruzi* and infected triatomines are found in spotty distributions from the southern United States to southern Argentina. Humans become involved in the cycle of transmission when infected vectors take up residence in the primitive wood, adobe, and stone houses common in much of Latin America. Thus, human *T. cruzi* infection is a health problem primarily among the poor in rural areas of Central and South America. Most new *T. cruzi* infections in rural settings occur in children, but the incidence is unknown because most cases go undiagnosed. Thousands of individuals also become infected every year through blood transfusions in urban areas. Several dozen patients with HIV and chronic *T. cruzi* infections who underwent acute recrudescence of the latter have been described. These patients generally presented with *T. cruzi* brain abscesses, a manifestation of the illness that does not occur in immunocompetent persons. Currently, it is estimated that 16 to 18 million people, more than a third of whom live in Brazil, are chronically infected with *T. cruzi*. Chronic Chagas' disease is a major cause of morbidity and mortality in many Latin American countries, including Mexico, since many chronically infected persons eventually develop symptomatic cardiac lesions or gastrointestinal disease.

In recent years, the rate of *T. cruzi* transmission has been decreasing in several endemic countries as a result of successful vector and blood-bank control programs. A major program in the "southern cone" nations of South America (Uruguay, Paraguay, Bolivia, Brazil, Chile, and Argentina), begun in 1991, has provided the framework for much of the progress achieved. If current trends continue, transmission will be essentially eliminated in much of the endemic range by the year 2003.

Acute Chagas' disease is rare in the United States. Five cases of autochthonous transmission and four instances of transmission by blood transfusion have been reported. Moreover, in the last 26 years, seven laboratory-acquired infections and nine imported cases of acute Chagas' disease were reported to the Centers for Disease Control and Prevention (CDC). In contrast, the prevalence of chronic *T. cruzi* infections in the United States has increased considerably in recent years. Since the mid-1970s, enormous numbers of Latin Americans have emigrated to the United States. In one study conducted in Washington, D.C., 5% of Salvadoran and Nicaraguan immigrants were found to have chronic *T. cruzi* infections. Estimates based on the latter study and on studies done in several United States blood banks put the total number of infected immigrants now living in the United States at more than 50,000. The presence of these carriers of *T. cruzi* creates a substantial risk of transmission by blood transfusion, as is evidenced by the four transfusion-associated cases just cited.

CLINICAL COURSE

The first signs of acute Chagas' disease develop at least 1 week after invasion by the parasites. When the organisms enter through a break in the skin, an indurated area of erythema and swelling (the chagoma), accompanied by local lymphadenopathy, may appear. Romana's sign -- the classic finding in acute Chagas' disease, which consists of unilateral painless edema of the palpebrae and periocular tissues -- can result when the conjunctiva is the portal of entry. These initial local signs are followed by malaise, fever, anorexia, and edema of the face and lower extremities. A morbilliform rash may also

appear. Generalized lymphadenopathy and hepatosplenomegaly may develop. Severe myocarditis develops rarely; most deaths in acute Chagas' disease are due to heart failure. Neurologic signs are not common, but meningoencephalitis has been reported. The acute symptoms resolve spontaneously in virtually all patients, who then enter the asymptomatic or indeterminate phase of chronic *T. cruzi* infection.

Symptomatic chronic Chagas' disease becomes apparent years or even decades after the initial infection. The heart is commonly involved, and symptoms are caused by rhythm disturbances, cardiomyopathy, and thromboembolism. Right bundle-branch block is the most common electrocardiographic abnormality, but other types of atrioventricular block, premature ventricular contractions, and tachy- and bradyarrhythmias occur frequently. Cardiomyopathy often results in right-sided or biventricular heart failure. Embolization of mural thrombi to the brain or other areas may take place. Patients with megaesophagus suffer from dysphagia, odynophagia, chest pain, and regurgitation. Aspiration can occur, especially during sleep, and repeated episodes of aspiration pneumonitis are common. Weight loss, cachexia, and pulmonary infection can result in death. Patients with megacolon are plagued by abdominal pain and chronic constipation, and advanced megacolon can cause obstruction, volvulus, septicemia, and death.

DIAGNOSIS

The diagnosis of acute Chagas' disease requires the detection of parasites. Microscopic examination of fresh anticoagulated blood or of the buffy coat is the simplest way to see the motile organisms. Parasites also can be seen in Giemsa-stained thin and thick blood smears. When repeated attempts to visualize the organisms are unsuccessful, mouse inoculation, culture of blood in specialized media, or xenodiagnosis can be performed. In the last technique, uninfected triatomine insects are allowed to feed on the patient's blood. When done properly, all of these methods yield positive results in a high proportion of patients with acute Chagas' disease and in at least half of those with chronic infections. Since early treatment of acute Chagas' disease is extremely important, however, the decision to initiate therapy for *T. cruzi* infection despite negative wet preparations and smears must be made on clinical and epidemiologic grounds before the results of these indirect methods become available. Serologic testing is of limited usefulness in diagnosing acute Chagas' disease.

The diagnosis of chronic Chagas' disease is made by the detection of antibodies that bind to *T. cruzi* antigens. Demonstration of the parasite is not of primary importance. Several highly sensitive serologic tests for antibodies to *T. cruzi* are used widely in Latin America, including complement-fixation and immunofluorescence tests and enzyme-linked immunosorbent assays (ELISAs). However, a persistent problem with these conventional assays is the occurrence of false-positive reactions, typically with sera from patients who have other parasitic infections or autoimmune diseases. For this reason, it is generally recommended that positivity in one assay be confirmed by two other tests and that well-characterized positive and negative comparison sera be included in each run. A highly sensitive and specific method for detecting antibodies to *T. cruzi* [approved by the Clinical Laboratory Improvement Amendment (CLIA) and available in the author's laboratory] employs immunoprecipitation of radiolabeled *T. cruzi* antigens and electrophoresis. Serodiagnostic assays that employ recombinant *T.*

cruzi proteins as target antigens are being developed, as are tests based on the amplification of *T. cruzi* DNA sequences by polymerase chain reaction. However, these tests are not yet available for general use.

TREATMENT

Therapy for Chagas' disease is unsatisfactory. Nifurtimox is the only drug active against *T. cruzi* that is available in the United States. In acute Chagas' disease, nifurtimox markedly reduces the duration of symptoms and parasitemia and decreases the mortality rate. Nevertheless, its efficacy at eradicating parasites is low. Limited studies have shown that only ~70% of acute infections are cured parasitologically by a full course of treatment. Despite its limitations, nifurtimox treatment should be initiated as early as possible in acute Chagas' disease. Moreover, when laboratory accidents occur in which it appears likely that *T. cruzi* infection could become established, nifurtimox therapy should be initiated without waiting for clinical or parasitologic indications of infection.

Common adverse effects of nifurtimox include abdominal pain, anorexia, nausea, vomiting, and weight loss. Neurologic reactions to the drug may include restlessness, disorientation, insomnia, twitching, paresthesia, polyneuritis, and seizures. These symptoms usually disappear when the dosage is reduced or treatment is discontinued. The recommended daily dosage is 8 to 10 mg/kg for adults, 12.5 to 15 mg/kg for adolescents, and 15 to 20 mg/kg for children 1 to 10 years of age. The drug should be given orally in four divided doses each day, and therapy should be continued for 90 to 120 days. Nifurtimox is available from the Drug Service of theCDC in Atlanta, Georgia (telephone number, 770-639-3670).

Benznidazole is a second agent used to treat Chagas' disease. Its efficacy is similar to that of nifurtimox, and its adverse effects include peripheral neuropathy, rash, and granulocytopenia. The recommended oral dosage is 5 mg/kg per day for 60 days. Benznidazole is used widely in Latin America.

The question of whether patients in the indeterminate or chronic symptomatic phases of Chagas' disease should be treated with nifurtimox or benznidazole has been debated for years. Studies of *T. cruzi*-infected laboratory animals and humans suggest that elimination of the parasites reduces the appearance or progression of cardiac pathology. In view of these findings, an international panel of experts has recommended that all patients infected with *T. cruzi* be treated with one drug or the other, regardless of their clinical status or the duration of infection.

The usefulness of allopurinol, fluconazole, and itraconazole for the treatment of acute Chagas' disease has been studied extensively in laboratory animals and to a lesser extent in humans. None of these drugs has exhibited a level of anti-*T. cruzi* activity that warrants its use in patients. Studies in mice have shown that recombinant interferon g decreases the duration and severity of acute *T. cruzi* infection; however, its usefulness in persons with acute Chagas' disease has not been evaluated systematically.

Patients who develop cardiac and/or gastrointestinal disease in association with *T. cruzi* infection should be referred to appropriate subspecialists for further evaluation and

treatment. Cardiac transplantation is an option for patients with end-stage chagasic cardiopathies. Postoperative prophylaxis with nifurtimox or benznidazole should be considered because without it the immunosuppression required after surgery has been shown to result in reactivation of *T. cruzi* infection, often with serious consequences or even death.

PREVENTION

Since drug therapy is unsatisfactory and vaccines are not available, the control of *T. cruzi* transmission in endemic countries must depend on reduction of domiciliary vector populations by spraying of insecticides, improvement of housing, and education. In addition, in endemic areas, programs for the screening of donated blood for *T. cruzi* need to be expanded and improved to reduce rates of transmission by transfusion. Tourists traveling in endemic areas should avoid sleeping in dilapidated houses outside urban areas. Mosquito nets and insect repellent provide additional protection.

In the United States, the question of how best to avoid transmission of *T. cruzi* by blood transfusion is not easily resolved. Since no assay for *T. cruzi* infection has received clearance from the Food and Drug Administration (FDA) for use in blood banks, serologic screening is not yet an option. The FDA currently mandates the use of a questionnaire for identifying and deferring donors at high risk for *T. cruzi* infection. This approach may be effective and not reduce the blood supply intolerably, but it is important to bear in mind that approaches based solely on questionnaires have not been entirely successful at eliminating transfusion-associated transmission of other infectious agents.

In view of the possibly serious consequences of chronic *T. cruzi* infection, it would be prudent for all immigrants from endemic regions to be tested for evidence of infection. Identification of infected persons is also important because the implantation of pacemakers benefits some patients who develop ominous rhythm disturbances. The possibility of congenital transmission is yet another justification for screening.

Laboratory personnel should wear gloves and eye protection when working with *T. cruzi* and infected vectors.

SLEEPING SICKNESS

DEFINITION

Sleeping sickness, or human African trypanosomiasis (HAT), is caused by flagellated protozoan parasites that belong to the *T. brucei* complex and are transmitted to humans by tsetse flies. In untreated patients, the trypanosomes first cause a febrile illness that is followed months or years later by progressive neurologic impairment and death.

THE PARASITES AND THEIR TRANSMISSION

The East African (*rhodesiense*) and the West African (*gambiense*) forms of sleeping sickness are caused, respectively, by two trypanosome subspecies: *T. brucei rhodesiense* and *T. brucei gambiense*. These subspecies are morphologically

indistinguishable but cause illnesses that are epidemiologically and clinically distinct. The parasites are transmitted by blood-sucking tsetse flies of the genus *Glossina*. The insects acquire the infection when they ingest blood from infected mammalian hosts. After many cycles of multiplication in the midgut of the vector, the parasites migrate to the salivary glands. Their transmission takes place when they are inoculated during a subsequent blood meal. The injected trypanosomes multiply in the blood and other extracellular spaces and evade immune destruction in mammalian hosts for long periods by undergoing antigenic variation, in which the antigenic structure of their surface coat of glycoproteins changes periodically.

PATHOGENESIS AND PATHOLOGY

A self-limited inflammatory lesion (trypanosomal chancre) may appear a week or so after the bite of an infected tsetse fly. A systemic febrile illness then evolves as the parasites are disseminated through the lymphatics and bloodstream. SystemicHATwithout central nervous system (CNS) involvement is generally referred to as *stage I disease*. In this stage, widespread lymphadenopathy and splenomegaly reflect marked lymphocytic and histiocytic proliferation and invasion of morular cells, which are plasmacytes that may be involved in the production of IgM. Endarteritis, with perivascular infiltration of both parasites and lymphocytes, may develop in lymph nodes and spleen. Myocarditis develops frequently in patients with stage I disease and is especially common in *T. b. rhodesiense* infections.

Hematologic manifestations that accompany stage IHATinclude moderate leukocytosis, thrombocytopenia, and anemia. High levels of immunoglobulins, consisting primarily of polyclonal IgM, are a constant feature, and heterophile antibodies, antibodies to DNA, and rheumatoid factor are often detected. High levels of antigen-antibody complexes may play a role in the tissue damage and increased vascular permeability that facilitate dissemination of the parasites.

Stage II disease involves invasion of theCNS. The presence of trypanosomes in perivascular areas is accompanied by intense infiltration of mononuclear cells. Abnormalities in cerebrospinal fluid (CSF) include increased pressure, elevated total protein concentration, and pleocytosis. In addition, trypanosomes are frequently found in CSF.

EPIDEMIOLOGY

The trypanosomes that cause sleeping sickness are found only in Africa. Approximately 50 million persons are at risk of acquiringHAT, and tens of thousands of new cases occur every year. Precise data are not available because health statistics are often incomplete in the developing countries where HAT is endemic. Sleeping sickness has undergone a resurgence in recent years, with major epidemics in the Sudan, Ivory Coast, Chad, the Central African Republic, and several other endemic countries.

Humans are the only reservoir of *T. b. gambiense*, which occurs in widely distributed foci in tropical rain forests of Central and West Africa. Gambiense trypanosomiasis is primarily a problem in rural populations; tourists rarely become infected. Trypanotolerant antelope species in savanna and woodland areas of Central and East Africa are the

principal reservoir of *T. b. rhodesiense*. Cattle also can become infected but generally succumb to the parasite. Since risk results for the most part from contact with tsetse flies that feed on wild animals, humans acquire *T. b. rhodesiense* infection only incidentally, usually while working in areas where infected game and vectors are present. In addition, occasional cases occur among visitors to game parks in East Africa. During the past 22 years, 21 cases of importedHAT have been reported to theCDC, most of which were caused by *T. b. rhodesiense*.

CLINICAL COURSE

A painful trypanosomal chancre appears in some patients at the site of inoculation of the parasite. Hematogenous and lymphatic dissemination (stage I disease) is marked by the onset of fever. Typically, bouts of high temperatures lasting several days are separated by afebrile periods. Lymphadenopathy is prominent in *T. b. gambiense* trypanosomiasis. The nodes are discrete, movable, rubbery, and nontender. Cervical nodes are often visible, and enlargement of the nodes of the posterior cervical triangle, or Winterbottom's sign, is a classic finding. Pruritus and maculopapular rashes are common. Inconstant findings include malaise, headache, arthralgias, weight loss, edema, hepatosplenomegaly, and tachycardia.

CNSinvasion (stage II disease) is characterized by the insidious development of protean neurologic manifestations that are accompanied by progressive abnormalities in theCSF. A picture of progressive indifference and daytime somnolence develops (hence the designation "sleeping sickness"), sometimes alternating with restlessness and insomnia at night. A listless gaze accompanies a loss of spontaneity, and speech may become halting and indistinct. Extrapyramidal signs may include choreiform movements, tremors, and fasciculations. Ataxia is frequent, and the patient may appear to have Parkinson's disease, with a shuffling gait, hypertonia, and tremors. In the final phase, progressive neurologic impairment ends in coma and death.

The most striking difference between the West African and East African trypanosomiases is that the latter illness tends to follow a more acute course. Typically, in tourists, systemic signs of infection, such as fever, malaise, and headache, appear before the end of the trip or shortly after the return home. Persistent tachycardia unrelated to fever is common early in the course of *T. b. rhodesiense* trypanosomiasis, and death may result from arrhythmias and congestive heart failure beforeCNSdisease develops. In general, untreated *T. b. rhodesiense* trypanosomiasis leads to death in a matter of weeks to months, often without a clear distinction between the hemolymphatic and CNS stages.

DIAGNOSIS

A definitive diagnosis ofHATrequires detection of the parasite. If a chancre is present, fluid should be expressed and examined directly by light microscopy for the highly motile trypanosomes. The fluid also should be fixed and stained with Giemsa. Material obtained by needle aspiration of lymph nodes early in the course of the illness should be examined similarly. Examination of wet preparations and Giemsa-stained thin and thick films of serial blood samples is also useful. If parasites are not seen in blood, efforts should be made to concentrate the organisms; the simplest method involves the use of

quantitative buffy coat analysis tubes (QBC, Becton-Dickinson, Franklin Lakes, NJ). In these tubes, which are coated with acridine orange, the parasites are separated from blood cells by centrifugation and are easily seen under light microscopy because of the stain. The buffy coat from 10 to 15 mL of anticoagulated blood or the pellet obtained by centrifugation of the eluate from 25 to 50 mL of blood passed through a DEAE-cellulose column also can be examined. Trypanosomes may be seen in material aspirated from the bone marrow; the aspirate can be inoculated into liquid culture medium, as can blood, buffy coat, lymph node aspirates, andCSF. Finally, *T. b. rhodesiense* infection can be detected by inoculation of these specimens into mice or rats, which results in patent parasitemias in a week or two. Although this method is highly sensitive for the detection of *T. b. rhodesiense*, it does not detect *T. b. gambiense* because of host specificity.

It is essential to examineCSF from all patients in whomHAT is suspected. An increase in the CSF cell count is the first abnormality to be detected; increases in opening pressure and in levels of total protein and IgM develop later. Trypanosomes may be seen in the sediment of centrifuged CSF. Any CSF abnormality in a patient in whom trypanosomes have been found at other sites must be viewed as pathognomonic forCNSinvolvement and thus must prompt specific treatment for CNS disease.

A number of serologic assays are available to aid in the diagnosis ofHAT, but their variable sensitivity and specificity mandate that decisions about treatment be based on demonstration of the parasite. These tests are of value for epidemiologic surveys.

TREATMENT

The drugs traditionally used for treatment ofHAT are suramin, pentamidine, and organic arsenicals. An addition to this list is eflornithine (difluoromethylornithine), which was approved by theFDA in November 1990 for the treatment of West African trypanosomiasis. In the United States these drugs can be obtained from theCDC. Therapy for HAT must be individualized on the basis of the infecting organism (*T. b. gambiense* or *T. b. rhodesiense*), the presence or absence ofCNSdisease, adverse reactions, and (occasionally) drug resistance. The choices of drugs for the treatment of HAT are summarized inTable 216-1.

Suramin is highly effective against stage I disease. However, it can cause serious adverse effects and must be administered under the close supervision of a physician. A 100- to 200-mg intravenous test dose should be administered to detect hypersensitivity. The dosage for adults is 1 g intravenously on days 1, 3, 7, 14, and 21. The regimen for children is 20 mg/kg (maximum, 1 g) intravenously on days 1, 3, 7, 14, and 21. The drug is given by slow intravenous infusion of a freshly prepared 10% aqueous solution. Approximately 1 patient in 20,000 has an immediate, severe, and potentially fatal reaction to the drug, developing nausea, vomiting, shock, and seizures. Less severe reactions include fever, photophobia, pruritus, arthralgias, and skin eruptions. Renal damage is the most common important adverse effect of suramin. Transient proteinuria often appears during treatment. A urinalysis should be done before each dose, and treatment should be discontinued if proteinuria increases or if casts and red cells appear in the sediment. Suramin should not be given to patients with renal insufficiency.

Eflornithine is highly effective for treatment of both stages of West African trypanosomiasis. In the trials on which theFDAbased its approval, this agent cured more than 90% of 600 patients with stage II disease. The recommended treatment schedule is 400 mg/kg per day intravenously in four divided doses for 2 weeks. Adverse reactions include diarrhea, anemia, thrombocytopenia, seizures, and hearing loss. The high dosage and duration of therapy required are disadvantages that make widespread use of eflornithine difficult.

Pentamidine is the alternative drug for patients with stage IHAT, although some *T. b. rhodesiense* infections are unresponsive to this agent. The dose for both adults and children is 4 mg/kg per day intramuscularly or intravenously for 10 days. Frequent, immediate adverse reactions include nausea, vomiting, tachycardia, and hypotension. These reactions are usually transient and do not warrant cessation of therapy. Other adverse reactions include nephrotoxicity, abnormal liver function tests, neutropenia, rashes, hypoglycemia, and sterile abscesses.

The arsenical melarsoprol is the drug of choice for the treatment of East African trypanosomiasis withCNSinvolvement. Melarsoprol cures both stages of the disease and therefore is also indicated for the treatment of stage I disease in patients who fail to respond to or cannot tolerate suramin and/or pentamidine. However, because of its relatively high toxicity, melarsoprol is never the first choice for the treatment of stage I disease. The drug should be given to adults in three courses of 3 days each. The dosage is 2 to 3.6 mg/kg per day intravenously in three divided doses for 3 days followed 1 week later by 3.6 mg/kg per day, also in three divided doses and for 3 days. The latter course is repeated 10 to 21 days later. In debilitated patients, suramin is administered for 2 to 4 days before therapy with melarsoprol is initiated. An 18-mg initial dose of the latter drug, followed by progressive increases to the standard dose, has been recommended. For children, a total of 18 to 25 mg/kg should be given over 1 month. A starting dose of 0.36 mg/kg intravenously should be increased gradually to a maximum of 3.6 mg/kg at 1- to 5-day intervals, for a total of 9 or 10 doses.

Melarsoprol is highly toxic and should be administered with great care. The incidence of reactive encephalopathy has been reported to be as high as 18% in some series. Clinical manifestations of reactive encephalopathy include high fever, headache, tremor, impaired speech, seizures, and even coma and death. Treatment with melarsoprol should be discontinued at the first sign of encephalopathy but may be restarted cautiously at lower doses a few days after signs have resolved. Extravasation of the drug results in intense local reactions. Vomiting, abdominal pain, nephrotoxicity, and myocardial damage can occur.

The treatment of patients with stage II East African disease who cannot tolerate melarsoprol is problematic. The combination of the arsenical tryparsamide and suramin is one possible approach, but its efficacy is limited because suramin does not penetrate theCNS well and tryparsamide is much less effective against *T. b. rhodesiense* than it is against *T. b. gambiense*. The schedule for tryparsamide therapy is 30 mg/kg (maximum, 2 g) in a single intravenous dose every 5 days for a total of 12 doses; that for suramin treatment is 10 mg/kg intravenously every 5 days, also for a total of 12 injections. Tryparsamide can cause encephalopathy, fever, vomiting, abdominal pain, rash, tinnitus, and a variety of ocular symptoms. Alternatively, eflornithine can be

administered as outlined above to patients who cannot tolerate melarsoprol, but, as noted, its effectiveness against *T. b. rhodesiense* is variable.

PREVENTION

HATposes complex public-health and epizootic problems in Africa. Considerable progress has been made in some areas through control programs that focus on eradication of vectors and drug treatment of infected humans; however, there is no consensus on the best approach to solving the overall problem, and major epidemics continue to occur. Individuals can reduce their risk of acquiring trypanosomiasis by avoiding areas known to harbor infected insects, by wearing protective clothing, and by using insect repellent. Chemoprophylaxis is not recommended, and no vaccine is available to prevent transmission of the parasites.

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217. *TOXOPLASMA* INFECTION - *Lloyd H. Kasper*

DEFINITION

Toxoplasmosis is the disease caused by infection with the obligate intracellular parasite *Toxoplasma gondii*. Acute infection acquired after birth may be asymptomatic but frequently results in the chronic persistence of cysts within the tissues of the host. Both acute and chronic toxoplasmosis are conditions in which the parasite is responsible for the development of clinically evident disease, including lymphadenopathy, encephalitis, myocarditis, and pneumonitis. Congenital toxoplasmosis is an infection of newborns that results from the transplacental passage of parasites from an infected mother to the fetus. These infants usually are asymptomatic at birth but later manifest a wide range of signs and symptoms, including chorioretinitis, strabismus, epilepsy, and psychomotor retardation.

ETIOLOGY

T. gondii is an intracellular coccidian that infects both birds and mammals. There are two distinct stages in the life cycle of *T. gondii*: the nonfeline and feline stages. In the nonfeline stage, tissue cysts that contain bradyzoites or sporulated oocysts are ingested by an intermediate host (e.g., a human, mouse, sheep, or pig). The cyst is rapidly digested by the acidic-pH gastric secretions. Bradyzoites or sporozoites are released, enter the small-intestinal epithelium, and transform into rapidly dividing tachyzoites. The tachyzoites can infect and replicate in all mammalian cells except red blood cells. Once attached to the host cell, the parasite penetrates the cell and forms a parasitophorous vacuole within which it divides. Parasite replication continues until the number of parasites within the cell approaches a critical mass and the cell ruptures, releasing parasites that infect adjoining cells.

As a result of this process, an infected organ soon shows evidence of cytopathology. Most tachyzoites are eliminated by means of the host's humoral and cell-mediated immune responses. Tissue cysts containing many bradyzoites develop 7 to 10 days after the systemic tachyzoite infection. These tissue cysts occur in a variety of host organs but persist principally within the central nervous system (CNS) and muscle. The development of this chronic stage completes the nonfeline portion of the life cycle. Active infection in the immunocompromised host is most likely due to the spontaneous release of encysted parasites that undergo rapid transformation into tachyzoites within the CNS.

The principal stage in the life cycle of the parasite takes place in the cat (the definitive host) and its prey. The parasite's sexual phase is defined by the formation of oocysts within the feline host. This enteroepithelial cycle begins with the ingestion of the bradyzoite tissue cysts and culminates after several intermediate stages in the production of gametes. Gamete fusion produces a zygote, which envelops itself in a rigid wall and is secreted in the feces as an unsporulated oocyst. After 2 to 3 days of exposure to air at ambient temperature, the noninfectious oocyst sporulates to produce eight sporozoite progeny. The sporulated oocyst can be ingested by an intermediate host, such as a person emptying a cat's litter box, a pig rummaging in a barnyard, or perhaps a mouse. It is in the intermediate host that the parasite completes its life cycle.

EPIDEMIOLOGY

T. gondii infects a wide range of mammals and birds. Its seroprevalence depends on the locale and the age of the population. Generally, hot arid climatic conditions are associated with a low prevalence of infection. In the United States and most European countries, the prevalence of seroconversion increases with age and exposure. For example, in the United States, 5 to 30% of individuals 10 to 19 years old and 10 to 67% of those over the age of 50 years show serologic evidence of exposure; seroprevalence increases by approximately 1% per year. In Central America, France, Turkey, and Brazil, the seroprevalence is higher.

TRANSMISSION

Oral Transmission The principal source of human *Toxoplasma* infection remains uncertain. Transmission usually takes place by the oral route and can be attributable to ingestion of either sporulated oocysts from contaminated soil or bradyzoites from undercooked meat. During acute feline infection, a cat may excrete as many as 100 million parasites per day. These very stable sporozoite-containing oocysts are highly infectious and may remain viable for many years in the soil. Humans infected during a well-documented outbreak of oocyst-transmitted infection develop stage-specific antibodies to the oocyst/sporozoite.

Children and adults also can acquire infection from tissue cysts containing bradyzoites. The ingestion of a single cyst is all that is required for human infection. Undercooking or insufficient freezing of meat is an important source of infection in the developed world. In the United States, 10 to 20% of lamb products and 25 to 35% of pork products show evidence of cysts that contain bradyzoites. The incidence in beef is much lower -- perhaps as low as 1%. Direct ingestion of bradyzoite cysts in these various meat products leads to acute infection.

Transmission via Blood or Organs In addition to oral transmission, direct transmission of the parasite by blood or organ products during transplantation takes place at a low rate. Viable parasites can be cultured from refrigerated anticoagulated blood, which may be a source of infection in individuals receiving blood transfusions. *T. gondii* infection also has been reported in kidney and heart transplant recipients who were uninfected before transplantation.

Transplacental Transmission About one-third of all women who acquire infection with *T. gondii* during pregnancy transmit the parasite to the fetus; the remainder give birth to normal, uninfected babies. Of the various factors that influence fetal outcome, gestational age at the time of infection is the most critical (see below). Few data support a role for recrudescent maternal infection as the source of congenital disease. Thus, women who are seropositive before pregnancy usually are protected against acute infection and do not give birth to congenitally infected neonates.

The following general guidelines can be used to evaluate congenital infection. There is essentially no risk if the mother becomes infected³6 months before conception. If infection is acquired <6 months before conception, the likelihood of transplacental

infection increases as the interval between infection and conception decreases. In pregnancy, if the mother becomes infected during the first trimester, the incidence of transplacental infection is lowest (about 15%), but the disease in the neonate is most severe. If maternal infection occurs during the third trimester, the incidence of transplacental infection is greatest (65%), but the infant is usually asymptomatic at birth. Infected infants who are normal at birth may have a higher incidence of learning disabilities and chronic neurologic sequelae than uninfected children. Only a small proportion (20%) of women infected with *T. gondii* develop clinical signs of infection. Often the diagnosis is first appreciated when routine postconception serologic tests show evidence of specific antibody.

PATHOGENESIS

Upon the host's ingestion of either tissue cysts containing bradyzoites or oocysts containing sporozoites, the parasites are released from the cysts by a digestive process. Bradyzoites are resistant to the effect of pepsin and invade the host's gastrointestinal tract. Within enterocytes, the parasites undergo morphologic transformation, giving rise to invasive tachyzoites. These tachyzoites induce a parasite-specific secretory IgA response. From the gastrointestinal tract, parasites are disseminated to a variety of organs, particularly lymphatic tissue, skeletal muscle, myocardium, retina, placenta, and theCNS. At these sites, the parasite infects host cells, replicates, and invades the adjoining cells. In this fashion, the hallmarks of the infection develop: cell death and focal necrosis surrounded by an acute inflammatory response.

In the normal immune host, both the humoral and the cellular immune responses control infection; parasite virulence and tissue tropism may be strain specific. Tachyzoites are sequestered by a variety of immune mechanisms, including induction of parasiticidal antibody, activation of macrophages with radical intermediates, production of interferong (IFN-g), and stimulation of cytotoxic T lymphocytes of the CD8+ phenotype. These antigen-specific lymphocytes are capable of killing both extracellular parasites and target cells infected with parasites. As tachyzoites are cleared from the acutely infected host, tissue cysts containing bradyzoites begin to appear, usually within theCNS and the retina. In the immunocompromised or fetal host, the immune factors necessary to control the spread of tachyzoite infection are lacking. This altered immune state allows the persistence of tachyzoites and gives rise to the progressive focal destruction that results in organ failure (i.e., necrotizing encephalitis, pneumonia, and myocarditis).

Persistence of infection with cysts containing bradyzoites is common in the immunocompetent host. This lifelong infection usually remains subclinical. Although bradyzoites are in a slow metabolic phase, cysts do degenerate and rupture within theCNS. This degenerative process, with the development of new bradyzoite-containing cysts, is the most probable source of recrudescent infection in immunocompromised individuals and the most likely stimulus for the persistence of antibody titers in the immunocompetent host.

PATHOLOGY

Cell death and focal necrosis due to replicating tachyzoites induce an intense mononuclear inflammatory response in any tissue or cell type infected. Tachyzoites

rarely can be visualized by routine histopathologic staining of these inflammatory lesions. However, immunofluorescence staining with parasitic antigen-specific antibodies can reveal either the organism itself or evidence of antigen. In contrast to this inflammatory process caused by tachyzoites, bradyzoite-containing cysts cause inflammation only at the early stages of development, and even this inflammation may be a response to the presence of tachyzoite antigens. Once the cysts reach maturity, the inflammatory process can no longer be detected, and the cysts remain immunologically quiescent within the brain matrix until they rupture.

Lymph Nodes During acute infection, lymph node biopsy demonstrates characteristic findings, including follicular hyperplasia and irregular clusters of tissue macrophages with eosinophilic cytoplasm. Granulomas rarely are evident in these specimens. Although tachyzoites are not usually visible, they can be sought either by subinoculation of infected tissue into mice, with resultant disease, or by the polymerase chain reaction (PCR). PCR amplification of DNA fragments representing either p30 (SAG-1) or p22 (SAG-2) surface antigen or B1 antigen is an effective and sensitive assay for establishing infection of lymph node tissue by tachyzoites.

Eyes In the eye, infiltrates of monocytes, lymphocytes, and plasma cells may produce uni- or multifocal lesions. Granulomatous lesions and chorioretinitis can be observed in the posterior chamber following acute necrotizing retinitis. Other ocular complications of infection include iridocyclitis, cataracts, and glaucoma.

Central Nervous System DuringCNSinvolvement, both focal and diffuse meningoencephalitis can be documented, with evidence of necrosis and microglial nodules. Necrotizing encephalitis in patients without AIDS is characterized by small diffuse lesions with perivascular cuffing in contiguous areas. In the AIDS population, polymorphonuclear leukocytes may be present in addition to monocytes, lymphocytes, and plasma cells. Cysts containing bradyzoites frequently are found contiguous with the necrotic tissue border.

Lungs Among patients with AIDS who die of toxoplasmosis, 40 to 70% have involvement of the heart and lung. Interstitial pneumonitis can develop in the neonate and the immunocompromised patient. Thickened and edematous alveolar septa infiltrated with mononuclear and plasma cells are apparent. This inflammation may extend to the endothelial walls. Tachyzoites and bradyzoite-containing cysts have been observed within the alveolar membrane. Superimposed bronchopneumonia can be caused by other microbial agents.

Heart Cysts and aggregates of parasites in cardiac muscle tissue are evident in patients with AIDS who die of toxoplasmosis. Focal necrosis surrounded by inflammatory cells is associated with hyaline necrosis and disrupted myocardial cells. Pericarditis is associated with toxoplasmosis in some patients.

Other Sites Pathologic changes during disseminated infection are similar to those described for the lymph nodes, eyes, andCNS. In patients with AIDS, the skeletal muscle, pancreas, stomach, and kidneys can be involved, with necrosis, invasion by inflammatory cells, and (rarely) the presence of tachyzoites detectable by routine staining. Large necrotic lesions may cause direct tissue destruction. In addition,

secondary effects from acute infection of these various organs, including pancreatitis, myositis, and glomerulonephritis, have been reported.

HOST IMMUNE RESPONSE

Acute *Toxoplasma* infection evokes a cascade of protective immune responses in the normal host. *Toxoplasma* enters the host at the gut mucosal level and evokes a mucosal immune response that includes the production of antigen-specific secretory IgA. Titers of serum IgA antibody directed at p30 (SAG-1) have been shown to be a useful marker of congenital and acute toxoplasmosis. Milk-whey IgA from acutely infected mothers contains a high titer of antibody to *T. gondii* and can block infection of enterocytes in vitro. In mice, IgA intestinal secretions directed at the parasite are abundant and are associated with the induction of mucosal T cells.

Within the host, *T. gondii* rapidly induces detectable levels of both IgM and IgG serum antibodies. Monoclonal gammopathy of the IgG class can occur in congenitally infected infants. IgM levels may be increased in newborns with congenital infection. The polyclonal IgG antibodies evoked by infection are parasiticidal in vitro in the presence of serum complement and are the basis for the Sabin-Feldman dye test. However, cell-mediated immunity is the major protective response evoked by the parasite during host infection. Macrophages are activated following phagocytosis of antibody-opsonized parasites. This activation can lead to death of the parasite by either an oxygen-dependent or an oxygen-independent process. If the parasite is not phagocytosed and enters the macrophage by active penetration, it continues to replicate, and this replication may represent the mechanism for transport and dissemination to distant organs. *Toxoplasma* stimulates a robust interleukin (IL) 12 response by human dendritic cells. The CD4+ and CD8+ T cell responses are antigen-specific and further stimulate the production of a variety of important lymphokines that expand the T cell and natural killer cell repertoire. *T. gondii* is a potent inducer of a T_H1 phenotype, with IL-12 and IFN-g playing an essential role in the control of the parasites' growth in the host. Regulation of the inflammatory response is at least partially under the control of a T_H2 response that includes the production of IL-4 and IL-10 in seropositive individuals. Both asymptomatic patients and those with active infection may show a depression in the ratio of CD4+ to CD8+ lymphocytes. This shift may be correlated with a disease syndrome but is not necessarily correlated with disease outcome. Human T cell clones of both the CD4+ and the CD8+ phenotypes are cytolytic against parasite-infected macrophages. These T cell clones produce cytokines that are "microbistatic." IL-18, IL-7, and IL-15 upregulate the production of IFN-g and may be important during acute and chronic infection. The effect of IFN-g may be paradoxical, with stimulation of a host downregulatory response as well.

Although in patients with AIDS *T. gondii* infection is believed to be recrudescent, determination of antibody titers is not helpful in establishing reactivation. Because of the severe depletion in CD4+ T cells, quite frequently there is no observed increase in antibody titer during exacerbation of infection. T cells from AIDS patients with reactivation of toxoplasmosis fail to secrete both IFN-g and IL-2. This alteration in the production of these critical immune cytokines contributes to the persistence of infection. *Toxoplasma* infection frequently develops late in the course of AIDS, when the loss of T cell-dependent protective mechanisms, particularly CD8+ T cells, becomes most

pronounced.

CLINICAL MANIFESTATIONS

In persons whose immune systems are intact, acute toxoplasmosis is usually asymptomatic and self-limited. This condition can go unrecognized in 80 to 90% of adults and children with acquired infection. The asymptomatic nature of this infection makes diagnosis difficult in mothers infected during pregnancy. In contrast, the wide range of clinical manifestations in congenitally infected children includes severe neurologic complications such as hydrocephalus, microcephaly, mental retardation, and chorioretinitis. If prenatal infection is severe, multiorgan failure and subsequent intrauterine fetal death can occur. In children and adults, chronic infection can persist throughout life, with little consequence to the immunocompetent host.

Toxoplasmosis in the Immunocompetent Person The most common manifestation of acute toxoplasmosis is cervical lymphadenopathy. The nodes may be single or multiple, are usually nontender, are discrete, and vary in firmness. Lymphadenopathy also may be found in suboccipital, supraclavicular, inguinal, and mediastinal areas. Generalized lymphadenopathy occurs in 20 to 30% of symptomatic patients. Between 20 and 40% of patients with lymphadenopathy also have headache, malaise, fatigue, and fever [usually with a temperature of<40°C (<104°F)]. A smaller proportion of symptomatic individuals have myalgia, sore throat, abdominal pain, maculopapular rash, meningoencephalitis, and confusion. Rare complications associated with infection in the normal immune host include pneumonia, myocarditis, encephalopathy, pericarditis, and polymyositis. Symptoms associated with acute infection usually resolve within several weeks, although the lymphadenopathy may persist for some months. In a recent epidemic, toxoplasmosis was diagnosed correctly in only 3 of the 25 patients who consulted physicians. If toxoplasmosis is considered in the differential diagnosis, routine laboratory and serologic screening should be performed before node biopsy.

The results of routine laboratory studies are usually unremarkable except for minimal lymphocytosis, an elevated sedimentation rate, and a nominal increase in liver aminotransferases. Evaluation of cerebrospinal fluid (CSF) in cases with evidence of encephalopathy or meningoencephalitis shows an elevation of intracranial pressure, mononuclear pleocytosis (10 to 50 cells/mL), a slight increase in protein concentration, and (occasionally) an increase in the gamma globulin level.PCRamplification of the *Toxoplasma* DNA target sequence in the CSF may be beneficial. The CSF of chronically infected individuals is normal.

Ocular Infection Infection with *T. gondii* is estimated to cause 35% of all cases of chorioretinitis in the United States and Europe. Most ocular involvement is believed to be due to congenital infection, with a very low incidence following acquired infection. Between 1 and 3% of all patients with AIDS develop debilitating chorioretinitis due to *T. gondii*. A variety of ocular manifestations are documented, including blurred vision, scotoma, photophobia, and eye pain. Macular involvement occurs with loss of central vision, and nystagmus is secondary to poor fixation. Involvement of the extraocular muscles may lead to disorders of convergence and to strabismus. Ophthalmologic examination should be undertaken in newborns with suspected congenital infection. As the inflammation resolves, vision improves, but episodic flare-ups of chorioretinitis,

which progressively destroy retinal tissue and lead to glaucoma, are common.

The ophthalmologic examination reveals yellow-white, cotton-like patches with indistinct margins of hyperemia. As the lesions age, white plaques with distinct borders and black spots within the retinal pigment become more apparent. Lesions usually are located near the posterior pole of the retina; they may be single but are more commonly multiple. Congenital lesions may be unilateral or bilateral and show evidence of massive chorioretinal degeneration with extensive fibrosis. Surrounding these areas of involvement are a normal retina and vasculature. In patients with AIDS, retinal lesions are often large, with diffuse retinal necrosis, and include both free tachyzoites and cysts containing bradyzoites. Toxoplasmic chorioretinitis may be a prodrome to the development of encephalitis.

Infection of the Immunocompromised Person Patients with AIDS and those receiving immunosuppressive therapy for lymphoproliferative disorders are at greatest risk for developing acute toxoplasmosis. This predilection may be due either to reactivation of latent infection or to acquisition of parasites from exogenous sources such as blood or transplanted organs. In individuals with AIDS, more than 95% of cases of *Toxoplasma* encephalitis are believed to be due to recrudescent infection. In most of these cases, encephalitis develops when the CD4+ cell count falls below 100/uL. In the immunocompromised individual, the disease may be rapidly fatal if untreated. Thus accurate diagnosis and initiation of appropriate therapy are necessary to prevent fulminant infection.

Toxoplasmosis is a principal opportunistic infection of theCNS in persons with AIDS. Although geographic origin may be related to frequency of infection, it has no correlation with the severity of disease in the immunocompromised host. Individuals with AIDS who are seropositive for *T. gondii* are at a very high risk for developing encephalitis. In the United States, about one-third of the 15 to 40% of adult patients with AIDS who are latently infected with the parasite develop *Toxoplasma* encephalitis.

The signs and symptoms of acute toxoplasmosis in the immunocompromised patient are principally within theCNS. More than 50% of patients with clinical manifestations have intracerebral involvement. Clinical findings at the time of presentation range from nonfocal to focal dysfunction. These findings include encephalopathy, meningoencephalitis, and mass lesions. Patients may present with altered mental status (75%), fever (10 to 72%), seizures (33%), headaches (56%), and focal neurologic findings (60%), including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual-field loss, and aphasia. Patients who present with evidence of diffuse cortical dysfunction develop evidence of focal neurologic disease as the infection progresses. This altered condition is due not only to the necrotizing encephalitis caused by direct invasion of the parasite but also to secondary effects, including vasculitis, edema, and hemorrhage. The onset of infection can range from an insidious process over several weeks to an acute confusional state with fulminant focal deficits, including hemiparesis, hemiplegia, visual-field defects, localized headache, and focal seizures.

Although lesions can occur anywhere within theCNS, the areas most involved appear to be the brainstem, basal ganglia, pituitary gland, and corticomedullary junction. Brainstem involvement gives rise to a variety of neurologic dysfunctions, including

cranial nerve palsy, dysmetria, and ataxia. With basal ganglionic infection, patients may develop hydrocephalus, choreiform movements, and choreoathetosis. Because *Toxoplasma* usually causes encephalitis, meningeal involvement is uncommon, and thusCSFfindings may be unremarkable or may include a modest increase in cell count and in protein -- but not glucose -- concentration.

Cerebral toxoplasmosis needs to be differentiated from other opportunistic infections or tumors within theCNS of those afflicted with AIDS. The differential diagnosis includes herpes simplex encephalitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Involvement of the pituitary gland can give rise to panhypopituitarism and hyponatremia from inappropriate secretion of vasopressin (antidiuretic hormone). AIDS-dementia complex may present as cognitive impairment, attention loss, and altered memory. Brain biopsy in those patients who have been treated for *Toxoplasma* encephalitis but who continue to exhibit neurologic dysfunction often fails to identify organisms.

Autopsies of patients infected with *Toxoplasma* have demonstrated the involvement of multiple organs, including the lungs, gastrointestinal tract, pancreas, skin, eyes, heart, and liver. *Toxoplasma* pneumonia can occur and can be confused with *Pneumocystis carinii* infection. Respiratory involvement usually presents as dyspnea, fever, and a nonproductive cough and may rapidly progress to acute respiratory failure with hemoptysis, metabolic acidosis, hypotension, and (occasionally) disseminated intravascular coagulation. Histopathologic studies demonstrate necrosis and a mixed cellular infiltrate. The presence of organisms is a helpful diagnostic indicator, but organisms can also be found in healthy tissue. Infection of the heart is usually asymptomatic but can be associated with cardiac tamponade or biventricular failure. Infections of the gastrointestinal tract and the liver have been documented.

A presumptive clinical diagnosis of toxoplasmic encephalitis in patients with AIDS is based on clinical presentation, history of exposure as evidenced by positive serology, and radiologic evaluation. When these criteria are used, the predictive value is as high as 80%. More than 97% of patients with AIDS and toxoplasmosis have IgG antibody to the parasite in their sera. IgM serum antibody is usually not demonstrable. Intrathecal antibody to *T. gondii* may be present. Neuroradiologic evaluation should include double-dose contrast computed tomography (CT) of the head. By this test, single and frequently multiple contrast-enhancing lesions (<2 cm) may be identified. Magnetic resonance imaging (MRI) usually demonstrates multiple lesions and provides a more sensitive evaluation of the efficacy of therapy than does CT. Patients with primaryCNSlymphoma are four times more likely than patients with *Toxoplasma* encephalitis to have solitary lesions on an MRI scan. A therapeutic trial of anti-*Toxoplasma* medications is frequently used to assess the diagnosis. Treatment of presumptive *Toxoplasma* encephalitis with pyrimethamine/clindamycin results in quantifiable clinical improvement in more than 50% of patients by day 3. By day 7, more than 90% of treated patients show evidence of improvement. In contrast, if patients fail to respond or have lymphoma, clinical signs and symptoms worsen by day 7. Patients in this category require brain biopsy with or without a change in therapy. This procedure can now be performed by a stereotactic CT-guided method that reduces the potential for complications. Brain biopsy for *T. gondii* identifies organisms in 50 to 75% of cases. Some studies indicate thatPCRamplification of target genes significantly increases the

sensitivity of detection of parasites.

Congenital Toxoplasmosis Between 400 and 4000 infants born each year in the United States are affected by congenital toxoplasmosis. Infection of the placenta leads to hematogenous infection of the fetus. As has already been stated, the proportion of fetuses that become infected increases but the clinical severity of the infection declines as gestation proceeds. Persistence of the parasite can ultimately result in reactivation and further damage decades later. Factors associated with relatively severe disabilities include delayed diagnosis and initiation of therapy, neonatal hypoxia and hypoglycemia, profound visual impairment, uncorrected hydrocephalus, and increased intracranial pressure. If treated appropriately, upwards of 70% of children have normal developmental, neurologic, and ophthalmologic findings at follow-up evaluations. Treatment for 1 year with pyrimethamine and sulfonamide is tolerated with minimal toxicity (see below).

DIAGNOSIS

Tissue and Body Fluids The diagnosis of acute toxoplasmosis can be made by isolation of the parasite from blood or other body fluids after subinoculation of the sample into the peritoneal cavity of mice. Mice should be tested for organisms in the peritoneal fluid 6 to 10 days after inoculation. If no parasites are found in the mouse's peritoneal fluid, its anti-*Toxoplasma* serum titer can be evaluated 4 to 6 weeks after inoculation. Isolation of *T. gondii* from the patient's body fluids reflects acute infection, whereas isolation from biopsied tissue is an indication only of the presence of tissue cysts and should not be misinterpreted as acute toxoplasmosis. Persistent parasitemia in patients with latent, asymptomatic infection is rare. Histologic examination of lymph nodes may suggest the characteristic changes described above. Demonstration of tachyzoites in lymph nodes establishes the diagnosis of acute toxoplasmosis. Like subinoculation into mice, histologic demonstration of cysts containing bradyzoites confirms prior infection with *T. gondii* but is nondiagnostic for acute infection.

Serology The procedures just described have great diagnostic value but are limited by difficulties encountered either in the growth of parasites in vivo or in the identification of tachyzoites by histochemical methods. Serologic testing has become the routine method of diagnosis. A wide range of serologic tests that can be used to measure antibody to *T. gondii* are available commercially.

Diagnosis of acute infection with *T. gondii* can be established by detection of the simultaneous presence of IgG and IgM antibody to *Toxoplasma* in serum. The presence of circulating IgA favors the diagnosis of an acute infection. The Sabin-Feldman dye test, the indirect fluorescent antibody test, and the enzyme-linked immunosorbent assay (ELISA) all satisfactorily measure circulating IgG antibody to *Toxoplasma*. Positive IgG titers (>1:10) can be detected as early as 2 to 3 weeks after infection. These titers usually peak at 6 to 8 weeks and decline slowly to a new baseline level that persists for life. It is necessary to measure the serum IgM titer in concert with the IgG titer to better establish the time of infection. The methods currently available for this determination are the double-sandwich IgM-ELISA and the IgM-immunosorbent assay (IgM-ISAGA). Both of these assays are specific and sensitive, and their use precludes the false-positive results associated with rheumatoid factor and antinuclear antibody. The

double-sandwich IgA-ELISA is more sensitive than the IgM-ELISA for detecting congenital infection in the fetus and newborn.

The Immunocompetent Adult or Child For the patient who presents with lymphadenopathy only, a positive IgM titer is an indication of acute infection -- and an indication for therapy, if that is clinically warranted (see "Treatment" below). The serum IgM titer should be determined again in 3 weeks. An elevation in the IgG titer without an increase in the IgM titer suggests that infection is present but that it is not acute. If there is a borderline increase in either IgG or IgM, the titers should be assessed again in 3 to 4 weeks.

Ocular Toxoplasmosis Because of the congenital nature of ocular toxoplasmosis, the serum antibody titer may not correlate with the presence of active lesions in the fundus. In general, a positive IgG titer (measured in undiluted serum if necessary) in conjunction with typical lesions establishes the diagnosis. If lesions are atypical and the titer is in the low-positive range, the diagnosis is presumptive. The parasitic antigen-specific polyclonal IgG assay as well as the parasitic antigen-specificPCR may facilitate the diagnosis.

The Immunocompromised Host As discussed above, in patients with AIDS, the presence of IgG and radiologic findings consistent with toxoplasmosis are grounds for a presumptive diagnosis. Attempts to evaluate rising IgG titers or to determine whether IgM is present are not productive. Serologic evidence of infection virtually always precedes the development of *Toxoplasma* encephalitis. It is therefore important to determine the *Toxoplasma* antibody status of all patients infected with HIV. Antibody titers may range from negative to 1:1024 in patients with AIDS and *Toxoplasma* encephalitis. Fewer than 3% of patients have no demonstrable antibody to *Toxoplasma* at the time of diagnosis. Determination of the intrathecal antibody titer may be useful in identifying prior infection.PCRamplification of genetic material of the parasite found in theCSF may prove diagnostically beneficial in the future.

Patients with toxoplasmic encephalitis have focal or multifocal abnormalities demonstrable byCT orMRI. These findings are not pathognomonic of *Toxoplasma* infection since 40% ofCNSlymphomas are multifocal and 50% are ring-enhancing. Lesions on MRI scan are multiple and are located in both hemispheres, with the basal ganglia and corticomedullary junction most commonly involved. For both MRI and CT scans, the rate of false-negative results is approximately 10%. The finding of a single lesion on an MRI scan increases the suspicion of primary lymphoma and strengthens the argument for the performance of a brain biopsy.

Now used in some centers, SPECT (single-photon emission CT) has been touted as a definitive means of detecting or ruling out *Toxoplasma* infection when a CNS lesion is suspected. In the future, SPECT may well be widely used for this purpose.

As in other conditions, the radiologic response may lag behind the clinical response. Resolution of lesions may take from 3 weeks to 6 months. Some patients show clinical improvement despite worsening radiographic findings.

A presumptive diagnosis of *Toxoplasma* encephalitis should prompt the immediate

initiation of therapy. After 3 weeks, repeat radiologic studies should detect improvement. If glucocorticoids have been administered, radiologic studies should be repeated at the time of discontinuation to determine whether an exacerbation of disease has occurred. If the patient's clinical condition becomes worse, performance of a biopsy must be strongly considered.

Congenital Infection The issue of concern when a pregnant woman has evidence of recent *T. gondii* infection is obviously whether the fetus is infected.PCR of the amniotic fluid to detect the B1 gene of the parasite has replaced fetal blood sampling. Serologic diagnosis is based on the persistence of IgG antibody or a positive IgM titer after the first week of life (a time frame that excludes placental leak). The IgG determination should be repeated every 2 months. An increase in IgM beyond the first week of life is indicative of acute infection. However, up to 25% of infected newborns may be seronegative and have normal routine physical examinations. Thus assessment of the eye and the brain, with ophthalmologic testing,CSFevaluation, and radiologic studies, is important in establishing the diagnosis.

TREATMENT

Current therapeutic protocols are directed at folate metabolism, protein synthesis, or nucleic acid synthesis of the parasite. Pyrimethamine and trimethoprim inhibit the enzyme dihydrofolate reductase. Inhibitors of protein synthesis, including clindamycin, chlortetracycline, and azithromycin, affect growth of the parasite. Inhibitors of purine synthesis, such as arprinocid, may prove to be important. Atovaquone, which blocks pyrimidine salvage, has demonstrated activity against both *T. gondii* and *P. carinii*.

Immunologically competent adults and older children who have only lymphadenopathy do not require specific therapy unless they have persistent and severe symptoms. Patients with ocular toxoplasmosis should be treated for 1 month with pyrimethamine plus either sulfadiazine or clindamycin. Prenatal antibiotic therapy can reduce the number of infants severely affected by *Toxoplasma* infection.

Congenital Infection Congenitally infected neonates are treated with daily oral pyrimethamine (0.5 to 1 mg/kg) and sulfadiazine (100 mg/kg) for 1 year. In addition, therapy with spiramycin (100 mg/kg per day) plus prednisone (1 mg/kg per day) has been shown to be efficacious for congenital infection.

Infection in Immunocompromised Patients Patients with AIDS should be treated for acute toxoplasmosis; in the immunocompromised patient, toxoplasmosis is rapidly fatal if untreated. The mainstay of treatment for *Toxoplasma* encephalitis in immunocompromised patients is a combination regimen. Administered together for 4 to 6 weeks or until radiologic improvement is documented, pyrimethamine (a 200-mg loading dose followed by 50 to 75 mg/d) and sulfadiazine (4 to 6 g/d in four divided doses) block folic acid metabolism and reduce the parasite burden. Leucovorin (calcium folinate, 10 to 15 mg/d) is given as an adjunct to prevent the bone marrow toxicity associated with pyrimethamine. Both pyrimethamine and sulfadiazine cross the blood-brain barrier. A prominent consequence of dual therapy is the high incidence of associated toxicity (40%). Rash may develop during the first 3 weeks in up to 20% of patients but does not preclude the use of this combination. Other complications include

hematologic effects, crystalluria, hematuria, radiolucent renal stones, and nephrotoxicity. During therapy, serum levels of these drugs may be erratic, but such fluctuations have not been correlated with these complications.

Pyrimethamine and sulfadiazine are active only against the tachyzoite stage of the parasite. Thus, after immunocompromised patients complete the initial 4- to 6-week course, they must receive lifelong suppressive therapy with pyrimethamine (25 to 50 mg/d) and sulfadiazine (2 to 4 g/d). If sulfadiazine cannot be tolerated, a combination of pyrimethamine (75 mg/d) plus clindamycin (450 mg tid) can be used. It is possible that pyrimethamine (50 to 75 mg/d) is sufficient for chronic suppressive therapy.

Alternative Regimens Alternative therapies have been established because of the toxicity associated with the long-term antimicrobial therapy necessary for many individuals infected with *T. gondii*. Dapsone (diaminodiphenyl sulfone), with its longer serum half-life and decreased toxicity, is an effective alternative to sulfadiazine. Spiramycin, which has been used in Europe to treat pregnant women, reduces transplacental transmission. However, spiramycin has been ineffective as primary prophylaxis in patients with AIDS. Clindamycin is well absorbed from the gastrointestinal tract, and serum levels peak 1 to 2 h after administration. The combination of oral pyrimethamine (25 to 75 mg/d) plus intravenous clindamycin (1200 to 4800 mg/d) is effective for patients with AIDS who have *Toxoplasma* encephalitis. Toxic effects of clindamycin include nausea, vomiting, neutropenia, rash, and pseudomembranous colitis. Other macrolides that have been evaluated include roxithromycin, clarithromycin, and azithromycin. Evidence suggests that the macrolides are not beneficial by themselves, but a combination of pyrimethamine and clarithromycin appears to be effective. Atovaquone (750 mg tid or qid) is an optional agent for the treatment of individuals who are intolerant of other agents. Glucocorticoids can be used to treat intracerebral edema, but their benefit has not yet been established. It is difficult to assess the benefit of glucocorticoids when they are administered in conjunction with anti-*Toxoplasma* medication. Anticonvulsants are sometimes necessary for the treatment of seizures, but attention should be given to the potential interaction between sulfadiazine and phenytoin. A regimen of trimethoprim-sulfamethoxazole or dapsone plus pyrimethamine with leucovorin may prevent the development of *Toxoplasma* encephalitis in individuals infected with HIV who are seropositive for *T. gondii* after their CD4+ T lymphocyte count falls to 100/uL.

PREVENTION

The chances of primary infection with *Toxoplasma* can be reduced by not eating undercooked meat and by avoiding oocyst-contaminated material (i.e., a cat's litter box). Meat should be heated to 60°C or frozen to kill cysts. Hands should be washed thoroughly after work in the garden, and all fruits and vegetables should be washed. Blood intended for transfusion into *Toxoplasma*-seronegative immunocompromised individuals should be screened for antibody to *T. gondii*. Although such serologic screening is not routinely performed, seronegative women should be screened for evidence of infection several times during pregnancy if they are exposed to environmental conditions that put them at risk for infection with *T. gondii*. HIV-positive individuals should adhere closely to these preventive measures.

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218. PROTOZOAL INTESTINAL INFECTIONS AND TRICHOMONIASIS - *Peter F. Weller*

PROTOZOAL INFECTIONS

GIARDIASIS

Giardia lamblia is a cosmopolitan protozoal parasite that inhabits the small intestines of humans and other mammals. Giardiasis is one of the most common parasitic diseases worldwide and causes both endemic and epidemic intestinal disease and diarrhea.

Life Cycle and Epidemiology Infection follows the ingestion of the environmentally hardy cysts, which excyst in the small intestine, releasing trophozoites that multiply by binary fission, occasionally to enormous numbers. *Giardia* remains a pathogen of the proximal small bowel and does not disseminate hematogenously. Trophozoites remain free in the lumen or attach to the mucosal epithelium by means of a ventral sucking disk. As a trophozoite encounters altered conditions, it forms a morphologically distinct cyst, which is the stage of the parasite usually found in the feces. Trophozoites may be present and even predominate in loose or watery stools, but it is the resistant cyst that survives outside the body and is responsible for transmission. Cysts do not tolerate heating, desiccation, or continued exposure to feces but do remain viable for months in cold fresh water. The number of cysts excreted varies widely but can approach 10^7 per gram of stool.

Giardia infections are common in both developed and developing countries. Ingestion of as few as 10 cysts is sufficient to cause infection in humans. Because cysts are infectious when excreted or shortly thereafter, person-to-person transmission occurs where fecal hygiene is poor. Giardiasis, as a symptomatic or an asymptomatic infection, is especially prevalent in day-care centers; person-to-person spread also takes place in other institutional settings with poor fecal hygiene and during homosexual contact. If food is contaminated with *Giardia* cysts after cooking or preparation, food-borne transmission can occur. Waterborne transmission accounts for episodic infections (e.g., in campers and other travelers) and for massive epidemics in metropolitan areas. Surface water, ranging from mountain streams to large municipal reservoirs, can become contaminated with fecally derived *Giardia* cysts; outmoded water systems are subject to cross-contamination from leaking sewer lines. The efficacy of water as a means of transmission is enhanced by the small infectious inoculum of *Giardia*, the prolonged survival of cysts in cold water, and the resistance of cysts to killing by routine chlorination methods that are adequate for controlling bacteria. Viable cysts can be eradicated from water by either boiling or filtration. In the United States, *Giardia* is a common agent identified in waterborne epidemics of gastroenteritis; it is also common in developing countries.

The importance of animal reservoirs as sources of infection for humans is unclear. *Giardia* parasites morphologically similar to those in humans are found in a large number of mammals, including beavers from reservoirs implicated in epidemics, dogs, cats, and ruminants. Although the high degree of isolate heterogeneity noted in humans is consistent with infections originating from different animal sources, animals have not been directly established as sources of human infection.

Giardiasis, like cryptosporidiosis, creates a significant economic burden because of the costs incurred in the installation of water filtration systems required to prevent waterborne epidemics, in the management of epidemics that involve large communities, and in the evaluation and treatment of endemic infections.

Pathophysiology The reasons that some, but not all, infected patients develop clinical manifestations and the mechanisms by which *Giardia* causes alterations in small-bowel function are largely unknown. Although trophozoites adhere to the epithelium, they do not cause invasive or locally destructive alterations. The lactose intolerance and significant malabsorption that develop in a minority of infected adults and children are clinical signs of the loss of brush border enzyme activities. In most infections the morphology of the bowel is unaltered, but in a few cases -- usually in chronically infected, symptomatic patients -- the histopathologic findings (including flattened villi) and the clinical manifestations resemble those of tropical sprue and gluten-sensitive enteropathy. The pathogenesis of diarrhea in giardiasis is not known.

The natural history of *Giardia* infection varies markedly. Infections may be aborted, transient, recurrent, or chronic. Parasite as well as host factors may be important in determining the course of infection and disease. Both cellular and humoral responses develop in human infections, but their precise roles in the control of infection and/or disease are unknown. Because patients with hypogammaglobulinemia commonly suffer from prolonged, severe infections that are poorly responsive to treatment, humoral immune responses appear to be important. The greater susceptibility of the young than of the old and of newly exposed persons than of chronically exposed populations also suggests that at least partial protective immunity may develop. Although no strains of the parasite that are clearly nonpathogenic have been identified, *Giardia* isolates vary biochemically and biologically. The marked biochemical differences among some isolates may help account for the different courses of infection in experimentally infected humans and animals. The surface of trophozoites is covered by a family of related cysteine-rich proteins that undergo surface antigenic variation and may contribute to prolonged and/or repeated infections.

Clinical Manifestations Disease manifestations of giardiasis range from asymptomatic carriage to fulminant diarrhea and malabsorption. Most infected persons are asymptomatic, but in epidemics the proportion of symptomatic cases may be higher. Symptoms may develop suddenly or gradually. In persons with acute giardiasis, symptoms develop after an incubation period that lasts at least 5 to 6 days and usually 1 to 3 weeks. Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting. Although diarrhea is common, upper intestinal manifestations such as nausea, vomiting, bloating, and abdominal pain may predominate. The duration of acute giardiasis is usually in excess of 1 week, although diarrhea often subsides. Individuals with chronic giardiasis may present with or without having experienced an antecedent acute symptomatic episode. Diarrhea is not necessarily prominent, but increased flatus, loose stools, sulfurous burping, and (in some instances) weight loss occur. Symptoms may be continual or episodic and can persist for years. Some persons who have relatively mild symptoms for long periods recognize the extent of their discomfort only in retrospect. Fever, the presence of blood and/or mucus in the stools, and other signs and symptoms of colitis are uncommon and

suggest a different diagnosis or a concomitant illness. Symptoms tend to be intermittent yet recurring and gradually debilitating, in contrast with the acute disabling symptoms associated with many enteric bacterial infections. Because of the less severe illness and the propensity for chronic infections, patients may seek medical advice late in the course of the illness; however, disease can be severe, resulting in malabsorption, weight loss, growth retardation, dehydration, and (in rare cases) death. A number of extraintestinal manifestations have been described, such as urticaria, anterior uveitis, and arthritis; whether these are caused by giardiasis or concomitant processes is unclear.

Giardiasis can be life-threatening in patients with hypogammaglobulinemia and is typically difficult to treat and eradicate. *Giardia* infections can complicate other preexisting intestinal diseases, such as cystic fibrosis. Although *Giardia* can cause enteric illness in patients with AIDS, neither the course of infection nor the response to treatment differs for patients with and without AIDS.

Diagnosis Giardiasis is diagnosed by the detection of parasite antigen in the feces or by the identification of cysts in the feces or of trophozoites in the feces or small intestines. Cysts are oval, measure 8 to 12 um ´ 7 to 10 um, and characteristically contain four nuclei. Trophozoites are pear-shaped, dorsally convex, flattened parasites with two nuclei and four pairs of flagella. The diagnosis is sometimes difficult to establish. Direct examination of fresh or properly preserved stools as well as concentration methods should be used. Because cyst excretion is variable and may be undetectable at times, repeated examination of stool, sampling of duodenal fluid, and biopsy of the small intestine may be required to detect the parasite. Tests for parasitic antigen in stool are at least as sensitive and specific as good microscopic examinations and are easier to perform. All of these methods occasionally yield false-negative results.

TREATMENT

Cure rates with metronidazole (250 mg tid for 5 days) are usually>80%; those with furazolidone (100 mg qid for 7 to 10 days) are somewhat lower. The latter agent is frequently used to treat children because it is available as a palatable elixir that is not bitter. Quinacrine, the first effective drug for the treatment of giardiasis, is available from a limited number of pharmacies. Albendazole (400 mg/d for 5 days) may be effective.

Patients in whom initial treatment fails can be re-treated with a longer course. Almost all patients respond to therapy and are cured, although some with chronic giardiasis experience delayed resolution of symptoms after eradication of *Giardia*. Those who remain infected after repeated treatments should be evaluated for reinfection through family members, close personal contacts, and environmental sources as well as for hypogammaglobulinemia. In cases refractory to multiple treatment courses, prolonged therapy with metronidazole (750 mg tid for 21 days) has been successful. Tinidazole, not available in the United States, is considered more effective than metronidazole or quinacrine. When children attending day-care centers infect an entire family, treatment of all infected family members, including asymptomatic carriers, may be required to prevent reinfection. Paromomycin, an oral aminoglycoside that is not well absorbed, can be given to symptomatic pregnant women, although the experience accumulated thus far is not a sufficient basis on which to judge how often this agent either eradicates

infection or ameliorates symptoms.

Prevention Although *Giardia* is extremely infectious, disease can be prevented by the exclusive consumption of noncontaminated food and water. Cooking food adequately and boiling or filtering potentially contaminated water prevent infection.

CRYPTOSPORIDIOSIS

The coccidian parasite *Cryptosporidium* is now known to cause diarrheal disease in immunocompetent human hosts and to be especially common among persons with AIDS or other forms of immunodeficiency.

Life Cycle and Epidemiology Cryptosporidiosis is acquired by the consumption of oocysts (50% infectious dose: ~132 oocysts in nonimmune individuals), which excyst to liberate sporozoites that in turn enter and infect intestinal epithelial cells. The parasite's further development involves both asexual and sexual cycles, which produce forms capable of infecting other epithelial cells and of generating oocysts that are passed in the feces. *Cryptosporidium* spp. infect a number of animals and can spread from infected animals to humans. Since oocysts are immediately infectious when passed in feces, person-to-person transmission takes place in day-care centers and among household contacts and medical providers. Waterborne transmission accounts for infections in travelers and for common-source epidemics. Oocysts are quite hardy and resist killing by routine chlorination. Both drinking water and recreational water (e.g., pools, waterslides) have been increasingly recognized as sources of infection.

Pathophysiology Although intestinal epithelial cells harbor the parasite in an intracellular vacuole, the means by which secretory diarrhea is elicited remain uncertain. No characteristic pathologic changes are found by biopsy. The distribution of infection can be spotty within the principal site of infection, the small bowel. Cryptosporidia are found in some patients in the pharynx, stomach, and large bowel and at times in the respiratory tract. Especially in patients with AIDS, involvement of the biliary tract can cause papillary stenosis, sclerosing cholangitis, or cholecystitis.

Clinical Manifestations Asymptomatic infections can occur in both immunocompetent and immunocompromised hosts. In immunocompetent persons, symptoms develop after an incubation period of about a week and consist principally of watery nonbloody diarrhea, at times in conjunction with abdominal pain, nausea, anorexia, fever, and/or weight loss. In these hosts, the illness usually subsides after 1 to 2 weeks, whereas in immunocompromised hosts, especially those with AIDS, diarrhea can be chronic, persistent, and remarkably profuse, causing clinically significant fluid and electrolyte depletion. Stool volumes may range from 1 to 25 L/d. Weight loss, wasting, and abdominal pain may be severe. Biliary tract involvement can manifest as midepigastric or right upper quadrant pain.

Diagnosis Evaluation usually starts with fecal examination for small oocysts, which are 4 to 5 um in diameter and are smaller than the fecal stages of most other parasites. Detection is enhanced by evaluation of stools (obtained on multiple days) by several techniques, including modified acid-fast and direct immunofluorescent stains and enzyme immunoassays. Cryptosporidia also can be identified by light and electron

microscopy at the apical surfaces of intestinal epithelium from biopsy specimens of the small bowel and, less frequently, the large bowel.

TREATMENT

To date, no chemotherapeutic agents effective against *Cryptosporidium* have been identified, although paromomycin (500 to 750 mg qid) may be partially effective for some patients infected with HIV. Improvement in immune status with antiretroviral therapy can lead to amelioration of cryptosporidiosis. Otherwise, treatment includes supportive care with replacement of fluids and electrolytes and administration of antidiarrheal agents. Biliary tract obstruction may require papillotomy or T-tube placement. Prevention requires minimizing exposure to infectious oocysts in human or animal feces. Use of submicron water filters may minimize acquisition of infection from drinking water.

ISOSPORIASIS

The coccidian parasite *Isospora belli* causes human intestinal disease. Infection is acquired by the consumption of oocysts, after which the parasite invades intestinal epithelial cells and undergoes both sexual and asexual cycles of development. Oocysts excreted in stool are not immediately infectious but must undergo further maturation. Although *I. belli* infects many animals, little is known about the epidemiology or prevalence of this parasite in humans. It appears to be most common in tropical and subtropical countries. Acute infections can begin abruptly with fever, abdominal pain, and watery nonbloody diarrhea and can last for weeks or months. In patients who have AIDS or are immunocompromised for other reasons, infections often are not self-limited but rather resemble cryptosporidiosis, with chronic, profuse watery diarrhea. Eosinophilia, which is not found in other enteric protozoan infections, may be detectable. The diagnosis is usually made by detection of the large (~25-um) oocysts in stool by modified acid-fast staining. Oocyst excretion may be low-level and intermittent; if repeated stool examinations are unrevealing, sampling of duodenal contents by aspiration or small-bowel biopsy (often with electron-microscopic examination) may be necessary.

In contrast to cryptosporidiosis, isosporiasis responds to chemotherapy. Trimethoprim-sulfamethoxazole (160/800 mg qid for 10 days and then bid for 3 weeks) has been effective; for patients intolerant of sulfonamides, pyrimethamine (50 to 75 mg/d) can be used. Relapses can occur in persons with AIDS and necessitate maintenance therapy with trimethoprim-sulfamethoxazole (160/800 mg three times a week) or combined sulfadoxine (500 mg) and pyrimethamine (25 mg) once weekly.

CYCLOSPORIASIS

Coccidian parasites of the genus *Cyclospora* have been identified as the causative organisms in diarrheal illness formerly ascribed to blue-green algal or *Cyanobacteria*-like forms. This parasite is globally distributed: illness due to *Cyclospora cayetanensis* has been reported in the United States, Asia, Africa, Latin America, and Europe. The epidemiology of this parasite has not yet been fully defined, but waterborne transmission and especially transmission in imported raspberries have been recognized.

The full spectrum of illness attributable to *Cyclospora* has not been delineated. Some patients may harbor the infection without symptoms, but many with cyclosporiasis have diarrhea, flulike symptoms, and flatulence and burping. The illness can be self-limited, can wax and wane, or (in many cases) can involve prolonged diarrhea, anorexia, and upper gastrointestinal symptoms, with sustained fatigue and weight loss in some instances. Diarrheal illness may persist for longer than a month. *Cyclospora* can cause enteric illness in patients infected with HIV, albeit at an unknown frequency.

The parasite is detectable in epithelial cells of small-bowel biopsy samples and elicits secretory diarrhea by an unknown means. The absence of fecal blood and leukocytes indicates that disease due to *Cyclospora* is not caused by destruction of the small-bowel mucosa. The diagnosis can be made by detection of spherical 8- to 10-um oocysts in the stool, although routine stool O and P examinations are not sufficient. Specific fecal examinations must be requested to detect the oocysts, which are variably acid-fast and are fluorescent when viewed with ultraviolet light microscopy. Cyclosporiasis should be considered in the differential diagnosis of prolonged diarrhea, with or without a history of travel by the patient to other countries.

Cyclosporiasis is effectively treated with trimethoprim-sulfamethoxazole (160/800 mg bid for 7 days). Patients infected with HIV, however, may experience relapses after such treatment and thus may require longer-term suppressive maintenance therapy.

MICROSPORIDIOSIS

Microsporidia are obligate intracellular spore-forming protozoa that infect many animals and cause disease in humans, especially as opportunistic pathogens in AIDS. Microsporidia are members of a distinct phylum, Microspora, which contains dozens of genera and hundreds of species. The various microsporidia are differentiated by their developmental life cycles, by ultrastructural features, and by molecular taxonomy based on ribosomal RNA. The complex life cycles of the organisms result in the production of infectious spores. Currently, six genera of microsporidia -- *Encephalitozoon*, *Pleistophora*, *Nosema*, *Vittaforma*, *Trachipleistophora*, and *Enterocytozoon* -- are recognized as causes of human disease; a seventh genus -- *Microsporidium*, which includes organisms of uncertain taxonomic status -- also causes disease in humans. Though some microsporidia are probably prevalent causes of self-limited or asymptomatic infections in immunocompetent patients, little is known of how microsporidiosis is acquired.

Microsporidiosis is most common among patients with AIDS, less common among patients with other types of immunocompromise, and rare among immunocompetent hosts. In patients with AIDS, intestinal infections with *Enterocytozoon bieneusi* and *Encephalitozoon* (formerly *Septata*) *intestinalis* are increasingly recognized to contribute to chronic diarrhea and wasting; these infections are found in 10 to 40% of patients with chronic diarrhea. Both organisms have been found in the biliary tracts of patients with cholecystitis. *E. intestinalis* may also disseminate to cause fever, diarrhea, sinusitis, cholangitis, and bronchiolitis. In patients with AIDS, *E. hellem* has caused superficial keratoconjunctivitis as well as sinusitis, respiratory tract disease, and disseminated infection. Myositis due to *Pleistophora* has been documented. *Nosema*, *Vittaforma*, and *Microsporidium* have caused stromal keratitis associated with trauma in

immunocompetent patients.

Microsporidia are small gram-positive organisms with mature spores measuring 0.5 to 2 um´ 1 to 4 um. Diagnosis of microsporidial infections in tissue often requires electron microscopy, although intracellular spores can be visualized by light microscopy with hematoxylin and eosin, Giemsa, or tissue Gram's stains. For the diagnosis of intestinal microsporidiosis, modified trichrome or chromotrope 2R-based staining and Uvitex 2B or calcofluor fluorescent staining reveal spores in smears of feces or duodenal aspirates. Definitive therapies for microsporidial infections remain to be established. For superficial keratoconjunctivitis due to *E. hellem*, topical therapy with fumagillin suspension has shown promise (Chap. 211). For enteric infections with *E. bieneusi* and *E. intestinalis* in HIV-infected patients, therapy with albendazole may be efficacious (Chap. 211).

OTHER INTESTINAL PROTOZOA

Balantidiasis *Balantidium coli* is a large ciliated protozoal parasite that can produce a spectrum of large-intestinal disease analogous to amebiasis. The parasite is widely distributed in the world. Since it infects pigs, cases in humans are more common where pigs are raised; in Muslim countries, rodents may be important carriers. Infective cysts can be transmitted from person to person and through water, but many cases are due to the ingestion of cysts derived from porcine feces in association with slaughtering, with use of pig feces for fertilizer, or with contamination of water supplies by pig feces.

Ingested cysts liberate trophozoites, which reside and replicate in the large bowel. Many patients remain asymptomatic, but some have persisting intermittent diarrhea, and a few develop more fulminant dysentery. In symptomatic individuals, the pathology in the bowel -- both gross and microscopic -- is similar to that seen in amebiasis, with varying degrees of mucosal invasion, focal necrosis, and ulceration. Balantidiasis, unlike amebiasis, does not spread hematogenously to other organs. The diagnosis is usually made by detection of the trophozoite stage in stool or sampled colonic tissue. Tetracycline (500 mg qid for 10 days) is an effective therapeutic agent.

***Blastocystis hominis* Infection** *B. hominis*, long considered a nonpathogenic yeast, is believed by some to be a protozoan capable of causing intestinal disease, although its taxonomy and inherent pathogenicity remain uncertain. Some patients who pass *B. hominis* in their stools are asymptomatic, whereas others have diarrhea and associated intestinal symptoms. Diligent evaluation reveals other potential bacterial, viral, or protozoal causes of diarrhea in some but not all patients with symptoms. Because the pathogenicity of *B. hominis* is uncertain and because therapy for *Blastocystis* infection is neither specific nor uniformly effective, patients with prominent intestinal symptoms should be fully evaluated for other infectious causes of diarrhea. If diarrheal symptoms associated with *Blastocystis* are prominent, either metronidazole (750 mg tid for 10 days) or iodoquinol (650 mg tid for 20 days) can be used.

***Dientamoeba fragilis* Infection** *D. fragilis* is unique among intestinal protozoa in that it has a trophozoite stage but not a cyst stage. How trophozoites survive to transmit infection is not known, but the unusually high prevalence of *D. fragilis* infection among persons with pinworm infection raises the possibility that eggs or larvae of *Enterobius* facilitate the transmission of *D. fragilis*. When symptoms develop in patients with *D.*

fragilis infection, they are generally mild and include intermittent diarrhea, abdominal pain, and anorexia. The diagnosis is made by the detection of trophozoites in stool; the lability of these forms accounts for the greater yield when fecal samples are preserved immediately after collection. Since fecal excretion rates vary, examination of several samples obtained on alternate days increases the rate of detection. Iodoquinol (650 mg tid for 20 days), paromomycin (25 to 30 mg/kg per day in three doses for 7 days), or tetracycline (500 mg qid for 10 days) is appropriate for treatment.

Sarcosporidiosis Various *Sarcocystis* spp. of coccidian parasites are widely distributed agents of infection in numerous animals. These parasites have an obligatory cycle of development involving two hosts. Sexual reproduction occurs in the intestine, with sporocysts passed in the feces; asexual multiplication leads to the development of muscle cysts. Humans can develop intestinal infections -- albeit apparently infrequently -- by ingesting muscle-stage cysts in undercooked pork or beef. While the full spectrum of the intestinal disease is not defined, a diarrheal illness can ensue, and sporocysts are found in the stool. Alternatively, ingestion of fecally derived sporocysts can lead to the development of cysts in striated or cardiac muscle. Some patients experience muscle pain and swelling, but the frequency and nature of symptoms elicited by muscle involvement are not clear, and these cysts, measuring 100 to 325 um, also have been found incidentally in muscle specimens. Muscle-stage infections are not followed by further spread in humans. No specific therapy exists for either intestinal or muscle-stage *Sarcocystis* infections in humans.

TRICHOMONIASIS

Various species of trichomonads can be found in the mouth (in association with periodontitis) and occasionally in the gastrointestinal tract. *Trichomonas vaginalis* -- one of the most prevalent protozoal parasites in the United States -- is a pathogen of the genitourinary tract and a major cause of symptomatic vaginitis.

Life Cycle and Epidemiology *T. vaginalis* is a pear-shaped, actively motile organism that measures about 10 by 7 um, replicates by binary fission, and inhabits the lower genital tract of females and the urethra and prostate of males. In the United States, it accounts for about 3 million infections per year in women. While the organism can survive for a few hours in moist environments and could be acquired by direct contact, person-to-person venereal transmission accounts for virtually all cases of trichomoniasis. Its prevalence is greatest among persons with multiple sexual partners and among those with other sexually transmitted diseases.

Clinical Manifestations Most men infected with *T. vaginalis* are asymptomatic, although some develop urethritis and a few have epididymitis or prostatitis. In contrast, infection in women, which has an incubation period of 5 to 28 days, is usually symptomatic and manifests with malodorous vaginal discharge (often yellow), vulvar erythema and itching, dysuria or urinary frequency (in 30 to 50% of patients), and dyspareunia. These manifestations, however, do not clearly distinguish trichomoniasis from other types of infectious vaginitis.

Diagnosis Detection of motile trichomonads by microscopy of wet mounts of vaginal or prostatic secretions has been the conventional means of diagnosis. Although such

microscopy provides an immediate diagnosis, its sensitivity for the detection of *T. vaginalis* is only ~50 to 60% in routine evaluations of vaginal secretions. Direct immunofluorescent antibody staining is more sensitive (70 to 90%) than wet-mount examinations. *T. vaginalis* can be recovered from the urethra of both males and females and is detectable in males after prostatic massage. Culture of the parasite is the most sensitive means of detection; however, the facilities for culture are not generally available, and detection of the organism takes 3 to 7 days.

TREATMENT

Metronidazole is the mainstay of treatment and may be given either as a single 2-g dose or as 250 mg tid for 7 days. All sexual partners must be treated concurrently to prevent reinfection, especially from asymptomatic males. Alternatives to metronidazole for treatment during pregnancy are not readily available, although use of 100-mg clotrimazole vaginal suppositories nightly for 2 weeks may cure some infections in pregnant women. Reinfection often accounts for apparent treatment failures, but strains of *T. vaginalis* exhibiting high-level resistance to metronidazole have been encountered. Treatment of these resistant infections with higher oral doses, parenteral doses, or concurrent oral and vaginal doses of metronidazole has been successful.

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SECTION 18 -HELMINTHIC INFECTIONS

219. *TRICHINELLA* AND OTHER TISSUE NEMATODES - *Peter F. Weller, Leo X. Liu*

Nematodes are elongated, symmetric roundworms. Parasitic nematodes of medical significance may be broadly classified as intestinal or tissue nematodes, but such a classification system is imprecise. This chapter covers trichinellosis, visceral and ocular larva migrans, cutaneous larva migrans, cerebral angiostrongyliasis, and gnathostomiasis. All are zoonotic infections caused by incidental exposure to infectious nematodes. The clinical symptoms of these infections are due largely to invasive larval stages that (except in the case of *Trichinella*) do not reach maturity in humans.

TRICHINELLOSIS

Trichinellosis develops after the ingestion of meat containing cysts of *Trichinella* -- for example, pork or other meat from a carnivore. While most infections are mild and asymptomatic, heavy infections can cause severe enteritis, periorbital edema, myositis, and (infrequently) death.

Life Cycle and Epidemiology Five species of *Trichinella* are now recognized as causes of infection in humans. Two species are distributed worldwide: *T. spiralis*, which is found in a great variety of carnivorous and omnivorous animals, and *T. pseudospiralis*, which is found in mammals and birds. *T. nativa* is present in Arctic regions and infects bears; *T. nelsoni* is found in equatorial Africa, where it is common among felid predators and scavengers such as hyenas and bush pigs; and *T. bitovi* is found in temperate areas of Europe and western Asia among carnivores but not among domestic swine.

After the consumption of trichinous meat by the host, encysted larvae are liberated by digestive acid and pepsin (Fig. 219-1). The larvae invade the small-bowel mucosa and mature rapidly into adult worms. After about 1 week, female worms release newborn larvae that migrate via the circulation to striated muscle. The larvae of all species except *T. pseudospiralis* then encyst by inducing a radical transformation in the muscle cell architecture. Although host immune responses may help to expel adult worms, they have little effect on muscle-dwelling larvae.

Human trichinellosis is most often caused by the ingestion of infected pork products and thus can occur in almost any location where the meat of domestic or wild swine is eaten. Human trichinellosis also may be acquired from the meat of other animals, including dogs (in parts of Asia and Africa), horses (in Italy and France), and bears and walruses (in northern regions). Although cattle (being herbivores) are not natural hosts of *Trichinella*, beef has been implicated in outbreaks when contaminated or adulterated with trichinous pork. Laws that prohibit the feeding of uncooked garbage to pigs have greatly reduced the transmission of trichinellosis in the United States. About 40 cases of trichinellosis are reported annually in this country, but most mild cases probably remain undiagnosed. Recent U.S. outbreaks have been attributable to undercooked ethnic pork dishes, homemade and commercial sausage, wild boar meat, and walrus meat.

Pathogenesis and Clinical Features Clinical symptoms of trichinellosis arise from the

successive phases of parasite enteric invasion, larval migration, and muscle encystment (Fig. 219-1). Most light infections (those with<10 larvae per gram of muscle) are asymptomatic, whereas heavy infections (which can involve >50 larvae per gram of muscle) can be life-threatening. Invasion of the gut by large numbers of parasites occasionally provokes diarrhea during the first week after infection. Abdominal pain, constipation, nausea, or vomiting also may be prominent. The prolonged and fulminant diarrhea noted with Arctic trichinellosis probably reflects a response to repeated infection.

Symptoms due to larval migration and muscle invasion begin to appear in the second week after infection. The migrating *Trichinella* larvae provoke a marked local and systemic hypersensitivity reaction, with fever and hypereosinophilia. Periorbital and facial edema is common, as are hemorrhages in the subconjunctivae, retina, and nail beds ("splinter" hemorrhages). A maculopapular rash, headache, cough, dyspnea, or dysphagia sometimes develops. Myocarditis with tachyarrhythmias or heart failure -- and, less commonly, encephalitis or pneumonitis -- may develop and accounts for most deaths of patients with trichinellosis.

Upon onset of larval encystment in muscle 2 to 3 weeks after infection, symptoms of myositis with myalgias, muscle edema, and weakness develop, usually overlapping with the inflammatory reactions to migrating larvae. The most commonly involved muscle groups include the extraocular muscles; the biceps; and the muscles of the jaw, neck, lower back, and diaphragm. Peaking about 3 weeks after infection, symptoms subside only gradually during a prolonged convalescence.

Laboratory Findings and Diagnosis Blood eosinophilia develops in >90% of patients with symptomatic trichinellosis and may peak at a level of>50% between 2 and 4 weeks after infection. Serum levels of IgE and muscle enzymes, including creatine phosphokinase, lactate dehydrogenase, and aspartate aminotransferase, are elevated in most symptomatic patients. Patients should be questioned thoroughly about their consumption of pork or wild-animal meat and about illness in other individuals who ate the same meat. A presumptive clinical diagnosis can be based on fevers, eosinophilia, periorbital edema, and myalgias after a suspect meal. A rise in the titer of parasite-specific antibody, which usually does not occur until after the third week of infection, confirms the diagnosis. Alternatively, a definitive diagnosis requires surgical biopsy of at least 1 g of involved muscle; the yields are highest near tendon insertions. The fresh muscle tissue should be compressed between glass slides and examined microscopically, because larvae may be overlooked by examination of routine histopathologic sections alone.

TREATMENT

Current anthelmintic drugs are ineffective against *Trichinella* larvae in muscle. Fortunately, most lightly infected patients recover uneventfully with bed rest, antipyretics, and analgesics. Glucocorticoids like prednisone (1 mg/kg daily for 5 days) are beneficial for severe myositis and myocarditis. Mebendazole and albendazole, like thiabendazole, appear to be active against enteric stages of the parasite, but their efficacy against encysted larvae has not been conclusively demonstrated.

Prevention Larvae may be killed by cooking pork until it is no longer pink or by freezing it at -15°C for 3 weeks. However, Arctic *T. nativa* larvae in walrus or bear meat are relatively resistant and may remain viable despite freezing.

VISCERAL AND OCULAR LARVA MIGRANS

Visceral larva migrans is a syndrome caused by nematodes that are normally parasitic for nonhuman host species. In humans, the nematode larvae do not typically develop into adult worms but instead migrate through host tissues and elicit eosinophilic inflammation. The most common form of visceral larva migrans is toxocariasis due to larvae of the canine ascarid *Toxocara canis* or, less commonly, the feline ascarid *T. cati*. Rare cases with eosinophilic meningoencephalitis have been caused by the raccoon ascarid *Baylisascaris procyonis*.

Life Cycle and Epidemiology The canine roundworm *T. canis* is distributed among dogs worldwide. Ingestion of infective eggs by dogs is followed by liberation of *Toxocara* larvae, which penetrate the gut wall and migrate intravascularly into the canine liver, muscle, and other tissues, where most remain in a developmentally arrested state. During pregnancy, some larvae resume migration in bitches and infect puppies prenatally (through transplacental transmission) or after birth (through suckling). Thus, in lactating bitches and puppies, larvae return to the intestinal tract and develop into adult worms, which produce eggs that are released in the feces. Humans acquire toxocariasis mainly by eating soil contaminated by puppy feces containing infective *T. canis* eggs. Visceral larva migrans is most common among children who habitually eat dirt, but most toxocaral infections are subclinical. Reported rates of *Toxocara* seropositivity range from 2% in an unselected American population to >20% among kindergarten children in the United States and England.

Pathogenesis and Clinical Features Clinical disease most commonly afflicts preschool children. After humans ingest *Toxocara* eggs, the larvae hatch and penetrate the intestinal mucosa, from which they are carried by the circulation to a wide variety of organs and tissues. The larvae invade the liver, lungs, central nervous system, and other sites, releasing toxic products and provoking intense local eosinophilic granulomatous responses. The degree of clinical illness depends on larval number and tissue distribution, reinfection, and host immune responses. Most light infections are asymptomatic and may be manifest only by blood eosinophilia. Characteristic symptoms of visceral larva migrans include fever, malaise, anorexia and weight loss, cough, wheezing, and rashes. Hepatosplenomegaly is common. These features are often accompanied by extraordinary peripheral eosinophilia, which may approach 90%. Uncommonly, seizures or behavioral disorders develop. The rare deaths in this disease are due to severe neurologic, pneumonic, or myocardial involvement.

Diagnosis In addition to prominent eosinophilia, leukocytosis and hypergammaglobulinemia are usually evident. Transient pulmonary infiltrates are apparent on chest x-rays of about half of patients with symptoms of pneumonitis. The clinical diagnosis can be confirmed by an enzyme-linked immunosorbent assay for toxocaral antibodies. Stool examination, while important in the evaluation of unexplained eosinophilia, is worthless for toxocariasis, since the larvae do not develop into egg-producing adults in humans.

The ocular form of the larva migrans syndrome occurs when *Toxocara* larvae invade the eye. An eosinophilic granulomatous mass, most commonly in the posterior pole of the retina, develops around the entrapped larva. The retinal lesion can mimic retinoblastoma in appearance, and mistaken diagnosis of the latter condition can lead to unnecessary enucleation. The spectrum of eye involvement also includes endophthalmitis, uveitis, and chorioretinitis. Unilateral visual disturbances, strabismus, and eye pain are the most common presenting symptoms. In contrast to visceral larva migrans, ocular toxocariasis usually develops in older children or young adults with no history of pica; these patients seldom have eosinophilia or visceral manifestations.

TREATMENT

The vast majority of *Toxocara* infections are self-limited and resolve without specific therapy. In patients with severe myocardial, central nervous system, or pulmonary involvement, glucocorticoids may be employed to reduce inflammatory complications. Available anthelmintic drugs, including diethylcarbamazine, mebendazole, and albendazole, have not been shown conclusively to alter the course of larva migrans. Control measures include prohibiting dog excreta in public parks and playgrounds, deworming dogs, and preventing pica in children. Treatment of ocular disease is unsatisfactory, and the role of glucocorticoids or anthelmintic drugs in management is controversial.

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans ("creeping eruption") is a serpiginous skin eruption (Fig. 219-CD1) caused by burrowing larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. The larvae hatch from eggs passed in dog and cat feces and mature in the soil. Humans become infected after skin contact with soil in areas frequented by dogs and cats, such as areas underneath house porches or scrub vegetation. Cutaneous larva migrans is especially prevalent among children and in regions with warm humid climates, including the southeastern United States.

After larvae penetrate the skin, erythematous lesions form along the tortuous tracts of their migration through the dermal-epidermal junction; the larvae advance several centimeters in a day. The intensely pruritic lesions may occur anywhere on the body and can be numerous if the patient has lain on the ground. Vesicles and bullae may form later. The animal hookworm larvae do not mature in humans and, without treatment, will die out after several weeks, with resolution of skin lesions. The diagnosis is made readily on clinical grounds, and a skin biopsy only rarely yields diagnostic parasite material. Symptoms can be alleviated by thiabendazole administered orally (25 mg/kg bid) or topically (10% aqueous or petroleum jelly suspension) for 2 to 5 days, by ivermectin (a single dose of 150 to 200 ug/kg), or by albendazole (200 mg bid for 2 days).

ANGIOSTRONGYLUS CANTONENSIS INFECTION

A. cantonensis, the rat lungworm, is the most common cause of human eosinophilic meningitis.

Life Cycle and Epidemiology This infection occurs principally in Southeast Asia and the Pacific Basin. *A. cantonensis* larvae produced by adult worms in the rat lung migrate to the gastrointestinal tract and are expelled with the feces. They develop into infective larvae in land snails and slugs. Humans acquire the infection by ingesting raw infected mollusks; vegetables contaminated by mollusk slime; or crabs, freshwater shrimp, and certain marine fish that have themselves eaten infected mollusks. The larvae then migrate to the brain.

Pathogenesis and Clinical Features The parasites eventually die in the central nervous system, but not before initiating pathologic consequences that, in heavy infections, can result in permanent neurologic sequelae or death. Migrating larvae cause proteolytic damage and marked local eosinophilic inflammation and hemorrhage, with subsequent necrosis and granuloma formation around dying worms. Clinical symptoms develop between 2 and 35 days after the ingestion of larvae. Patients usually present with an insidious or abrupt excruciating frontal, occipital, or bitemporal headache. Neck stiffness, nausea and vomiting, and paresthesias are also common. Fever, cranial and extraocular nerve palsies, seizures, paralysis, and lethargy are uncommon.

Laboratory Findings Examination of the cerebrospinal fluid is mandatory in suspected cases and usually reveals an elevated opening pressure, a white blood cell count of 150 to 2000/uL, and an eosinophilic pleocytosis of>20%. The protein concentration is usually elevated and the glucose level normal. The motile larvae of *A. cantonensis* are only rarely seen in the cerebrospinal fluid. Peripheral-blood eosinophilia may be mild. The diagnosis is generally based on the clinical presentation of eosinophilic meningitis together with a compatible epidemiologic history.

TREATMENT

Specific chemotherapy is not of benefit in angiostrongyliasis; larvicidal agents may actually exacerbate inflammatory brain lesions. Management consists of supportive measures, including the administration of analgesics, sedatives, and -- in severe cases -- glucocorticoids. In most patients, cerebral angiostrongyliasis has a self-limited course, and recovery is complete. The infection may be prevented by adequately cooking snails, crabs, and prawns and inspecting vegetables for mollusk infestation. Other parasitic causes of eosinophilic meningitis in endemic areas may include gnathostomiasis, paragonimiasis, schistosomiasis, and neurocysticercosis.

GNATHOSTOMIASIS

Infection of human tissues with larvae of *Gnathostoma spinigerum* can cause eosinophilic meningoencephalitis, migratory cutaneous swellings, or invasive masses of the eye and visceral organs.

Life Cycle and Epidemiology Human gnathostomiasis occurs in many countries and is notably endemic in Southeast Asia and parts of China and Japan. In nature, the mature adult worms parasitize the gastrointestinal tract of dogs and cats. First-stage larvae hatch from eggs passed into water and are ingested by *Cyclops* species (water fleas). Infective third-stage larvae develop in the flesh of many animal species (including fish,

frogs, eels, snakes, chickens, and ducks) that have eaten either infected *Cyclops* or another infected second intermediate host. Humans typically acquire the infection by eating raw or undercooked fish or poultry. The raw fish dishes of *somfak* in Thailand and *sashimi* in Japan account for most cases of human gnathostomiasis. Some cases in Thailand result from the local practice of applying frog or snake flesh as a poultice.

Pathogenesis and Clinical Features Clinical symptoms are due to the aberrant migration of a single larva into cutaneous, visceral, neural, or ocular tissues. After invasion, larval migration may cause local inflammation, with pain, cough, or hematuria accompanied by fever and eosinophilia. Painful, itchy, migratory swellings may develop in the skin, particularly in the distal extremities or periorbital area. Cutaneous swellings usually last about a week but often recur intermittently over many years. Larval invasion of the eye can provoke a sight-threatening inflammatory response. Finally, invasion of the central nervous system results in eosinophilic meningitis with myeloencephalitis, a serious complication due to ascending larval migration along a large nerve track. Patients characteristically present with agonizing radicular pain and paresthesias in the trunk or a limb, which are followed shortly by paraplegia. Cerebral involvement, with focal hemorrhages and tissue destruction, is often fatal.

Diagnosis and Treatment Cutaneous migratory swellings with marked peripheral eosinophilia, supported by an appropriate geographic and dietary history, generally constitute an adequate basis for a clinical diagnosis of gnathostomiasis. However, patients may present with ocular or cerebrospinal involvement without antecedent cutaneous swellings. In the latter case, eosinophilic pleocytosis is demonstrable (usually along with hemorrhagic or xanthochromic cerebrospinal fluid), but worms are almost never recovered from the cerebrospinal fluid. Surgical removal of the parasite from subcutaneous or ocular tissue, though rarely feasible, is both diagnostic and therapeutic. Albendazole (400 to 800 mg daily for 21 days) may be helpful. At present, cerebrospinal involvement is managed with supportive measures and generally with a course of glucocorticoids. Gnathostomiasis can be prevented by adequate cooking of fish and poultry in endemic areas.

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220. INTESTINAL NEMATODES - *Peter F. Weller*, *Thomas B. Nutman*

More than a billion people worldwide are infected with one or more species of intestinal nematodes. Table 220-1 summarizes biologic and clinical features of infections due to the major intestinal parasitic nematodes. These parasites are most common in regions with poor fecal sanitation, particularly in developing countries in the tropics and subtropics but also in the United States. Although nematode infections are not usually fatal, they contribute to malnutrition and diminished work capacity. Humans may on occasion be infected with nematode parasites that ordinarily infect animals; these zoonotic infections include trichostrongyliasis, anisakiasis, capillariasis, and abdominal angiostrongyliasis.

Intestinal nematodes are roundworms; they range in length from 1 mm to many centimeters when mature (Table 220-1). Their life cycles are complex and highly varied; some species, including *Strongyloides stercoralis* and *Enterobius vermicularis*, can be transmitted directly from person to person, while others, such as *Ascaris lumbricoides*, *Necator americanus*, and *Ancylostoma duodenale*, require a soil phase for development. Because most helminth parasites do not self-replicate, the acquisition of a heavy burden of adult worms requires repeated exposure to the parasite in its infectious stage, whether larva or egg. Hence, clinical disease, as opposed to asymptomatic infection, generally develops only with prolonged residence in an endemic area. In persons with marginal nutrition, intestinal helminth infections may impair growth and development. Eosinophilia and elevated serum IgE levels are features of many helminthic infections and, when unexplained, should always prompt a search for occult helminthiasis. Significant protective immunity to intestinal nematodes appears not to develop in humans, although mechanisms of parasite immune evasion and host immune responses to these infections have not been elucidated in detail.

ASCARIASIS

A. lumbricoides is the largest intestinal nematode parasite of humans, reaching up to 40 cm in length. Most infected individuals have low worm burdens and are asymptomatic. Clinical disease arises from larval migration in the lungs or effects of the adult worms in the intestines.

Life Cycle Adult worms live in the lumen of the small intestine. Mature female *Ascaris* worms are extraordinarily fecund, each producing up to 240,000 eggs a day, which pass with the feces. Ascarid eggs, which are remarkably resistant to environmental stresses, become infective after several weeks of maturation in the soil and can remain infective for years. After infective eggs are swallowed, larvae hatched in the intestine invade the mucosa, migrate through the circulation to the lungs, break into the alveoli, ascend the bronchial tree, and return via swallowing to the small intestine, where they develop into adult worms. Between 2 and 3 months elapse between initial infection and egg production. The adult worms live for ~1 to 2 years.

Epidemiology *Ascaris* is widely distributed in tropical and subtropical regions as well as in other humid areas, including the rural southeastern United States. Transmission typically occurs through fecally contaminated soil and is due either to a lack of sanitary facilities or to the use of human manure ("night soil") as fertilizer. With their propensity

for hand-to-mouth fecal carriage, younger children in impoverished rural areas are most affected. Infection outside endemic areas, though uncommon, can occur from eggs borne on transported vegetables.

Clinical Features During the lung phase of larval migration, about 9 to 12 days after egg ingestion, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing or deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever is usually reported, with temperatures sometimes exceeding 38.5°C (101.3°F). Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. Chest x-rays may reveal evidence of eosinophilic pneumonitis (Loffler's syndrome), with round or oval infiltrates a few millimeters to several centimeters in size. These infiltrates may be transient and intermittent, clearing after several weeks. Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophilia may develop in previously infected and sensitized hosts.

In established infections, adult worms in the small intestine usually cause no symptoms. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction, sometimes complicated by perforation, intussusception, or volvulus. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, or (rarely) intrahepatic abscesses. Migration of an adult worm up the esophagus can provoke coughing and oral expulsion of the worm. In highly endemic areas, intestinal and biliary ascariasis can rival acute appendicitis and gallstones as causes of surgical acute abdomen.

Laboratory Findings Most cases of ascariasis can be diagnosed by the microscopic detection of characteristic mamillated *Ascaris* eggs (65 by 45 um) in fecal samples. Occasionally, patients present after passing an adult worm -- identifiable by its large size and smooth cream-colored surface -- in the stool or through the mouth or nose. During the early transpulmonary migratory phase, when eosinophilic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool. The eosinophilia that is prominent during this early stage usually decreases to minimal levels in established infection. The large adult worms may be visualized, occasionally serendipitously, on contrast studies of the gastrointestinal tract. A plain abdominal film may reveal masses of worms in gas-filled loops of bowel in patients with intestinal obstruction. Pancreaticobiliary worms can be detected by ultrasound and endoscopic retrograde cholangiopancreatography; the latter method also has been used to extract biliary *Ascaris* worms.

TREATMENT

Ascariasis should always be treated to prevent potentially serious complications. Mebendazole or albendazole (which is considered an investigational drug by the Food and Drug Administration for this indication) is effective. These benzimidazoles are contraindicated in pregnancy and in heavy infections, in which they may provoke ectopic migration. Pyrantel pamoate and piperazine citrate are safe in pregnancy. Mild diarrhea and abdominal pain are uncommon side effects of these agents. Partial intestinal obstruction should be managed with nasogastric suction, intravenous fluid

administration, and instillation of piperazine through the nasogastric tube, but complete obstruction and its severe complications require immediate surgical intervention.

HOOKWORM

One-fourth of the world's population is infected with one of the two hookworm species (*A. duodenale* and *N. americanus*). Most infected individuals are asymptomatic. Hookworm disease develops from a combination of factors -- a heavy worm burden, a prolonged duration of infection, and an inadequate iron intake -- and results in iron-deficiency anemia and, on occasion, hypoproteinemia.

Life Cycle Adult hookworms, which are about 1 cm long, use buccal teeth (*Ancylostoma*) or cutting plates (*Necator*) to attach to the small-bowel mucosa and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid. The adult hookworms produce thousands of eggs daily. The eggs are deposited with feces in soil, where rhabditiform larvae hatch and develop over a 1-week period into infectious filariform larvae. Infective larvae penetrate the skin and reach the lungs by way of the bloodstream. There they invade alveoli and ascend the airways before being swallowed and reaching the small intestine. The prepatent period from skin invasion to appearance of eggs in the feces is about 6 to 8 weeks, but it may be longer with *A. duodenale*. Larvae of *A. duodenale*, if swallowed, can survive and develop directly in the intestinal mucosa. Adult hookworms may survive over a decade but usually live about 6 to 8 years for *A. duodenale* and 2 to 5 years for *N. americanus*.

Epidemiology *A. duodenale* is prevalent in southern Europe, North Africa, and northern Asia, and *N. americanus* is the predominant species in the western hemisphere and equatorial Africa. The two species overlap in many tropical regions, particularly Southeast Asia. In most areas, older children have the greatest incidence and intensity of hookworm infection. In rural areas where fields are fertilized with night soil, older working adults also may be heavily affected.

Clinical Features Most hookworm infections are asymptomatic. Infective larvae may provoke pruritic maculopapular dermatitis ("ground itch") at the site of skin penetration as well as serpiginous tracts of subcutaneous migration (similar to cutaneous larva migrans) in previously sensitized hosts. Larvae migrating through the lungs occasionally cause mild transient pneumonitis, but this condition develops less frequently in hookworm infection than in ascariasis. In the early intestinal phase, infected persons may develop epigastric pain (often with postprandial accentuation), inflammatory diarrhea, or other abdominal symptoms accompanied by eosinophilia. The major consequence of chronic hookworm infection is iron deficiency. Symptoms are minimal if iron intake is adequate, but marginally nourished individuals develop symptoms of progressive iron-deficiency anemia and hypoproteinemia, including weakness, shortness of breath, and skin depigmentation.

Laboratory Findings The diagnosis is established by the finding of characteristic 40- by 60-um oval hookworm eggs in the feces. Stool-concentration procedures may be required to detect light infections. Eggs of the two species are indistinguishable. In a stool sample that is not fresh, the eggs may have hatched to release rhabditiform larvae, which need to be differentiated from those of *S. stercoralis*. Hypochromic

microcytic anemia, occasionally with eosinophilia or hypoalbuminemia, is characteristic of hookworm disease.

TREATMENT

Hookworm infection can be eradicated with several safe and highly effective anthelmintic drugs, including mebendazole, albendazole, and pyrantel pamoate (Chap. 212). Mild iron-deficiency anemia often can be treated with oral iron alone. Severe hookworm disease with protein loss and malabsorption necessitates nutritional support and oral iron replacement along with deworming.

Ancylostoma caninum This parasite, the canine hookworm, has been identified as a cause of human eosinophilic enteritis, especially in northeastern Australia. In this zoonotic infection, adult hookworms attach to the small intestine (where they may be visualized by endoscopy) and elicit abdominal pain and intense local eosinophilia. Treatment with mebendazole (100 mg twice daily for 3 days) is effective.

STRONGYLOIDIASIS

S. stercoralis is distinguished by its ability, unusual among helminths, to replicate in the human host. This capacity permits ongoing cycles of autoinfection as infective larvae are internally produced. Strongyloidiasis can thus persist for decades without further exposure of the host to exogenous infective larvae. In immunocompromised hosts, large numbers of invasive *Strongyloides* larvae can disseminate widely and can be fatal.

Life Cycle In addition to a parasitic cycle of development, *Strongyloides* can undergo a free-living cycle of development in the soil. This adaptability facilitates the parasite's survival in the absence of mammalian hosts. Rhabditiform larvae passed in feces can transform into infectious filariform larvae either directly or after a free-living phase of development. Humans acquire strongyloidiasis when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes. The larvae then travel through the bloodstream to the lungs, where they break into the alveolar spaces, ascend the bronchial tree, are swallowed, and thereby reach the small intestine. There the larvae mature into adult worms that penetrate the mucosa of the proximal small bowel. The minute (2-mm-long) parasitic adult female worms reproduce by parthenogenesis; parasitic adult males do not exist. Eggs hatch locally in the intestinal mucosa, releasing rhabditiform larvae that migrate to the lumen and pass with the feces into soil. Alternatively, rhabditiform larvae in the bowel can develop directly into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to repeat the migration that establishes ongoing internal reinfection. This autoinfection cycle allows strongyloidiasis to persist for decades after the host has left an endemic area.

Epidemiology *S. stercoralis* is spottily distributed in tropical areas and other hot, humid regions and is particularly common in Southeast Asia, sub-Saharan Africa, and Brazil. In the United States, the parasite is endemic in parts of the South and is found in residents of mental institutions who practice poor hygiene and in immigrants and military veterans who have lived in endemic areas abroad.

Clinical Features In uncomplicated strongyloidiasis, many patients are asymptomatic

or have mild cutaneous and/or abdominal symptoms. Recurrent urticaria, often involving the buttocks and wrists, is the most common cutaneous manifestation. Migrating larvae can elicit a pathognomonic serpiginous eruption, *larva currens* ("running larva" Fig. 220-CD1) -- a pruritic, raised, erythematous lesion that advances as rapidly as 10 cm/h along the course of larval migration. Adult parasites burrow into the duodenojejunal mucosa and can cause abdominal (usually midepigastric) pain, which resembles peptic ulcer pain except that it is aggravated by food ingestion. Nausea, diarrhea, gastrointestinal bleeding, mild chronic colitis, and weight loss can occur. Small-bowel obstruction may develop with early, heavy infection. Pulmonary symptoms are rare in uncomplicated strongyloidiasis. Eosinophilia is common, with levels fluctuating over time.

The ongoing autoinfection cycle of strongyloidiasis is normally contained by unknown factors of the host's immune system. Abrogation of host immunity, especially with glucocorticoid therapy and much less commonly with other immunosuppressive medications, leads to hyperinfection, with the generation of large numbers of filariform larvae. Colitis, enteritis, or malabsorption may develop. In disseminated strongyloidiasis, larvae may invade not only gastrointestinal tissues and the lungs but also the central nervous system, peritoneum, liver, and kidney. Moreover, bacteremia may develop because of the entry of enteric flora through disrupted mucosal barriers. Gram-negative sepsis, pneumonia, or meningitis may complicate or dominate the clinical course. Eosinophilia is often absent in severely infected patients. Disseminated strongyloidiasis, particularly in patients with unsuspected infection who are given glucocorticoids, can be fatal. Strongyloidiasis is a frequent complication of infection with human T cell lymphotropic virus type I, but disseminated strongyloidiasis is not common among patients infected with HIV.

Diagnosis In uncomplicated strongyloidiasis, the finding of rhabditiform larvae in feces is diagnostic. The eggs are almost never detectable because they hatch in the intestine. Rhabditiform larvae are 200 to 250 um long, with a short buccal cavity that distinguishes them from hookworm rhabditiform larvae. Single stool examinations detect only about one-third of uncomplicated infections, in which few larvae are passed. Serial examinations and the use of the agar plate detection method improve the sensitivity of stool diagnosis. In uncomplicated -- but not hyperinfection -- strongyloidiasis, stool examinations may be repeatedly negative. If stool examinations are negative, *Strongyloides* can be assayed by sampling of the duodenojejunal contents by aspiration or biopsy. An enzyme-linked immunosorbent assay for antibodies to excretory-secretory or somatic antigens of *Strongyloides* is a sensitive method of diagnosing uncomplicated infections. In disseminated strongyloidiasis, filariform larvae (550 um long) should be sought in stool as well as in samples obtained from sites of potential larval migration, including sputum, bronchoalveolar lavage fluid, or surgical drainage fluid.

TREATMENT

Even in the asymptomatic state, strongyloidiasis must be treated because of the potential for fatal hyperinfection. Ivermectin (200 ug/kg daily for 1 or 2 days) is more effective and better tolerated than thiabendazole (25 mg/kg bid for 2 days), whose common adverse effects include nausea, vomiting, diarrhea, dizziness, and neuropsychiatric disturbances. Because thiabendazole is not uniformly effective, stool

examinations, eosinophil counts, and monitoring of clinical symptoms should be continued after treatment. For disseminated strongyloidiasis, treatment should be extended for at least 5 to 7 days or until the parasites are eradicated.

Strongyloides fulleborni This unusual species, which has been encountered in Africa and Papua New Guinea, is thought to be transmitted from person to person and through maternal milk. *S. fulleborni* releases membranous sacs filled with eggs into the stool. Most commonly affected are infants and young children, who present with abdominal distention, respiratory distress, vomiting, or diarrhea.

TRICHURIASIS

Most infections with the whipworm *Trichuris trichiura* are asymptomatic, but heavy infections may cause gastrointestinal symptoms. Like the other soil-transmitted helminths, whipworm is distributed globally in the tropics and subtropics and is most common among poor children.

Life Cycle A broad posterior section and a thin anterior portion give *Trichuris* its characteristic whiplike shape. The adult worms reside in the colon and cecum, the anterior portions threaded into the superficial mucosa. Thousands of eggs laid daily by adult female worms pass with the feces and mature in the soil. After ingestion, infective eggs hatch in the duodenum, releasing larvae that mature before migrating to the large bowel. The entire cycle takes about 3 months, and adult worms may live for several years.

Clinical Features Tissue reactions to whipworms are mild. Most infected individuals have no symptoms or eosinophilia. Heavy infections may result in abdominal pain, anorexia, and bloody or mucoid diarrhea resembling inflammatory bowel disease. Rectal prolapse can result from massive infections in children, who often suffer from malnourishment and other diarrheal illnesses. Moderately heavy whipworm burdens also contribute to growth retardation.

Diagnosis and Treatment The characteristic 50- by 20-um lemon-shaped whipworm eggs are readily detected on stool examination. Adult worms, which are 3 to 5 cm long, occasionally can be seen on proctoscopy. Mebendazole or albendazole is safe and effective for treatment (Chap. 212).

ENTEROBIASIS (PINWORM)

E. vermicularis is more common in temperate countries than in the tropics. More than 40 million Americans, particularly schoolchildren, are estimated to be infected with pinworms.

Life Cycle and Epidemiology *Enterobius* adult worms are about 1 cm long and dwell in the bowel lumen. The gravid female worm migrates nocturnally out into the perianal region and releases up to 10,000 immature eggs. The eggs become infective within hours and are transmitted by hand-to-mouth passage. The larvae hatch and mature entirely within the intestine. This life cycle takes about 1 month, and adult worms survive for about 2 months. Self-infection results from perianal scratching and transport of

infective eggs on the hands or under the nails to the mouth. Owing to the ease of person-to-person spread, pinworm infections are common among family members and institutionalized populations.

Clinical Features Most pinworm infections are asymptomatic. Perianal pruritus is the cardinal symptom. The itching is often worse at night owing to the nocturnal migration of the female worms, and it may lead to excoriation and bacterial superinfection. Heavy infections have been claimed to cause abdominal pain and weight loss. On rare occasions, pinworms invade the female genital tract, causing vulvovaginitis and pelvic or peritoneal granulomas. Eosinophilia or elevated levels of serum IgE are rare.

Diagnosis Since pinworm eggs are not usually released in the bowel, the diagnosis cannot be made by looking for eggs in the feces. Instead, eggs deposited in the perianal region are detected by the application of clear cellulose acetate tape to the perianal region in the morning. After the tape is transferred to a microscope slide, low-power examination will reveal the characteristic pinworm eggs, which are oval, measure 55 by 25 um, and are flattened along one side.

TREATMENT

All affected individuals should be given a dose of mebendazole or pyrantel pamoate, with treatment repeated after 10 to 14 days (Chap. 212). Treatment of household members is also advocated to eliminate asymptomatic reservoirs of potential reinfection.

TRICHOSTRONGYLIASIS

Trichostrongylus species that are normally parasites of herbivorous animals occasionally infect humans, particularly in Asia and Africa. This parasite has been termed *pseudo hookworm* because of similarities to the hookworms in life cycle and egg morphology. Humans acquire the infection by accidentally ingesting *Trichostrongylus* larvae on contaminated leafy vegetables. The larvae do not migrate in humans but mature directly into adult worms in the small bowel. These worms ingest far less blood than hookworms; most infected people are asymptomatic, but heavy infections may give rise to mild anemia and eosinophilia. *Trichostrongylus* eggs encountered on stool examination resemble those of hookworms but are larger (85 by 115 um). Appropriate treatment consists of mebendazole or albendazole (Chap. 212).

ANISAKIASIS

Anisakiasis is a gastrointestinal infection caused by the accidental ingestion in uncooked saltwater fish of nematode larvae belonging to the family Anisakidae. The incidence of anisakiasis in the United States has increased as a result of the growing popularity of raw fish dishes. Most cases occur in Japan, the Netherlands, and Chile, where raw fish -- sushi, pickled green herring, and seviche, respectively -- are national culinary staples. Anisakid nematodes parasitize large sea mammals such as whales, dolphins, and seals. As part of a complex parasitic life cycle involving marine food chains, infectious larvae migrate to the musculature of a variety of fish. Both *Anisakis simplex* and *Pseudoterranova decipiens* have been implicated in human anisakiasis, but an identical gastric syndrome may be caused by the red larvae of eustrongylid parasites

of fish-eating birds.

When humans consume infected raw fish, live larvae may be coughed up within 48 h. Alternatively, larvae may immediately penetrate the mucosa of the stomach. Within hours, violent upper abdominal pain accompanied by nausea and occasionally vomiting ensues, mimicking an acute abdomen. The diagnosis can be established by direct visualization on upper endoscopy, outlining of the worm by contrast radiographic studies, or histopathologic examination of extracted tissue. In experienced hands, the first technique is preferable because extraction of the burrowing larvae by endoscopic technique is curative. In addition, larvae may pass to the small bowel, where they penetrate the mucosa and provoke a vigorous eosinophilic granulomatous response. Symptoms may appear 1 or 2 weeks after the infective meal, with intermittent abdominal pain, diarrhea, nausea, and fever resembling the manifestations of Crohn's disease. The diagnosis may be suggested by barium studies and confirmed by curative surgical resection of a granuloma in which the worm is embedded. Anisakid eggs are not found in the stool, since the larvae do not mature in humans. Anisakid larvae in saltwater fish are killed by cooking to 60°C, freezing at-20°C for 3 days, or commercial blast freezing, but not usually by salting, marinating, or cold smoking. No medical treatment is available; if possible, surgical or endoscopic removal should be undertaken.

CAPILLARIASIS

Intestinal capillariasis is caused by ingestion of raw fish infected with *Capillaria philippinensis*. Subsequent autoinfection can lead to a severe wasting syndrome. The disease occurs in the Philippines and Thailand and, on occasion, elsewhere in Asia. The natural cycle of *C. philippinensis* involves fish from fresh and brackish water. When humans eat infected raw fish, the larvae mature in the intestine into adult worms, which produce invasive larvae that cause intestinal inflammation and villus loss. Capillariasis has an insidious onset with nonspecific abdominal pain and watery diarrhea. If untreated, progressive autoinfection can lead to protein-losing enteropathy and severe malabsorption and ultimately to death from cachexia, cardiac failure, or superinfection. The diagnosis is established by identification of the characteristic peanut-shaped (20- by 40-um) eggs on stool examination. Severely ill patients require hospitalization and supportive therapy in addition to prolonged anthelmintic treatment with mebendazole or albendazole (Chap. 212).

ABDOMINAL ANGIOSTRONGYLIASIS

Abdominal angiostrongyliasis is found in Latin America and Africa. The zoonotic parasite *Angiostrongylus costaricensis* causes eosinophilic ileocolitis after the ingestion of contaminated vegetation. *A. costaricensis* normally parasitizes the cotton rat and other rodents, with slugs and snails serving as intermediate hosts. Humans become infected by accidentally ingesting infective larvae in mollusk slime deposited on fruits and vegetables; children are at highest risk. The larvae penetrate the gut wall and migrate to the mesenteric artery, where they develop into adult worms. Eggs deposited in the gut wall provoke an intense eosinophilic granulomatous reaction, and adult worms may cause mesenteric arteritis, thrombosis, or frank bowel infarction. Symptoms may mimic those of appendicitis, including abdominal pain and tenderness, fever, vomiting, and a palpable mass in the right iliac fossa. Leukocytosis and eosinophilia are

prominent. A barium enema may reveal ileocecal filling defects, but a definitive diagnosis is usually made surgically with partial bowel resection. Pathologic study reveals a thickened bowel wall with eosinophilic granulomas surrounding the *Angiostrongylus* eggs. In nonsurgical cases, the diagnosis rests solely on clinical grounds because larvae and eggs cannot be detected in the stool. Medical therapy for abdominal angiostrongyliasis (thiabendazole; Chap. 212) is of uncertain efficacy. Careful observation and surgical resection for severe symptoms are the mainstays of treatment.

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221. FILARIASIS AND RELATED INFECTIONS (LOIASIS, ONCHOCERCIASIS, AND DRACUNCULIASIS) - *Thomas B. Nutman*, *Peter F. Weller*

Filarial worms are nematodes that dwell in the subcutaneous tissues and the lymphatics. Eight filarial species infect humans (Table 221-1); of these, four -- *Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa* -- are responsible for most serious filarial infections. Filarial parasites, which infect an estimated 170 million persons worldwide, are transmitted by specific species of mosquitoes or other arthropods and have a complex life cycle including infective larval stages carried by insects and adult worms that reside in either lymphatic or subcutaneous tissues of humans. The offspring of adults are microfilariae, which, depending on their species, are 200 to 250 um long and 5 to 7 um wide, may or may not be enveloped in a loose sheath, and either circulate in the blood or migrate through the skin (Table 221-1). To complete the life cycle, microfilariae are ingested by the arthropod vector and develop over 1 to 2 weeks into new infective larvae. Adult worms live for many years, whereas microfilariae survive from 3 to 36 months.

Usually, infection is established only with repeated and prolonged exposures to infective larvae. Since the clinical manifestations of filarial diseases develop relatively slowly, these infections should be considered chronic diseases with possible long-term debilitating effects. In terms of the nature, severity, and timing of clinical manifestations, patients with filariasis who are native to endemic areas and undergo lifelong exposure may differ significantly from those who are travelers or who have recently moved to these areas. Characteristically, the disease is more acute and intense in newly exposed individuals than in natives of endemic areas.

LYMPHATIC FILARIASIS

Lymphatic filariasis is caused by *W. bancrofti*, *B. malayi*, or *B. timori*. The threadlike adult parasites reside in lymphatic channels or lymph nodes, where they may remain viable for more than two decades.

EPIDEMIOLOGY

W. bancrofti, the most widely distributed human filarial parasite, affects an estimated 115 million people and is found throughout the tropics and subtropics, including Asia and the Pacific Islands, Africa, areas of South America, and the Caribbean basin. Humans are the only definitive host for the parasite. Generally, the subperiodic form is found only in the Pacific Islands; elsewhere, *W. bancrofti* is nocturnally periodic. (Nocturnally periodic forms of microfilariae are scarce in peripheral blood by day and increase at night, whereas subperiodic forms are present in peripheral blood at all times and reach maximal levels in the afternoon.) Natural vectors for *W. bancrofti* are *Culex fatigans* mosquitoes in urban settings and anopheline or aedean mosquitoes in rural areas.

Brugian filariasis due to *B. malayi* occurs primarily in China, India, Indonesia, Korea, Japan, Malaysia, and the Philippines. *B. malayi* also has two forms distinguished by the periodicity of microfilaremia. The more common nocturnal form is transmitted in areas of coastal rice fields, while the subperiodic form is found in forests. *B. malayi* naturally

infects cats as well as humans. *B. timori* exists only on islands of the Indonesian archipelago.

PATHOLOGY

The principal pathologic changes result from inflammatory damage to the lymphatics, which is caused by adult worms and not by microfilariae. Adult worms live in afferent lymphatics or sinuses of lymph nodes and cause lymphatic dilatation and thickening of the vessel walls. The infiltration of plasma cells, eosinophils, and macrophages in and around the infected vessels, along with endothelial and connective tissue proliferation, leads to tortuosity of the lymphatics and damaged or incompetent lymph valves. Lymphedema and chronic-stasis changes with hard or brawny edema develop in the overlying skin. These consequences of filariasis are due both to direct effects of the worms and to the immune response of the host to the parasite. These immune responses are believed to cause the granulomatous and proliferative processes that precede total lymphatic obstruction. It is thought that the vessel remains patent as long as the worm remains viable and that death of the worm leads to enhanced granulomatous reaction and fibrosis. Lymphatic obstruction results, and, despite collateralization of the lymphatics, lymphatic function is compromised.

CLINICAL FEATURES

The most common presentations of the lymphatic filariases are asymptomatic (or subclinical) microfilaremia, hydrocele, acute adenolymphangitis (ADL), and chronic lymphatic disease. In areas where *W. bancrofti* or *B. malayi* is endemic, the overwhelming majority of infected individuals have few overt clinical manifestations of filarial infection despite large numbers of circulating microfilariae in the peripheral blood. Although they may be clinically asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of subclinical disease that includes microscopic hematuria and/or proteinuria, dilated (and tortuous) lymphatics (visualized by imaging), and -- in men -- scrotal lymphangiectasia (detectable by ultrasound). Despite these findings, the majority of individuals appear to remain clinically asymptomatic for years; relatively few progress to the acute and chronic stages of infection.

ADLis characterized by high fever, lymphatic inflammation (lymphangitis and lymphadenitis), and transient local edema. The lymphangitis is retrograde, extending peripherally from the lymph node draining the area where the adult parasites reside. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can occur as well. In brugian filariasis, a single local abscess may form along the involved lymphatic tract and subsequently rupture to the surface. The lymphadenitis and lymphangitis involve both the upper and lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with *W. bancrofti* infection. This genital involvement can be manifested by funiculitis, epididymitis, scrotal pain, and tenderness. In endemic areas, another type of acute disease -- dermatolymphangioadenitis (DLA) -- is recognized as a syndrome that includes high fever, chills, myalgias, and headache. Edematous inflammatory plaques clearly demarcated from normal skin are seen. Vesicles, ulcers, and hyperpigmentation may

also be noted. There is often a history of trauma, burns, radiation, insect bites, punctiform lesions, or chemical injury. Entry lesions, especially in the interdigital area, are common. DLA is often diagnosed as cellulitis.

If lymphatic damage progresses, transient lymphedema can develop into *lymphatic obstruction* and the permanent changes associated with elephantiasis. Brawny edema follows early pitting edema, and thickening of the subcutaneous tissues and hyperkeratosis occur. Fissuring of the skin develops, as do hyperplastic changes. Superinfection of these poorly vascularized tissues becomes a problem. In bancroftian filariasis, in which genital involvement is common, hydroceles may develop; in advanced stages, this condition may evolve into scrotal lymphedema and scrotal elephantiasis. Furthermore, if there is obstruction of the retroperitoneal lymphatics, the increased renal lymphatic pressure leads to rupture of the renal lymphatics and the development of chyluria, which is usually intermittent and most prominent in the morning.

The clinical manifestations of filarial infections in travelers or transmigrants who have recently entered an endemic region are distinctive. Given a sufficient number of bites by infected vectors, usually over a 3- to 6-month period, recently exposed patients can develop acute lymphatic or scrotal inflammation with or without urticaria and localized angioedema. Lymphadenitis of epitrochlear, axillary, femoral, or inguinal lymph nodes is often followed by retrogradely evolving lymphangitis. Acute attacks are short-lived and, in contrast to filarial fevers in patients native to endemic areas, are usually not accompanied by fever. With prolonged exposure to infected mosquitoes, these attacks, if untreated, become more severe and lead to permanent lymphatic inflammation and obstruction.

DIAGNOSIS

A definitive diagnosis can be made only by detection of the parasites and hence can be difficult. Adult worms localized in lymphatic vessels or nodes are largely inaccessible. Microfilariae can be found in blood, in hydrocele fluid, or (occasionally) in other body fluids. Such fluids can be examined microscopically, either directly or -- for greater sensitivity -- after concentration of the parasites by the passage of fluid through a polycarbonate cylindrical pore filter (pore size, 3 um) or by the centrifugation of fluid fixed in 2% formalin (Knott's concentration technique). The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved. Many infected individuals do not have microfilaremia, and definitive diagnosis in such cases can be difficult. Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. Two tests are commercially available: one is an enzyme-linked immunosorbent assay (ELISA) and the other a rapid-format immunochromatographic card test. Both assays have sensitivities that range from 96 to 100% and specificities that approach 100%. There are currently no tests for circulating antigens in brugian filariasis.

Polymerase chain reaction (PCR)-based assays for DNA of *W. bancrofti* and *B. malayi* in blood have been developed. A number of studies indicate that this diagnostic method is of equivalent or greater sensitivity compared with parasitologic methods, detecting patent infection in almost all infected subjects.

In cases of suspected lymphatic filariasis, examination of the scrotum or the female breast using high-frequency ultrasound in conjunction with Doppler techniques may result in the identification of motile adult worms within dilated lymphatics. Worms may be visualized in the lymphatics of the spermatic cord in up to 80% of infected men. Live adult worms have a distinctive pattern of movement within the lymphatic vessels (termed the *filaria dance sign*).

Radionuclide lymphoscintigraphic imaging of the limbs reliably demonstrates widespread lymphatic abnormalities in both asymptomatic microfilaremic persons and those with clinical manifestations of lymphatic pathology. While of potential utility in the delineation of anatomic changes associated with infection, lymphoscintigraphy is unlikely to assume primacy in the diagnostic evaluation of individuals with suspected infection; it is principally a research tool, and the radionuclide-protein conjugates are not commercially available or approved by the U.S. Food and Drug Administration (FDA).

Eosinophilia and elevated serum concentrations of IgE and antifilarial antibody support the diagnosis of lymphatic filariasis. There is, however, extensive cross-reactivity between filarial antigens and antigens of other helminths, including the common intestinal roundworms; thus, interpretations of serologic findings can be difficult. In addition, residents of endemic areas can become sensitized to filarial antigens through exposure to infected mosquitoes without having patent filarial infections.

In acute episodes, lymphatic filariasis must be distinguished from thrombophlebitis, infection, and trauma. Retrogradely evolving lymphangitis is a characteristic feature that helps distinguish filarial lymphangitis from typically ascending bacterial lymphangitis. Chronic filarial lymphedema must be distinguished from the lymphedema of malignancy, postoperative scarring, trauma, chronic edematous states, and congenital lymphatic system abnormalities.

TREATMENT

With new definitions of clinical syndromes in lymphatic filariasis and new tools to assess clinical status (e.g., ultrasound, lymphoscintigraphy, circulating filarial antigen assays), approaches to treatment based on infection status can be considered. Diethylcarbamazine (DEC, 6 mg/kg daily for 12 days), which has both macro- and microfilaricidal properties, remains the treatment of choice for the individual with active lymphatic filariasis (microfilaremia, antigen positivity, or adult worms on ultrasound), although albendazole (400 mg twice daily for 21 days) has demonstrated macrofilaricidal efficacy.

As has already been mentioned, a growing body of evidence indicates that, although they may be asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of subclinical disease (hematuria, proteinuria, abnormalities on lymphoscintigraphy). Thus, early treatment of asymptomatic persons is recommended to prevent further lymphatic damage. ForADL, supportive treatment (including the administration of antipyretics and analgesics) is recommended, as is antibiotic therapy if secondary bacterial infection is likely. Similarly, because lymphatic disease is associated with the presence of adult worms, treatment withDEC is recommended for microfilaria-negative adult-worm carriers.

In persons with chronic manifestations of lymphatic filariasis, treatment regimens that emphasize hygiene, prevention of secondary bacterial infections, and physiotherapy have gained wide acceptance for morbidity control. These regimens are similar to those recommended for lymphedema of most nonfilarial causes and known by a variety of names, including *complex decongestive physiotherapy* and *complex lymphedema therapy*. Hydroceles can be drained repeatedly or managed surgically. In patients with chronic manifestations of lymphatic filariasis, drug treatment should be reserved for cases with evidence of active infection.

The recommended course ofDECtreatment (12 days; total dose, 72 mg/kg) has remained standard for many years; however, data indicate that single-dose DEC treatment with 6 mg/kg may be equally efficacious. The 12-day course provides more rapid short-term microfilarial suppression. Regimens that utilize single-dose DEC or ivermectin or combinations of single doses of albendazole and either DEC or ivermectin have all been demonstrated to have a sustained microfilaricidal effect.

Side effects ofDECtreatment include fever, chills, arthralgias, headaches, nausea, and vomiting. Both the development and the severity of these reactions are directly related to the number of microfilariae circulating in the bloodstream and may represent an acute hypersensitivity reaction to the antigens being released by dead and dying parasites.

PREVENTION AND CONTROL

Avoidance of mosquito bites is usually not feasible for residents of endemic areas, but visitors should make use of insect repellent and mosquito nets.DEC can kill developing forms of filarial parasites and has been shown to be useful as a prophylactic agent in humans.

Community-based intervention is the current approach to elimination of lymphatic filariasis as a public health problem. The underlying tenet of this approach is that mass annual distribution of antimicrofilarial chemotherapy (albendazole with eitherDEC or ivermectin) will profoundly suppress microfilaremia. If the suppression is sustained, then transmission can be interrupted. As an added benefit, these combinations have secondary effects on gastrointestinal helminths. An alternative approach to the control of lymphatic filariasis is the use of salt fortified with DEC. Community use of DEC-fortified salt dramatically reduces microfilarial density with no apparent adverse reactions. Community education and clinical care for persons already suffering from the chronic sequelae of lymphatic filariasis are important components of filariasis control and elimination programs.

TROPICAL PULMONARY EOSINOPHILIA

Tropical pulmonary eosinophilia (TPE) is a distinct syndrome that develops in some individuals infected with lymphatic filarial species. This syndrome affects males and females at a ratio of 4:1, often during the third decade of life. The majority of cases have been reported from India, Pakistan, Sri Lanka, Brazil, and Southeast Asia.

CLINICAL FEATURES

The main features include a history of residence in filarial endemic regions, paroxysmal cough and wheezing that are usually nocturnal (and probably related to the nocturnal periodicity of microfilariae), weight loss, low-grade fever, adenopathy, and pronounced blood eosinophilia (>3000 eosinophils/uL). Chest x-rays may be normal but generally show increased bronchovascular markings; diffuse miliary lesions or mottled opacities may be present in the middle and lower lung fields. Tests of pulmonary function show restrictive abnormalities in most cases and obstructive defects in half. Total serum IgE levels (10,000 to 100,000 ng/mL) and antifilarial antibody titers are characteristically elevated.

PATHOLOGY

InTPEthere is rapid clearance of microfilariae and parasite antigens from the bloodstream by the lungs, and the clinical symptoms result from allergic and inflammatory reactions elicited by the cleared parasites. In some subjects, trapping of microfilariae in other reticuloendothelial organs can cause hepatomegaly, splenomegaly, or lymphadenopathy. A prominent, eosinophil-enriched, intraalveolar infiltrate is often reported. In the absence of successful treatment, interstitial fibrosis can lead to progressive pulmonary damage.

DIFFERENTIAL DIAGNOSIS

TPEmust be distinguished from asthma, Loffler's syndrome, allergic bronchopulmonary aspergillosis, allergic granulomatosis with angiitis (Churg-Strauss syndrome), the systemic vasculitides (most notably periarteritis nodosa and Wegener's granulomatosis), chronic eosinophilic pneumonia, and the idiopathic hypereosinophilic syndrome. In addition to a geographic history of filarial exposure, useful features for distinguishing TPE include wheezing that is solely nocturnal, very high levels of antifilarial antibodies, and a rapid initial response to treatment withDEC.

TREATMENT

DECis used at a dosage of 4 to 6 mg/kg of body weight per day for 14 days. Symptoms usually resolve within 3 to 7 days after the initiation of therapy. Relapse, which occurs in ~12 to 25% of cases (sometimes after an interval of years), requires re-treatment.

ONCHOCERCIASIS

Onchocerciasis ("river blindness") is caused by the filarial nematode *O. volvulus*, which infects an estimated 13 million individuals. The majority of individuals infected with *O. volvulus* live in the equatorial region of Africa extending from the Atlantic coast to the Red Sea. About 70,000 persons are infected in Guatemala and Mexico, with smaller foci in Venezuela, Colombia, Brazil, Ecuador, Yemen, and Saudi Arabia. Onchocerciasis is the second leading cause of infectious blindness worldwide.

ETIOLOGY AND EPIDEMIOLOGY

Infection in humans begins with the deposition of infective larvae on the skin by the bite

of an infected blackfly. The larvae develop into adults, which are typically found in subcutaneous nodules. About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodule and throughout the tissues, concentrating in the dermis. Infection is transmitted to other persons when a female fly ingests microfilariae from the host's skin and these microfilariae then develop into infective larvae. Adult *O. volvulus* females and males are about 40 to 60 cm and 3 to 6 cm in length, respectively. The life span of adults can be as long as 18 years, with an average of ~9 years. Because the blackfly vector breeds along free-flowing rivers and streams (particularly in rapids) and generally restricts its flight to an area within several kilometers of these breeding sites, both biting and disease transmission are most intense in these locations.

PATHOLOGY

Onchocerciasis affects primarily the skin, eyes, and lymph nodes. In contrast to that in lymphatic filariasis, the damage in onchocerciasis is elicited by microfilariae and not by adults. In the skin, there are mild but chronic inflammatory changes that can result in loss of elastic fibers, atrophy, and fibrosis. The subcutaneous nodules, or onchocercomata, consist primarily of fibrous tissues surrounding the adult worm, often with a peripheral ring of inflammatory cells. In the eye, neovascularization and corneal scarring lead to corneal opacities and blindness. Inflammation in the anterior and posterior chambers frequently results in anterior uveitis, chorioretinitis, and optic atrophy. Although punctate opacities are due to an inflammatory reaction surrounding dead or dying microfilariae, the pathogenesis of most manifestations of onchocerciasis is still unclear.

CLINICAL FEATURES

Skin Pruritus and rash are the most frequent manifestations of onchocerciasis. The pruritus can be incapacitating; the rash is typically a papular eruption that is generalized rather than localized to a particular region of the body. Long-term infection results in exaggerated and premature wrinkling of the skin, loss of elastic fibers, and epidermal atrophy that can lead to loose, redundant skin and hypo- or hyperpigmentation. Localized eczematoid dermatitis can cause hyperkeratosis, scaling, and pigmentary changes. Such lesions are often seen in the lower extremities but can be distributed more extensively.

Onchocercomata These subcutaneous nodules, which can be palpable and/or visible, contain the adult worm. In African patients, they are common over the coccyx and sacrum, the trochanter of the femur, the lateral anterior crest, and other bony prominences; in Latin American patients, they tend to develop preferentially in the upper part of the body, particularly on the head, neck, and shoulders. Nodules vary in size and characteristically are firm and not tender. It has been estimated that, for every palpable nodule, there are four deeper nonpalpable ones.

Ocular Tissue Visual impairment is the most serious complication of onchocerciasis and usually affects only those persons with moderate or heavy infections. Lesions may develop in all parts of the eye. The most common early finding is conjunctivitis with photophobia. In the cornea, punctate keratitis -- consisting of acute inflammatory

reactions surrounding dying microfilariae manifested as "snowflake" opacities -- is frequent in younger patients and resolves without apparent complications. Sclerosing keratitis occurs in 1 to 5% of infected persons and is the leading cause of onchocercal blindness in Africa. Anterior uveitis and iridocyclitis develop in ~5% of infected persons in Africa. In Latin America, complications of the anterior uveal tract (pupillary deformity) may cause secondary glaucoma. Characteristic chorioretinal lesions develop as a result of atrophy and hyperpigmentation of the retinal pigment epithelium. Constriction of the visual field and frank optic atrophy may occur.

Lymph Nodes Mild to moderate lymphadenopathy is frequent, particularly in the inguinal and femoral areas, where the enlarged nodes may hang down in response to gravity ("hanging groin"), sometimes predisposing to inguinal and femoral hernias.

Systemic Manifestations Some heavily infected individuals develop cachexia with loss of adipose tissue and muscle mass. Among adults who become blind, there is a three- to fourfold increase in the mortality rate.

DIAGNOSIS

Definitive diagnosis depends on the detection of an adult worm in an excised nodule or, more commonly, of microfilariae in a skin snip. Skin snips are obtained with a corneal-scleral punch, which collects a blood-free skin biopsy sample extending to just below the epidermis, or by lifting of the skin with the tip of a needle and excision of a small (1- to 3-mm) piece with a sterile scalpel blade. The biopsy tissue is incubated in tissue culture medium or in saline on a glass slide or flat-bottomed microtiter plate. After incubation for 2 to 4 h (or occasionally overnight in light infections), microfilariae emergent from the skin can be visualized by low-power microscopy.

Eosinophilia and elevated serum IgE levels are common but, because they occur in many parasitic infections, are not diagnostic in themselves. Assays to detect specific antibodies to *Onchocerca* andPCR to detect onchocercal DNA in skin snips are now in use in specialized laboratories and are highly sensitive and specific.

The *Mazzotti test* is a provocative technique that can be used in cases where the diagnosis of onchocerciasis is still in doubt (i.e., when skin snips and ocular examination reveal no microfilariae). A small dose ofDEC (0.5 to 1.0 mg/kg) is given orally; the development or exacerbation of pruritus or rash within hours is highly suggestive of onchocerciasis.

TREATMENT

The main goals of therapy are to prevent the development of irreversible lesions and to alleviate symptoms. Surgical excision is recommended when nodules are located on the head (because of the proximity of microfilaria-producing adult worms to the eye), but chemotherapy is the mainstay of management. Ivermectin, a semisynthetic macrocyclic lactone active against microfilariae, is the first-line agent for the treatment of onchocerciasis. It is given orally in a single dose of 150 ug/kg, either yearly or semiannually. After treatment, most individuals have few or no reactions. Pruritus, cutaneous edema, and/or maculopapular rash occurs in ~1 to 10% of treated

individuals. In areas of Africa coendemic for *O. volvulus* and *L. loa*, however, ivermectin is contraindicated (as it is for pregnant or breastfeeding women) because of severe posttreatment encephalopathy seen in patients, especially children, who are heavily microfilaremic for *L. loa* (>2000 to 5000 microfilariae per milliliter). Although ivermectin treatment results in a marked drop in microfilarial density, its effect can be short-lived (<6 months in some cases). Thus, it is occasionally necessary to give ivermectin more frequently for persistent symptoms. No currently available agent kills adult *O. volvulus*.

PREVENTION

Vector control has been beneficial in highly endemic areas in which breeding sites are vulnerable to insecticide spraying, but most areas endemic for onchocerciasis are not suited to this type of control. Community-based administration of ivermectin every 6 to 12 months is now being used to interrupt transmission in endemic areas. This measure, in conjunction with vector control, has already helped reduce the prevalence of disease in endemic foci in Africa and Latin America. No drug has proven useful for prophylaxis of *O. volvulus* infection.

LOIASIS

ETIOLOGY AND EPIDEMIOLOGY

Loiasis is caused by *L. loa* (the African eye worm), which is present in the rain forests of West and Central Africa. Adult parasites (females, 50 to 70 mm long and 0.5 mm wide; males, 25 to 35 mm long and 0.25 mm wide) live in subcutaneous tissues; microfilariae circulate in the blood with a diurnal periodicity that peaks between 12:00 noon and 2:00 P.M.

CLINICAL FEATURES

Manifestations of loiasis in natives of endemic areas may differ from those in temporary residents or visitors. Among the indigenous population, loiasis is often an asymptomatic infection with microfilaremia. Infection may be recognized only after subconjunctival migration of an adult worm or may be manifested by episodic Calabar swellings, evanescent localized areas of angioedema and erythema developing on the extremities and less frequently at other sites. Nephropathy, encephalopathy, and cardiomyopathy are rare. In patients who are not residents of endemic areas, allergic symptoms predominate, episodes of Calabar swelling tend to be more frequent and debilitating, microfilaremia is rare, and eosinophilia and increased levels of antifilarial antibodies are characteristic.

PATHOLOGY

The pathogenesis of the manifestations of loiasis is poorly understood. Calabar swellings are thought to result from a hypersensitivity reaction to the adult worm.

DIAGNOSIS

Definitive diagnosis of loiasis requires the detection of microfilariae in the peripheral

blood or the isolation of the adult worm from the eye or from a subcutaneous biopsy specimen from a site of swelling developing after treatment.PCR-based assays for the detection of *L. loa* DNA in blood are now available in specialized laboratories and are highly sensitive and specific. In practice, the diagnosis must often be based on a characteristic history and clinical presentation, blood eosinophilia, and elevated levels of antifilarial antibodies, particularly in travelers to an endemic region, who are usually amicrofilaremic. Other clinical findings in the latter individuals include hypergammaglobulinemia, elevated levels of serum IgE, and elevated leukocyte and eosinophil counts.

TREATMENT

DEC(8 to 10 mg/kg per day for 21 days) is effective against both the adult and the microfilarial forms of *L. loa*, but multiple courses are frequently necessary before the disease resolves completely. In cases of heavy microfilaremia, allergic or other inflammatory reactions can take place during treatment, including central nervous system involvement with coma and encephalitis. Heavy infections can be treated initially with apheresis to remove the microfilariae and with glucocorticoids (40 to 60 mg of prednisone per day) followed by doses of DEC (0.5 mg/kg per day). If antifilarial treatment has no adverse effects, the prednisone dose can be rapidly tapered and the dose of DEC gradually increased to 8 to 10 mg/kg per day.

Albendazole and ivermectin (although not approved by theFDA) have been shown to be effective in reducing microfilarial loads.DEC (300 mg weekly) is an effective prophylactic regimen for loiasis.

STREPTOCERCIASIS

Mansonella streptocerca, found mainly in the tropical forest belt of Africa from Ghana to Zaire, is transmitted by biting midges. The major clinical manifestations involve the skin and include pruritus, papular rashes, and pigmentation changes. Many infected individuals have inguinal adenopathy, although most are asymptomatic. The diagnosis is made by detection of the characteristic microfilariae in skin snips.DEC (6 mg/kg per day in divided doses for 14 to 21 days) is effective in killing both microfilariae and adult worms. As in onchocerciasis, treatment is sometimes accompanied by urticaria, arthralgias, myalgias, headaches, and abdominal discomfort. Ivermectin at a single dose of 150 ug/kg leads to sustained suppression of microfilariae in the skin and is likely to assume primacy in the treatment of streptocerciasis.

MANSONELLA PERSTANS INFECTION

Mansonella perstans, distributed across the center of Africa and in northeastern South America, is transmitted by midges. Adult worms reside in serous cavities -- pericardial, pleural, and peritoneal -- as well as in the mesentery and the perirenal and retroperitoneal tissues. Microfilariae circulate in the blood without periodicity. The clinical and pathologic features of the infection are poorly defined. Most patients appear to be asymptomatic, but manifestations may include transient angioedema and pruritus of the arms, face, or other parts of the body (analogous to the Calabar swellings of loiasis); fever; headache; arthralgias; and right upper quadrant pain. Occasionally, pericarditis

and hepatitis occur. The diagnosis is based on the demonstration of microfilariae in blood or serosal effusions. Perstans filariasis is often associated with peripheral blood eosinophilia and antifilarial antibody elevations. AlthoughDEC (8 to 10 mg/kg per day for 21 days) is the standard therapeutic agent, there is little evidence that it is effective. Cure is indicated by the disappearance of symptoms and eosinophilia; multiple courses of therapy are usually required. Both mebendazole (100 mg twice daily for 30 days) and albendazole (400 mg twice daily for 10 days) have been reported to be effective.

MANSONELLA OZZARDI INFECTION

The distribution of *Mansonella ozzardi* is restricted to Central and South America and certain Caribbean islands. Adult worms are rarely recovered from humans. Microfilariae circulate in the blood without periodicity. Although this organism has often been considered nonpathogenic, headache, articular pain, fever, pulmonary symptoms, adenopathy, hepatomegaly, pruritus, and eosinophilia have been ascribed to *M. ozzardi* infection. Diagnosis is made by the detection of microfilariae in peripheral blood. Ivermectin (a single dose of 6 mg) has been shown to be effective in treating this infection.

DRACUNCULIASIS (GUINEA WORM INFECTION)

ETIOLOGY AND EPIDEMIOLOGY

Dracunculiasis, caused by *Dracunculus medinensis*, is a parasitic infection whose incidence has declined dramatically because of global eradication efforts. Current estimates suggest that there are only 78,000 cases worldwide, the majority in Sudan. Humans acquire this infection when they ingest water containing infective larvae derived from *Cyclops*, a crustacean that is the intermediate host. Larvae penetrate the stomach or intestinal wall, mate, and mature. The adult male probably dies; the female *Dracunculus* develops over a year and migrates to subcutaneous tissues, usually in the lower extremity. As the thin female *Dracunculus*, ranging in length from 300 cm to 1 m, approaches the skin, a blister forms that, over days, breaks down and forms an ulcer. When the blister opens, large numbers of motile, rhabditiform larvae can be released into stagnant water; ingestion by *Cyclops* completes the life cycle.

CLINICAL FEATURES

Few or no clinical manifestations of dracunculiasis are evident until just before the blister forms, when there is an onset of fever and generalized allergic symptoms, including periorbital edema, wheezing, and urticaria. The emergence of the worm is associated with local pain and swelling. When the blister ruptures (usually as a result of immersion in water), the adult worm releases larva-rich fluid, and this release is associated with a relief of symptoms. The shallow ulcer surrounding the emerging adult worm heals over weeks to months. Such ulcers, however, can become secondarily infected, the result being cellulitis, local inflammation, abscess formation, or (uncommonly) tetanus. Occasionally, the adult worm does not emerge but becomes encapsulated and calcified.

DIAGNOSIS

The diagnosis is based on the findings developing with the emergence of the adult worm, as described above.

TREATMENT

Gradual extraction of the worm by winding of a few centimeters on a stick each day remains the common and effective practice. Worms may be excised surgically. The administration of thiabendazole (25 mg/kg twice daily for 3 days) or metronidazole (250 mg three times daily for 10 days) may relieve symptoms but has no proven activity against the worm.

PREVENTION

Prevention, which remains the only real control measure, depends on the provision of safe drinking water.

ZOONOTIC FILARIAL INFECTIONS

Dirofilariae that affect primarily dogs, cats, and raccoons and *Brugia* parasites that affect small mammals occasionally infect humans incidentally. Because humans are an abnormal host, the parasites never develop fully. Pulmonary dirofilarial infection caused by the canine heartworm *Dirofilaria immitis* generally presents in humans as a solitary pulmonary nodule. Chest pain, hemoptysis, and cough are uncommon. Infections with *D. repens* (from dogs) or *D. tenuis* (from raccoons) can cause local subcutaneous nodules in humans. Zoonotic *Brugia* infection can produce isolated lymph node enlargement. Eosinophilia levels and antifilarial antibody titers are not commonly elevated. Excisional biopsy is both diagnostic and curative; these infections usually do not respond to chemotherapy.

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222. SCHISTOSOMIASIS AND OTHER TREMATODE INFECTIONS - *Adel A.F. Mahmoud*

Trematodes, or flatworms, are a group of morphologically and biologically heterogeneous parasitic helminths that belong to the phylum Platyhelminthes. Human infection with trematodes occurs in many geographic areas and can cause considerable morbidity and mortality. For clinical purposes, the significant trematode infections of humans may be divided according to the tissues invaded by adult flukes: blood, biliary tree, intestines, and lungs (Table 222-1).

Trematodes share some common morphologic features, including macroscopic size (from 1 cm to several cm); dorsoventral, flattened, bilaterally symmetric bodies (adult worms); and the prominence of two suckers. Except for the schistosomes, all trematodes that parasitize humans are hermaphroditic. The life cycle of trematodes involves a definitive host (mammalian/human), in which adult worms initiate sexual reproduction, and an intermediate host (snails, fish, etc.), in which asexual multiplication of the larval forms occurs. More than one intermediate host may be necessary for some species of trematodes. Human infection is initiated either by direct penetration of intact skin or by ingestion. Upon maturation within the human host, adult flukes initiate sexual reproduction that results in egg production. Helminth ova leave the definitive host in excreta or sputum and, upon reaching suitable environmental conditions, they hatch, releasing free-living miracidia that must find a specific snail intermediate host. After asexual reproduction, cercariae are released from infected snails; these organisms either infect humans (schistosomes) or must find another intermediate host to allow encystment into metacercariae.

The host-parasite relationship in trematode infections is a product of the biologic features of these organisms: they are multicellular, undergo several developmental changes within the host, and usually result in chronic infections. In general, the distribution of worm infections in human populations is overdispersed; i.e., it follows a negative binomial mathematical relationship in which most infected individuals harbor low worm burdens while a small percentage are heavily infected. It is the heavily infected minority who are particularly prone to disease sequelae and who represent an epidemiologically significant reservoir of infection in endemic areas. It is important to appreciate that worms do not multiply within the definitive host and that they have a relatively long life span, ranging from a few months to a few years. Morbidity and mortality due to trematode infections reflect a multifactorial process that results from the tipping of a delicate balance based on the intensity of infection and the host reactions that initiate and modulate pathologic outcome. The genetics of the parasite and the human host contribute to the outcome of infection and disease. Furthermore, infections with trematodes that migrate through or reside in host tissues are associated with a moderate to high degree of peripheral blood eosinophilia; this association is of significance in protective and immunopathologic sequelae and is a useful clinical indicator of infection.

Approach to the Patient

The approach to individuals with suspected trematode infection begins with the question: Where have you been? Details of geographic history, exposure to freshwater

bodies, and indulgence in local eating habits without ensuring safety of food and drink are all essential elements in the history. The workup plan must include a detailed physical examination and tests appropriate for the suspected infection. Diagnosis is based either on detection of the relevant stage of the parasite in excreta, sputum, or (rarely) tissue samples or on sensitive and specific serologic tests. Consultation with physicians familiar with these infections or with the U.S. Centers for Disease Control and Prevention (CDC) is helpful in guiding diagnosis and selecting therapy.

BLOOD FLUKES: SCHISTOSOMIASIS

Human schistosomiasis is caused by five species of this parasitic trematode belonging to the subclass Digenea: the intestinal species *Schistosoma mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* and the urinary species *S. haematobium*. Infection may cause considerable morbidity in the intestines, liver, and urinary tract, and a proportion of affected individuals die. Other schistosome species (e.g., avian species) may invade human skin but then die in subcutaneous tissue, producing only self-limiting cutaneous manifestations.

Information on the prevalence and geographic distribution of human schistosomiasis is inexact. The five species are estimated to infect 200 to 300 million people in South America, the Caribbean, Africa, the Middle East, and Southeast Asia. The total population living under conditions favoring transmission approximates double or triple that number -- a fact reflecting the public health significance of schistosomiasis.

ETIOLOGY

Human infection is initiated by penetration of intact skin with infective cercariae. These organisms are released from infected snails in freshwater bodies; they measure ~2 mm in length and possess an anterior and a ventral sucker that attaches to the skin surface and facilitates penetration. Once in the subcutaneous tissue, the organism transforms into the next stage: the schistosomula. This transformation involves morphologic, membrane, and immunologic changes, prominent among which is the transformation of the cercarial outer membrane from a trilaminar to a heptalaminar structure that is then maintained throughout the life span of the worms in humans. The transformation to a heptalaminar structure is thought to be the schistosome's main adaptive mechanism for survival in humans. Schistosomula begin their migration within 2 to 4 days via venous or lymphatic vessels, reaching the lungs and finally the liver parenchyma. Sexually mature worms descend in pairs into the venous system at specific anatomic locations: intestinal veins (*S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*) and vesical veins (*S. haematobium*). Adult gravid females then travel against venous blood flow to small tributaries, where they deposit their ova intravascularly. Schistosome ova have specific morphologic features that can be used to differentiate species. Aided by enzymatic secretions through minipores in eggshells, ova move through the venous wall, traversing host tissues to reach the lumen of the intestinal or urinary tract, and are voided with stools or urine. Approximately 50% of ova, however, fail in their attempt to be transported to the outside environment and are either retained in host tissues locally (intestines or urinary tract) or carried by venous blood flow to the liver and other organs. Schistosome ova that reach freshwater bodies hatch, releasing free-living miracidia that seek the snail intermediate host to undergo several asexual multiplication cycles.

Finally, infective cercariae are shed from snails.

Adult schistosome worms measure ~1 to 2 cm in length. The male is slightly shorter, with a flattened body; its edges curve anteriorly to form the gynecophoral canal, in which mature adult females are usually held. The females are longer, slender, and rounded in cross-section. The precise nature of biochemical and reproductive exchanges between the two sexes is unknown, as are the regulatory mechanisms for pairing. Adult schistosomes parasitize specific sites in the host venous system. What guides adult intestinal schistosomes to branches of the superior or inferior mesenteric veins or adult *S. haematobium* worms to the vesical plexus is unknown. In addition, the evasion mechanisms by which adult worms inhibit the coagulation cascade and the effector arms of the host immune responses are not fully understood.

A systematic examination of schistosomal molecular phylogeny as well as gene structure and organization has begun. Analysis of the sequence of nuclear ribosome and internal transcribed spacer 2 and mitochondrial 16 sRNA indicates that human schistosomes may be divided into three monophyletic groups: the *S. haematobium* group, including *S. haematobium* and *S. intercalatum*; the *S. mansoni* group, including *S. mansoni* and *S. rodhaini*; and a group containing the two Asian schistosomes, *S. japonicum* and *S. mekongi*. These molecular groupings coincide with results of previous attempts to use morphologic or nucleic acid data to produce a taxonomic framework. In other studies, the schistosome genome was determined to be made up of 16 chromosomes; sexual differentiation is related to the presence of ZW chromosomes in females and ZZ chromosomes in males.

EPIDEMIOLOGY

The distribution of schistosome infection and related disease syndromes in human populations is dependent on both parasite and host factors. In endemic areas, the rate of yearly onset of new infection, or incidence, is low. Prevalence, on the other hand, starts to be appreciable by the age of 3 to 4 years and builds to a maximum that varies by endemic region (up to 100%) in the 15- to 20-year age group. Prevalence then stabilizes or decreases slightly in older age groups (>40 years). Intensity of infection (as measured by fecal or urinary egg counts, which correlate with adult worm burdens in most circumstances) follows the increase in prevalence up to the age of 15 to 20 years and then declines markedly in older age groups. This decline may reflect acquisition of resistance, or it may be due to changes in water contact patterns, since older people are exposed less. Furthermore, the unique distribution of schistosomes in human populations, which fits a negative binomial pattern (see above), may be due to heterogeneity of worm populations, with some more invasive than others; alternatively, it may be due to differences in the genetic susceptibility of host populations.

Disease due to schistosomiasis is the outcome of parasitologic, host, and additional infectious, nutritional, and environmental factors. Most of the disease syndromes relate to the presence of one or more of the parasite stages in the human host. The distribution of disease manifestations in the populations of endemic areas correlates with the intensity and duration of infection as well as with the age and genetic susceptibility of the host. Overall, disease manifestations are clinically relevant in only a small proportion of persons infected with any of the intestinal schistosomes. In contrast,

urinary schistosomiasis manifests clinically in most infected individuals.

Patients with both HIV infection and schistosomiasis have been found to excrete far fewer eggs in their stools than those infected with *S. mansoni* alone. The two groups have responded equally to treatment with praziquantel.

PATHOGENESIS AND IMMUNITY

During the invasive stage, cercaria-associated dermatitis reflects dermal and subdermal inflammatory responses -- both humoral and cell-mediated. As the parasites approach sexual maturity and the commencement of oviposition, acute schistosomiasis or Katayama fever (a serum sickness-like illness; see "Clinical Features," below) may occur. The associated antigen excess results in the formation of soluble immune complexes, which may be deposited in several tissues, initiating the sequence of pathologic events. In chronic schistosomiasis, most disease manifestations are due to eggs retained in host tissue. The granulomatous response around these ova is cell-mediated and is regulated both positively and negatively by a cascade of cytokine, cellular, and humoral responses. Granuloma formation begins with recruitment of a host of inflammatory cells in response to antigens secreted by the living organism within the ova. Cells recruited initially include phagocytes, antigen-specific T cells, and eosinophils. Fibroblasts, giant cells, and B lymphocytes predominate later. Once activated, T cells produce cytokines [such as tumor necrosis factora (TNF-a), interleukin (IL) 2, IL-4, and IL-5, which in turn activate endothelial cells] and produce specific chemokines such as monocyte chemotactic protein 1 (MCP-1). The result is recruitment of the cellular elements that organize in the form of granulomas around parasite eggs. These lesions reach a size many times that of the eggs, thus inducing organomegaly and obstruction. Immunomodulation or downregulation of host responses to schistosome eggs plays a significant role in limiting the extent of the granulomatous lesions -- and consequently disease -- in chronically infected experimental animals or humans. The underlying mechanisms involve another cascade of regulatory cytokines (IL-10, IL-12) and idiotypic antibodies. Subsequent to the granulomatous response, fibrosis sets in, resulting in more permanent disease sequelae. Because schistosomiasis is a chronic infection, the accumulation of antigen-antibody complexes results in deposits in renal glomeruli and may cause significant kidney disease.

The better-studied pathologic sequelae in schistosomiasis are those observed in liver disease. Ova that are carried by portal blood embolize to the liver. Because of their size (~150´ 60 um in the case of *S. mansoni*), they lodge at presinusoidal sites, where granulomas are formed. The granulomas contribute to the liver enlargement observed in infected individuals. Schistosomal hepatomegaly is also associated with certain class I and class II HLA markers; its genetic basis appears to be multigenic. Presinusoidal portal blockage causes several hemodynamic changes, including portal hypertension and associated development of portosystemic collaterals at the esophagogastric junction and other sites. Esophageal varices are most likely to break and cause repeated episodes of hematemesis. Because changes in liver hemodynamics in schistosomiasis are slow, compensatory arterialization of blood flow through the liver is established. While this compensatory mechanism may be associated with certain metabolic side effects, the retention of hepatocyte perfusion may permit the maintenance of normal liver function for several years.

After granuloma formation, the second most significant pathologic change in the liver relates to the onset of fibrosis. It is characteristically periportal (Symmers' clay-pipe stem fibrosis) but may be diffuse. Fibrosis, when diffuse, may be seen in areas of egg deposition and granuloma formation, but it is also seen in distant locations such as portal tracts. Schistosomiasis alone results in pure fibrotic lesions in the liver; cirrhosis occurs when other nutritional or infectious agents (e.g., hepatitis B or C virus) are involved. In recent years, it has been recognized that deposition of fibrotic tissue in the extracellular matrix results from the interaction of T lymphocytes with cells of the fibroblast series; several cytokines, such asIL-2, IL-4, IL-1, and transforming growth factor b(TGF-b), are known to stimulate fibrogenesis. The process may be dependent on the genetic constitution of the host. Furthermore, regulatory cytokines that can suppress fibrogenesis, such as interferong (IFN-g) or IL-12, may play a role in modulating the response.

While the above description focuses on granuloma formation and fibrosis of the liver, similar processes occur in urinary schistosomiasis. Granuloma formation at the lower end of the ureters obstructs urinary flow, with subsequent development of hydroureter and hydronephrosis. Similar lesions in the urinary bladder cause the protrusion of papillomatous structures into its cavity; these may ulcerate and/or bleed. The chronic stage of infection is associated with scarring and deposition of calcium in the bladder wall.

Immunomodulation is an essential mechanism in shaping the clinical and pathologic outcome of schistosomiasis. While most detailed immunologic analyses have been performed in experimental animals, enough evidence exists from studies in humans to delineate the suppression of T cell responses in association with active infections and a regulatory role forIL-10.

Studies on immunity to schistosomiasis, whether innate or acquired, have expanded our knowledge of the components of these responses and the target antigens. The concept of innate immunity is illustrated by the inability of avian schistosomes, which cause swimmers' itch, to reach maturity in humans. The critical question, however, is whether humans acquire immunity to schistosomes. Epidemiologic evidence suggests the onset of acquired immunity during the course of infection in young adults. Curative treatment of infection divides populations in endemic areas into those who acquire reinfection rapidly (susceptible) and those who follow a protracted course (resistant). This difference may be explained by differences in transmission, immunologic response, or genetic susceptibility. The mechanism of acquired immunity involves antibodies, complement, and several effector cells, particularly eosinophils. Furthermore, the intensity of schistosome infection has been correlated with a region in chromosome 5. In other studies, several protective schistosome antigens have been identified as vaccine candidates.

CLINICAL FEATURES

In general, disease manifestations of schistosomiasis occur in three stages, which vary not only by species but also by intensity of infection and other host factors, such as age and genetics. During the phase of cercarial invasion, a form of dermatitis may be

observed. This so-called swimmers' itch (Fig. 222-CD1) occurs most often with *S. mansoni* and *S. japonicum* infections, manifesting 2 or 3 days after invasion as an itchy maculopapular rash on the affected areas of the skin. The condition is particularly severe when humans are exposed to avian schistosomes. This form of cercarial dermatitis is seen around the freshwater lakes in the northern United States, particularly in the spring. Cercarial dermatitis is a self-limiting clinical entity. During worm maturation and at the beginning of oviposition (i.e., 4 to 8 weeks after skin invasion), acute schistosomiasis or Katayama fever -- a serum sickness-like syndrome with fever, generalized lymphadenopathy, and hepatosplenomegaly -- may develop. Individuals suffering from acute schistosomiasis show a high degree of peripheral blood eosinophilia. Parasite-specific antibodies may be detected before schistosome eggs are identified in excreta. Acute schistosomiasis has become an important clinical entity worldwide because of increased travel to endemic areas. Travelers are exposed to the parasite while swimming or wading in freshwater bodies and upon their return present with the acute manifestations of the disease. The course of acute schistosomiasis is generally benign, but deaths are occasionally reported in association with heavy exposure to schistosomes.

The main clinical manifestations of chronic schistosomiasis are species-dependent. Intestinal species (*S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*) cause intestinal and hepatosplenic disease as well as several manifestations associated with portal hypertension. During the intestinal phase, which may begin a few months after infection and may last for years, symptomatic patients characteristically have colicky abdominal pain and bloody diarrhea. Patients may also report fatigue and an inability to perform daily routine functions and may show evidence of growth retardation. The severity of intestinal schistosomiasis is often related to the intensity of the worm burden. The disease runs a chronic course but rarely progresses to a functional level (e.g., malabsorption) or to anatomic lesions of the gut. The exception is colonic polyposis, which has been seen in some endemic areas, such as Egypt.

The hepatosplenic phase of disease manifests early (during the first year of infection, particularly in children) with enlargement of the liver due to parasite-induced granulomatous lesions. Hepatomegaly is seen in ~15 to 20% of infected individuals when whole communities in endemic areas are studied. It correlates roughly with the intensity of infection, occurs more often in children than in adults, and may be related to specific HLA haplotypes. In subsequent phases of infection, presinusoidal blockage of blood flow leads to portal hypertension and splenomegaly. Moreover, portal hypertension may lead to varices at the lower end of the esophagus and at other sites. Patients with schistosomal liver disease may have right-upper-quadrant "dragging" pain during the hepatomegaly phase, and this pain may move to the left upper quadrant as splenomegaly progresses. Bleeding from esophageal varices may, however, be the first clinical manifestation of this phase. Patients may experience repeated bleeding but seem to tolerate its impact, since an adequate total hepatic blood flow permits normal liver function for a considerable period in schistosomal hepatomegaly. In late-stage disease, typical fibrotic changes occur along with liver function deterioration and the onset of ascites, hypoalbuminemia, and defects in coagulation. Intercurrent viral infections of the liver or nutritional deficiencies may well accelerate or exacerbate the deterioration of hepatic function.

The extent and severity of intestinal and hepatic disease in schistosomiasis mansoni and japonica have been well described. While it was originally thought that *S. japonicum* might induce more severe disease manifestations because the adult worms can produce ten times more eggs than *S. mansoni*, subsequent field studies have not supported this claim. Clinical observations of individuals infected with *S. mekongi* or *S. intercalatum* have been less detailed, partly because of the far more limited geographic distribution of these organisms.

The clinical manifestations of *S. haematobium* infection occur relatively early and involve a relatively high percentage of individuals. Up to 80% of children infected with *S. haematobium* have dysuria, frequency, and hematuria, which may be terminal. Urine examination reveals blood and albumin as well as an unusually high frequency of bacterial urinary tract infection. These manifestations correlate with intense infection, the presence of urinary bladder granulomas, and subsequent ulceration. Along with the local effects of granuloma formation in the urinary bladder, obstruction of the lower end of the ureters results in hydroureter and hydronephrosis, which can be seen in 25 to 50% of infected children. As infection progresses, bladder granulomas undergo fibrosis; the result is the presence of typical sandy patches visible on cystoscopy. In many endemic areas, an association between squamous cell carcinoma of the bladder and *S. haematobium* infection has been observed. Such malignancy is detected in a younger age group than transitional cell carcinoma. In fact, *S. haematobium* has now been classified as a human carcinogen.

Significant disease may occur in other organs during chronic schistosomiasis. Most important is disease in the lungs and central nervous system; other locations, such as the skin and the genital organs, are far less frequently affected. In pulmonary schistosomiasis, embolized eggs lodge in small arterioles, producing acute necrotizing arteriolitis and granuloma formation. During *S. mansoni* and *S. japonicum* infection, schistosome eggs reach the lungs after the development of portosystemic collateral circulation; in *S. haematobium* infection, ova may reach the lungs directly via connections between the vesical and systemic circulation. After the development of arteriolitis and granuloma formation, fibrous tissue deposition is detected and leads to endarteritis obliterans, pulmonary hypertension, and cor pulmonale. This clinical entity is an uncommon presentation during chronic schistosomiasis. The most frequent symptoms are cough, fever, and dyspnea; ascites and hemoptysis are less frequently encountered. Cor pulmonale may be diagnosed radiologically on the basis of prominent right side of the heart and dilation of the pulmonary artery. Frank evidence of right-sided heart failure may be seen in late cases.

Central nervous system schistosomiasis is important but less frequent than pulmonary schistosomiasis. It characteristically occurs as cerebral disease due to *S. japonicum* infection. Migratory worms deposit eggs in the brain and induce a granulomatous response. The frequency of this manifestation among infected individuals in some endemic areas (e.g., the Philippines) is calculated at 2 to 4%. Jacksonian epilepsy due to *S. japonicum* infection is the second most common cause of epilepsy in these areas. *S. mansoni* and *S. haematobium* infections have been associated with transverse myelitis. This syndrome is thought to be due to eggs traveling to the venous plexus around the spinal cord. In schistosomiasis mansoni, transverse myelitis is usually seen in the chronic stage after the development of portal hypertension and portosystemic

shunts, which allow ova to travel to the spinal cord veins. This proposed sequence of events has been challenged because of a few reports of transverse myelitis occurring early in the course of *S. mansoni* infection. More information is needed to confirm these observations. During schistosomiasis haematobia, ova may travel through communication between vesical and systemic veins, resulting in spinal cord disease that may be detected at any stage of infection. Pathologic study of lesions in schistosomal transverse myelitis may reveal eggs along with necrotic or granulomatous lesions. Patients usually present with acute or rapidly progressing lower-leg weakness accompanied by sphincter dysfunction.

DIAGNOSIS

Physicians in areas not endemic for schistosomiasis face considerable diagnostic challenges. In the most common clinical presentation, a returning traveler exhibits symptoms and signs of any of the acute syndromes of schistosomiasis -- namely, cercarial dermatitis or Katayama fever. Central to correct diagnosis is a thorough inquiry into travel history and exposure to freshwater bodies, whether slow or fast running. Differential diagnosis of fever in returned travelers includes a spectrum of infections whose etiologies are viral (e.g., Dengue fever), bacterial (e.g., enteric fever, leptospirosis), rickettsial, or protozoal (e.g., malaria). In cases of Katayama fever, prompt diagnosis is essential and is based on clinical presentation, high-level peripheral blood eosinophilia, and a positive serologic assay for schistosomal antibodies. Two tests are available at theCDC: the Falcon assay screening test/enzyme-linked immunosorbent assay (FAST-ELISA) and the confirmatory enzyme-linked immunoelectrotransfer blot (EITB). Both tests are highly sensitive and ~96% specific. In some instances, examination of stool or urine for ova may yield positive results.

Individuals with established infection are diagnosed by a combination of geographic history, characteristic clinical presentation, and presence of schistosome ova in excreta. The diagnosis may also be established with the serologic assays mentioned above or with those that detect circulating schistosome antigens. These assays can be applied either to blood or to other body fluids (e.g., cerebrospinal fluid). For stool examination, the Kato thick smear or any other concentration method generally identifies all but the most lightly infected individuals. Urine may be examined by microscopy of sediment or by filtration of a known volume through Nuclepore filters. Kato thick smear and Nuclepore filtration provide quantitative data on the intensity of infection, which is of value in assessing the degree of tissue damage and in monitoring the effect of chemotherapy. Finally, schistosome infection may be diagnosed by examination of tissue samples, typically rectal biopsies; other biopsy procedures (e.g., liver biopsy) are not needed, except in special circumstances.

Differential diagnosis of schistosomal hepatomegaly must include viral hepatitis of all etiologies, miliary tuberculosis, malaria, visceral leishmaniasis, ethanol abuse, and causes of hepatic and portal vein obstruction. Of patients with these conditions, only a few may present with organomegaly and relatively intact liver function. The differential diagnosis of hematuria in *S. haematobium* infection includes bacterial cystitis, tuberculosis, urinary stones, and malignancy.

TREATMENT

Treatment of schistosomiasis depends on the stage of infection and the clinical presentation. Other than topical dermatologic applications for relief of itching, no specific treatment is indicated for cercarial dermatitis caused by avian schistosomes. Therapy for acute schistosomiasis or Katayama fever needs to be adjusted appropriately for each case. While antischistosomal chemotherapy is indicated, it does not address immediate pathologic changes. In severe acute schistosomiasis, management in an acute-care setting is necessary, with supportive measures and consideration of glucocorticoid treatment. Once the acute critical phase is over, specific chemotherapy is indicated. For all individuals with infection established by either the demonstration of schistosome eggs or positive serology, treatment to eradicate the parasite should be administered. The drug of choice is praziquantel, which -- depending on the infecting species (Table 222-2) -- is administered orally as 40 or 60 mg/kg in two or three doses over a single day. Praziquantel treatment results in parasitologic cure in ~85% of cases and reduces egg counts by >90%. Few side effects have been encountered, and those that do develop usually do not interfere with completion of treatment. Other antischistosomal chemotherapeutic agents are currently considered only as alternatives when praziquantel is unavailable. The effect of antischistosomal treatment on disease manifestations varies by stage. Early hepatomegaly and bladder lesions are known to resolve following chemotherapy, but the late established manifestations, such as fibrosis, do not change. Additional management modalities are needed for individuals with other manifestations, such as hepatocellular failure or recurrent hematemesis. The use of these interventions is guided by general medical and surgical principles.

PREVENTION AND CONTROL

Since transmission of schistosomiasis is dependent on human behavior, it is theoretically possible to devise an effective preventive strategy. The geographic distribution of infections in endemic regions of the world is not clearly demarcated. It is therefore prudent for travelers to avoid contact with all freshwater bodies, irrespective of the speed of water flow or unsubstantiated claims of safety. Some topical agents, when applied to the skin, may conceivably inhibit cercarial penetration, but none of these agents is currently available. If exposure occurs, a follow-up visit with a health care provider is strongly recommended. Prevention of infection in inhabitants of endemic areas is a significant challenge. People of these regions use freshwater bodies for sanitary, domestic, recreational, and agricultural purposes. In the absence of adequate alternatives, several control measures have been used, including application of molluscicides, provision of sanitary water and means for sewage disposal, chemotherapy, and health education. Current recommendations to countries endemic for schistosomiasis emphasize the use of multiple approaches. Particularly with the advent of a single-oral-dose, safe, and effective antischistosomal agent, chemotherapy has been most successful in reducing the intensity of infection and reversing disease. The duration of this positive impact depends on transmission dynamics in a specific endemic region. The ultimate goal of research on prevention and control is the development of a vaccine. Although there are a few promising leads, this goal is probably not within reach during the next decade or so.

LIVER (BILIARY) FLUKES

Several species of biliary fluke infecting humans are particularly common in Southeast Asia and Russia. Other species are transmitted in Europe, Africa, and the Americas. On the basis of their migratory pathway in humans, these infections may be divided into the *Clonorchis* and *Fasciola* groups.

CLONORCHIASIS AND OPISTHORCHIASIS

Infection with *C. sinensis*, the Chinese or oriental fluke, is endemic among fish-eating mammals in Southeast Asia. Humans are an incidental host; the prevalence of human infection is highest in China, Vietnam, and Korea. Infection with *Opisthorchis viverrini* and *O. felineus* is zoonotic in cats and dogs. Transmission to humans occurs occasionally, particularly in Thailand (*O. viverrini*) and in Southeast Asia and eastern Europe (*O. felineus*). Data on the exact geographic distribution of these infectious agents in human populations are rudimentary.

Infection with any of these three species is established by ingestion of raw or inadequately cooked freshwater fish harboring metacercariae. These organisms excyst in the duodenum, releasing larvae that travel through the ampulla of Vater and mature into adult worms in the bile canaliculi. Mature flukes are flat and elongated, measuring 1 to 2 cm in length. The hermaphroditic worms reproduce by releasing small operculated eggs, which pass with bile into the intestines and are voided with stools. The life cycle is completed in the environment in specific freshwater snails (the first intermediate host) and encystment of metacercariae in freshwater fish.

Except for late sequelae, the exact clinical syndromes caused by clonorchiasis and opisthorchiasis are not well defined. Since most infected individuals harbor a low worm burden, many are asymptomatic. Moderate to heavy infection may be associated with vague right-upper-quadrant pain. In contrast, chronic or repeated infection is associated with manifestations such as cholangitis, cholangiohepatitis, and biliary obstruction. Cholangiocarcinoma is epidemiologically related to *C. sinensis* infection in China and to *O. viverrini* infection in northeastern Thailand. This association has resulted in the classification of these infectious agents as human carcinogens.

FASCIOLIASIS

Infections with *F. hepatica* and *F. gigantica* are worldwide zoonoses that are particularly endemic in sheep-raising countries. Human cases have been reported in South America, Europe, Africa, Australia, and the Far East. Recent estimates indicate a worldwide prevalence of 17 million cases. High endemicity has been reported in certain areas of Peru and Bolivia. In most endemic areas the predominant species is *F. hepatica*, but in Asia and Africa a varying degree of overlap with *F. gigantica* has been observed.

Humans acquire fascioliasis by ingestion of metacercariae attached to certain aquatic plants, such as watercress. Infection may also be acquired by consumption of contaminated water or ingestion of food items washed with such water. Acquisition of human infection through consumption of freshly prepared raw liver containing immature flukes has been reported. Infection is initiated when metacercariae excyst, penetrate the gut wall, and travel through the peritoneal cavity to invade the liver capsule. Adult

worms finally reach the bile ducts, where they produce large operculated eggs, which are voided in the bile and through the gastrointestinal tract to the outside environment. The flukes' life cycle is completed in specific snails (the first intermediate host) and encystment on aquatic plants.

The clinical features of fascioliasis relate to the intensity of infection, but even more to the stage of infection. Acute disease develops during the parasites' migration (1 to 2 weeks after infection) and includes fever, right-upper-quadrant pain, hepatomegaly, and eosinophilia. Computed tomography of the liver may show migratory tracks. Symptoms and signs usually subside as the parasites reach their final habitat. In individuals with chronic infection, bile duct obstruction and biliary cirrhosis are infrequently demonstrated. No relation to hepatic malignancy has been ascribed to fascioliasis.

DIAGNOSIS

The diagnosis of infection with any of the biliary flukes depends on a high degree of suspicion, the elicitation of an appropriate geographic history, and stool examination for the characteristically shaped parasite ova. Additional evidence may be obtained by documenting peripheral blood eosinophilia or imaging the liver. Serologic testing is helpful, particularly in lightly infected individuals.

TREATMENT

Drug therapy (praziquantel or triclabendazole) is summarized inTable 222-2. Patients with anatomic lesions in the biliary tract or malignancy are managed according to general medical guidelines.

INTESTINAL FLUKES

Two species of intestinal flukes cause human infection in defined geographic areas worldwide. The large *Fasciolopsis buski* (adults measure 2 by 7 cm) is endemic in Southeast Asia, while the smaller *Heterophyes heterophyes* is found in the Nile Delta of Egypt and in the Far East. Infection is initiated by ingestion of metacercariae attached to aquatic plants (*F. buski*) or encysted in freshwater or brackish-water fish (*H. heterophyes*). Flukes mature in human intestines, and eggs are passed with stools. Most individuals infected with intestinal flukes are asymptomatic. In heavy *F. buski* infection, diarrhea, abdominal pain, and malabsorption may be encountered. Heavy infection with *H. heterophyes* may be associated with abdominal pain and mucous diarrhea. The diagnosis is established by detection of the characteristically shaped ova in stool samples. The drug of choice for treatment is praziquantel (Table 222-2).

LUNG FLUKES

Infection with the lung fluke *Paragonimus westermani* and related species (e.g., *P. africanus*) is endemic in many parts of the world, excluding North America and Europe. Endemicity is particularly noticeable in West Africa, Central and South America, and Asia. In nature, the reservoir hosts of *P. westermani* are wild and domestic felines. In Africa, *P. africanus* has been found in other species, such as dogs. Adult lung flukes, which are 7 to 12 mm in length, are found encapsulated in the lungs of infected persons.

In rare circumstances, flukes are found encysted in the central nervous system (cerebral paragonimiasis) or abdominal cavity. Humans acquire lung fluke infection by ingesting infective metacercariae encysted in the muscles and viscera of crayfish and freshwater crabs. In endemic areas, these crustaceans are consumed either raw or pickled. Once the organisms reach the duodenum, they excyst, penetrate the gut wall, and travel through the peritoneal cavity, diaphragm, and pleural space to reach the lungs. Mature flukes are found in the bronchioles surrounded by cystic lesions. Parasite eggs are either expectorated with sputum or swallowed and passed to the outside environment with feces. The life cycle is completed in snails and freshwater crustacea.

When maturing flukes lodge in lung tissues, they cause hemorrhage and necrosis, resulting in cyst formation. The adjacent lung parenchyma shows evidence of inflammatory infiltration, predominantly by eosinophils. Cysts usually measure 1 to 2 cm in diameter and may contain 1 or 2 worms each. With the onset of oviposition, cysts usually rupture in adjacent bronchioles -- an event allowing ova to exit from the human host. Older cysts develop thickened walls, which may undergo calcification. During the active phase of paragonimiasis, lung tissues surrounding parasite cysts may contain evidence of pneumonia, bronchitis, bronchiectasis, and fibrosis.

Pulmonary paragonimiasis is particularly symptomatic in persons with moderate to heavy infection. Productive cough with brownish sputum or frank hemoptysis associated with peripheral blood eosinophilia is usually the presenting feature. Chest examination may reveal signs of pleurisy. In chronic cases, bronchitis or bronchiectasis may predominate, but these conditions rarely proceed to lung abscess. Imaging of the lungs demonstrates characteristic features, including patchy densities, cavities, pleural effusion, and ring shadows. Cerebral paragonimiasis presents as either space-occupying lesions or epilepsy. Pulmonary paragonimiasis is diagnosed by the detection of parasite ova in sputum and/or stools. Serology is of considerable help in egg-negative cases and in cerebral paragonimiasis. The drug of choice for treatment is praziquantel (Table 222-2). Other medical or surgical management may be needed for pulmonary or cerebral lesions.

CONTROL AND PREVENTION OF TISSUE FLUKES

For residents of nonendemic areas who are visiting an endemic region, the only effective preventive measure is to avoid ingestion of local plants, fish, or crustaceans; if their ingestion is necessary, they should be washed or cooked thoroughly. Instruction on water and food preparation and consumption should be included in physicians' advice to travelers (Chap. 123). Interruption of transmission among residents of endemic areas depends on avoiding ingestion of the infective stage of the helminths and appropriate disposal of feces and sputum to prevent the hatching of eggs in the environment. These two approaches rely greatly on socioeconomic development and health education. In countries where economic progress has resulted in financial and social improvements, transmission has decreased. The third approach to control in endemic communities entails selective use of chemotherapy for individuals posing the highest risk of transmission -- i.e., those with heavy infections. The availability of praziquantel -- a broad-spectrum, safe, and effective antihelminthic agent -- provides a means for reducing the reservoirs of infection in human populations. However, the existence of most of these helminths as zoonoses in several animal species complicates control

efforts.

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223. CESTODES - *A. Clinton White, Jr.*, *Peter F. Weller*

Cestodes, or tapeworms, are segmented worms. The adults reside in the gastrointestinal tract, but the larvae can be found in almost any organ. Human tapeworm infections can be divided into two major clinical groups. In one group, humans are the definitive hosts, and the adult tapeworms live in the gastrointestinal tract (*Taenia saginata*, *Diphyllobothrium*, *Hymenolepis*, and *Dipylidium caninum*). In the other, humans are intermediate hosts, and larval-stage parasites are present in the tissues. Diseases in this category include echinococcosis, sparganosis, and coenurosis. For *T. solium*, the human may be either the definitive or the intermediate host.

The ribbon-shaped tapeworm attaches to the intestinal mucosa by means of sucking cups or grooves located on the head (scolex). Behind the scolex is a short, narrow neck from which proglottids (segments) form. As each proglottid matures, it is displaced further back from the neck by the formation of new, less mature segments. The progressively elongating chain of attached proglottids, called the *strobila*, constitutes the bulk of the tapeworm. The length varies among species. In some, the tapeworm may consist of more than 1000 proglottids and may be several meters long. As each proglottid becomes gravid, eggs are released. Since eggs of the different *Taenia* species are morphologically identical, differences in the morphology of the scolex or proglottids provide the basis for diagnostic identification to the species level. Most human tapeworms require at least one intermediate host for complete larval development. After ingestion by an intermediate host, an egg releases the larval oncosphere, which penetrates the intestinal mucosa. The oncosphere migrates to tissues and develops into an encysted form known as a *cysticercus* (single scolex), a *coenurus* (multiple scolices), or a *hydatid* (cyst with daughter cysts, each containing several protoscolices). Ingestion by the definitive host of tissues containing a cyst enables a scolex to develop into a tapeworm.

TAENIASIS SAGINATA

The beef tapeworm *T. saginata* occurs in all countries where raw or undercooked beef is eaten. It is most prevalent in sub-Saharan African and Middle Eastern countries.

Etiology and Pathogenesis Humans are the only definitive host for the adult stage of *T. saginata*. This tapeworm, which can reach 8 m in length, inhabits the upper jejunum and has a scolex with four prominent suckers and 1000 to 2000 proglottids. Each gravid segment has 15 to 30 uterine branches (in contrast to 8 to 12 for *T. solium*). The eggs are indistinguishable from those of *T. solium*; each measures 30 to 40 um and has a thick brown striated shell containing the embryo. Eggs deposited on vegetation can live for months to years until they are ingested by cattle or other herbivores. The embryo released after ingestion invades the intestinal wall and is carried to striated muscle, where it transforms into a cysticercus. When ingested in raw or undercooked beef, this form can infect humans. After the cysticercus is ingested, it takes about 2 months for an adult worm to develop.

Clinical Manifestations Patients become aware of the infection most commonly by noting passage of proglottids in their feces. The proglottids are often motile, and patients may experience perianal discomfort when proglottids are discharged. Mild

abdominal pain or discomfort, nausea, change in appetite, weakness, and weight loss can occur with *T. saginata* infection.

Diagnosis The diagnosis is made by the detection of eggs or proglottids in the stool. Eggs may also be present in the perianal area; thus, if proglottids or eggs are not found in the stool, the perianal region should be examined with use of a cellophane-tape swab (as in pinworm infection). Distinguishing *T. saginata* from *T. solium* requires examination of mature proglottids or the scolex. Serologic tests are not helpful diagnostically. Eosinophilia and elevated levels of serum IgE may be detected.

TREATMENT

A single dose of praziquantel (5 to 10 mg/kg) is highly effective.

Prevention The major method of preventing infection is the adequate cooking of beef; exposure to temperatures as low as 56°C for 5 min will destroy cysticerci. Refrigeration or salting for long periods or freezing at-10°C for 9 days also kills cysticerci in beef. General preventive measures include inspection of beef and proper disposal of human feces.

TAENIASIS SOLIUM AND CYSTICERCOSIS

The pork tapeworm *T. solium* can cause two distinct forms of infection. The form that develops depends on whether humans are infected with adult tapeworms in the intestine or with larval forms in the tissues (cysticercosis). Humans are the only definitive hosts for *T. solium*; pigs are the usual intermediate hosts, although dogs, cats, and sheep may harbor the larval forms. *T. solium* exists worldwide but is most prevalent in Latin America, Africa, South and Southeast Asia, and eastern Europe. Cysticercosis occurs in industrialized nations largely as a result of the immigration of infected persons from endemic areas.

Etiology and Pathogenesis The adult tapeworm generally resides in the upper jejunum. Its globular scolex attaches by both sucking disks and two rows of hooklets. Often only one adult worm is present, but that worm may live for years. The tapeworm, usually about 3 m in length, may have as many as 1000 proglottids, each of which produces up to 50,000 eggs. Groups of three to five proglottids are generally released and excreted into the feces, and the eggs in these proglottids are infective for both humans and animals. The eggs may survive in the environment for several months. After ingestion by the intermediate host, eggs embryonate, penetrate the intestinal wall, and are carried to many tissues, with a predilection for striated muscle of the neck, tongue, and trunk. Within 60 to 90 days, the encysted larval stage develops. These cysticerci can survive for long periods. Humans acquire infections that lead to intestinal tapeworms by ingesting undercooked pork containing cysticerci. Infections that cause human cysticercosis follow the ingestion of *T. solium* eggs, usually from fecally contaminated food. Autoinfection may occur if an individual with an egg-producing tapeworm ingests eggs derived from his or her own feces.

Clinical Manifestations Intestinal infections with *T. solium* may be asymptomatic. Epigastric discomfort, nausea, a sensation of hunger, weight loss, and diarrhea are

infrequent. Fecal passage of proglottids may be noted by patients.

In cysticercosis, the clinical manifestations are entirely different. Cysticerci can be found anywhere in the body, most commonly in the brain and the skeletal muscle. The clinical presentation of cysticercosis depends on the number and location of cysticerci as well as the extent of associated inflammatory responses or scarring. Neurologic manifestations are the most common. When inflammation surrounds cysticerci in the brain parenchyma, seizures are frequent. These seizures may be generalized, focal, or Jacksonian. Hydrocephalus results from obstruction of cerebrospinal fluid (CSF) flow by cysticerci and accompanying inflammation or by CSF outflow obstruction from arachnoiditis. Signs of increased intracranial pressure, including headache, nausea, vomiting, changes in vision, dizziness, ataxia, or confusion, are often evident. Patients with hydrocephalus may develop papilledema or display altered mental status. When cysticerci develop at the base of the brain or in the subarachnoid space, they cause chronic meningitis or arachnoiditis, communicating hydrocephalus, or strokes.

Diagnosis The diagnosis of intestinal *T. solium* infection is made by the detection of eggs or proglottids, as described for *T. saginata*. In cysticercosis, diagnosis can be difficult. A consensus conference has proposed absolute, major, minor, and epidemiologic criteria for diagnosis (Table 223-1). Diagnostic certainty is possible only with definite demonstration of the parasite (absolute criteria). This task can be accomplished by histologic observation of the parasite in excised tissue, by funduscopic visualization of the parasite in the eye (in the anterior chamber, vitreous, or subretinal spaces), or by neuroimaging studies demonstrating cystic lesions containing a scolex. In most cases, diagnostic certainty is not possible. Instead, a clinical diagnosis is made on the basis of a combination of clinical presentation, radiographic studies, serologic tests, and exposure history.

Neuroimaging findings suggestive of neurocysticercosis constitute the primary major diagnostic criterion. These findings include cystic lesions with or without enhancement (e.g., ring enhancement), one or more calcifications (which may also have associated enhancement), or focal enhancing lesions. Cysticerci in the brain parenchyma are usually 5 to 10 mm in diameter and rounded. Cystic lesions in the subarachnoid space or fissures may enlarge up to 5 cm in diameter and may be lobulated. For cysticerci within the subarachnoid space or ventricles, the walls may be very thin and the cyst fluid is often isodense withCSF. Thus, obstructive hydrocephalus or enhancement of the basilar meninges may be the only finding on computed tomography (CT) in neurocysticercosis. Cysticerci in the ventricles or subarachnoid space are usually visible to an experienced neuroradiologist on magnetic resonance imaging (MRI) or with intraventricular contrast injection. CT is more sensitive than MRI in identifying calcified lesions, whereas MRI is better for identifying cystic lesions and enhancement. Typical cigar-shaped calcifications in muscle are a second major diagnostic criterion.

The third major diagnostic criterion is detection of specific antibodies to cysticerci. While most tests employing unfractionated antigen have high rates of false-positive and -negative results, this problem can be overcome by using the more specific immunoblot assay. An immunoblot assay using lentil-lectin purified glycoproteins has>99% specificity and is highly sensitive. However, patients with single intracranial lesions or with calcifications may be seronegative. With this assay, serum samples provide greater

diagnostic sensitivity thanCSF. However, CSF may be useful when only unfractionated antigens are used.

Minor diagnostic criteria include the presence of subcutaneous nodules, punctate soft tissue or intracranial calcifications, clinical manifestations suggestive of neurocysticercosis (such as seizures, hydrocephalus, or altered mental status), or disappearance of lesions in conjunction with anticysticercal drug therapy. Epidemiologic criteria include current or prior residence in an endemic area, frequent travel to an endemic area, or exposure to a tapeworm carrier or household member infected with *T. solium*. Diagnosis is confirmed in patients with a combination of either two major criteria or one major criterion with two minor criteria and one epidemiologic criterion. The fulfillment of one major criterion and two other criteria or of three minor criteria with epidemiologic exposure supports a probable diagnosis. While theCSF is usually abnormal in neurocysticercosis, CSF abnormalities are not pathognomonic. Patients may have CSF pleocytosis with a predominance of lymphocytes, neutrophils, or eosinophils. The protein level in CSF may be elevated; the glucose concentration is usually normal but may be depressed.

TREATMENT

Intestinal *T. solium* infection is treated with a single dose of praziquantel (5 to 10 mg/kg). However, praziquantel can evoke an inflammatory response in the central nervous system if concomitant cryptic cysticercosis is present.

The management of neurocysticercosis focuses primarily on symptomatic treatment of seizures or hydrocephalus. Seizures can usually be controlled with anticonvulsants. If parenchymal lesions resolve without development of calcifications and patients remain free of seizures, anticonvulsant therapy can usually be discontinued after 2 years. Four placebo-controlled trials failed to identify any clinical advantage of antiparasitic drugs for parenchymal neurocysticercosis. However, trends toward faster resolution of neuroradiologic abnormalities were observed. Thus, some authorities favor use of antiparasitic drugs, including praziquantel (50 to 60 mg/kg daily in three divided doses for 15 days or 100 mg/kg in three doses given over a single day) or albendazole (15 mg/kg per day for 8 to 28 days). Both agents may exacerbate the inflammatory response around the dying parasite, exacerbating seizures or hydrocephalus. Thus, patients receiving these drugs should be carefully monitored. High-dose glucocorticoids can be used during treatment or if symptoms worsen. Since glucocorticoids induce first-pass metabolism of praziquantel and may decrease its antiparasitic effect, cimetidine should be coadministered to inhibit praziquantel metabolism.

For patients with hydrocephalus, the emergent reduction of intracranial pressure is the mainstay of therapy. In the case of obstructive hydrocephalus, this task requires either a diverting procedure, such as ventriculoperitoneal shunting, or removal of the cysticerci by craniotomy or via ventriculoscopy. Historically, shunts have usually failed. However, low failure rates have been attained with treatment with antiparasitic drugs or chronic glucocorticoids or with use of flow-sensitive shunts. In patients with subarachnoid cysts, glucocorticoids are needed to reduce arachnoiditis and accompanying vasculitis. Patients may benefit from prolonged courses of antiparasitic drugs and shunting for hydrocephalus. In patients with elevated intracranial pressure due to multiple inflamed

lesions, glucocorticoids are the mainstay of therapy, and antiparasitic drugs should be avoided until the elevated pressure resolves. For ocular and spinal medullary lesions, drug-induced inflammation may cause irreversible damage. Most patients should be managed surgically, although case reports have described cures with medical therapy.

Prevention Measures for the prevention of intestinal *T. solium* infection consist of the application to pork of precautions similar to those described above for beef with regard to *T. saginata* infection. The prevention of cysticercosis involves minimizing the opportunities for ingestion of fecally derived eggs by means of good personal hygiene, effective fecal disposal, and treatment and prevention of human intestinal infections.

ECHINOCOCCOSIS

Echinococcosis is an infection of humans caused by the larval stage of *Echinococcus granulosus*, *E. multilocularis*, or *E. vogeli*. *E. granulosus*, which produces unilocular cystic lesions, is prevalent in areas where livestock is raised in association with dogs. This tapeworm species is found in Australia, Argentina, Chile, Africa, eastern Europe, the Middle East, New Zealand, and the Mediterranean region, particularly Lebanon and Greece. *E. multilocularis*, which causes multilocular alveolar lesions that are locally invasive, is found in Alpine, sub-Arctic, or Arctic regions, including Canada, the United States, and central and northern Europe and Asia. *E. vogeli* causes polycystic hydatid disease and is found only in Central and South America. Like other cestodes, echinococcal species have both intermediate and definitive hosts. The definitive hosts are dogs that pass eggs in their feces. Cysts develop in the intermediate hosts -- sheep, cattle, humans, goats, camels, and horses for *E. granulosus* and mice and other rodents for *E. multilocularis* -- after the ingestion of eggs. When a dog ingests beef or lamb containing cysts, the life cycle is completed.

Etiology The small (5 mm long) adult *E. granulosus* worm, which lives for 5 to 20 months in the jejunum of dogs, has only three proglottids -- one immature, one mature, and one gravid. The gravid segment splits to release eggs that are morphologically similar to *Taenia* eggs and are extremely hardy. After humans ingest the eggs, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to various organs, most commonly the liver and lungs. Larvae develop into fluid-filled unilocular hydatid cysts that consist of an external membrane and an inner germinal layer. Daughter cysts develop from the inner aspect of the germinal layer, as do germinating cystic structures called *brood capsules*. New larvae, called *protoscolices*, develop in large numbers within the brood capsule. The cysts expand slowly over a period of years.

The life cycle of *E. multilocularis* is similar except that small rodents serve as the intermediate hosts. The cyst of *E. multilocularis*, however, is quite different in that the larval form remains in the proliferative phase, the hydatid cyst is always multilocular, and vesicles progressively invade the host tissue by peripheral extension of processes from the germinal layer.

Clinical Manifestations Slowly enlarging echinococcal cysts generally remain asymptomatic until their expanding size or their space-occupying effect in an involved organ elicits symptoms. The liver and the lungs are the most common sites of these

cysts. Since a period of years elapses before cysts enlarge sufficiently to cause symptoms, they may be discovered incidentally on a routine x-ray or ultrasound study.

Patients with hepatic echinococcosis who are symptomatic most often present with abdominal pain or a palpable mass in the right upper quadrant. Compression of a bile duct or leakage of cyst fluid into the biliary tree may mimic recurrent cholelithiasis, and biliary obstruction can result in jaundice. Rupture of or episodic leakage from a hydatid cyst may produce fever, pruritus, urticaria, eosinophilia, or anaphylaxis. Pulmonary hydatid cysts may rupture into the bronchial tree or peritoneal cavity and produce cough, chest pain, or hemoptysis. Rupture of hydatid cysts may lead to multifocal dissemination of protoscolices, which can form additional cysts. Rupture can occur spontaneously or at surgery. Other presentations are due to the involvement of bone (invasion of the medullary cavity with slow bone erosion producing pathologic fractures), the central nervous system (space-occupying lesions), and the heart (conduction defects, pericarditis).

The cysts of *E. multilocularis* characteristically present as a slowly growing hepatic tumor, with progressive destruction of the liver and extension into vital structures. Patients commonly complain of upper quadrant and epigastric pain, and obstructive jaundice may be apparent. A minority of patients experience the metastasis of lesions to the lung and brain.

Diagnosis Radiographic and related imaging studies are important in detecting and evaluating echinococcal cysts. Plain films will define pulmonary cysts -- usually as rounded irregular masses of uniform density -- but may miss cysts in other organs unless there is cyst wall calcification (as occurs in the liver).MRI,CT, and ultrasound reveal well-defined cysts with thick or thin walls. When older cysts contain a layer of hydatid sand that is rich in accumulated scolices, these imaging methods may detect this fluid layer of different density. However, the most pathognomonic finding, if demonstrable, is that of daughter cysts within the larger cyst. This finding, like eggshell or mural calcification on CT, is indicative of *E. granulosus* infection and helps to distinguish the cyst from carcinomas, bacterial or amebic liver abscesses, or hemangiomas. CT of alveolar hydatid cysts reveals indistinct solid masses with central necrosis and plaquelike calcifications.

A specific diagnosis can be made by the examination of aspirated fluids for scoliceal hooklets, but diagnostic aspiration is not usually recommended because of the risk of fluid leakage resulting in either dissemination of infection or anaphylactic reactions. Serodiagnostic assays can be useful, although a negative test does not exclude the diagnosis of echinococcosis. Cysts in the liver elicit positive antibody responses in ~90% of cases, whereas up to 50% of individuals with cysts in the lungs are seronegative. Detection of antibody to specific echinococcal antigens by immunoblotting has the highest degree of specificity.

TREATMENT

Therapy for echinococcosis is based on considerations of the size, location, and manifestations of cysts and the overall health of the patient. Surgery has traditionally been the principal definitive method of treatment; *E. granulosus* cysts are excised, or

tissue containing *E. multilocularis* cysts is resected. Risks at surgery from leakage of fluid include anaphylaxis and dissemination of infectious scolices. The latter complication has been minimized by the instillation of scolicidal solutions such as hypertonic saline or ethanol, which may cause hypernatremia, intoxication, or sclerosing cholangitis. Albendazole, which is active against *Echinococcus*, should be administered adjunctively, beginning before resection and continuing for several weeks for *E. granulosus* and for up to 2 years for *E. multilocularis*. *P*ercutaneous *a*spiration, *i*nfusion of scolicidal agents, and *r*easpiration (PAIR) can be used instead of surgery in many cases of cystic echinococcosis. PAIR is contraindicated for superficially located cysts (because of the risk of rupture), for cysts with multiple thick internal septal divisions (honeycombing pattern), and for cysts communicating with the biliary tree. Therapy with albendazole (15 mg/kg daily in two divided doses) should be initiated at least 4 days before the procedure and continued for at least 4 weeks afterward. Ultrasound- orCT-guided aspiration allows confirmation of the diagnosis by demonstration of protoscolices in the aspirate. Either alcohol or hypertonic saline should then be infused. Daughter cysts within the primary cyst may need to be punctured separately. In experienced hands, this approach yields rates of cure and relapse equivalent to those following surgery, with less perioperative morbidity and shorter hospitalization. Medical therapy with albendazole alone for 12 weeks to 6 months results in cure in ~30% of cases and improvement in another 50%. Many of the failures are subsequently treated successfully with PAIR or additional courses of medical therapy. Response to treatment is best assessed by serial imaging studies with attention to cyst size and consistency.

Prevention In endemic areas, echinococcosis can be prevented by administering praziquantel to infected dogs, by denying dogs access to infected animals, or by vaccinating sheep. Limitation of the number of stray dogs is helpful in reducing the prevalence of infection among humans.

HYMENOLEPIASIS NANA

Infection with *Hymenolepis nana*, the dwarf tapeworm, is the most common of all the cestode infections. *H. nana* is endemic in both temperate and tropical regions of the world. Infection is spread by fecal/oral contamination and is common among institutionalized children.

Etiology and Pathogenesis *H. nana* is the only cestode of humans that does not require an intermediate host. Both the larval and adult phases take place in the human. The adult, the smallest tapeworm parasitizing humans, is about 2 cm long and dwells in the proximal ileum. Proglottids, which are quite small and are rarely seen in the stool, release spherical eggs 30 to 44 um in diameter, each of which contains an oncosphere with six hooklets. The eggs are immediately infective and are unable to survive in the external environment for more than 10 days. *H. nana* can also be acquired by the ingestion of infected insects (especially larval meal-worms and larval fleas). When the egg is ingested by a new host, the oncosphere is freed and penetrates the intestinal villi, becoming a cysticercoid larva. Larvae migrate back into the intestinal lumen, attach to the mucosa, and mature over 10 to 12 days into adult worms. Eggs may also hatch before passing into the stool, causing internal autoinfection with increasing numbers of intestinal worms. Although the life span of adult *H. nana* is only about 4 to 10 weeks, the autoinfection cycle perpetuates the infection.

Clinical Manifestations *H. nana* infection, even with many intestinal worms, is usually asymptomatic. When infection is intense, anorexia, abdominal pain, and diarrhea develop.

Diagnosis Infection is diagnosed by the finding of eggs in the stool.

TREATMENT

Praziquantel (25 mg/kg once) is the treatment of choice, since it acts against both the adult worms and the cysticercoids in the intestinal villi.

Prevention Good personal hygiene and improved sanitation can eradicate the disease. Epidemics have been controlled by mass chemotherapy coupled with improved hygiene.

HYMENOLEPIASIS DIMINUTA

Hymenolepis diminuta, a cestode of rodents, occasionally infects small children, who ingest the adult worm in uncooked cereal foods contaminated by fleas and other insects in which larvae develop. Infection is usually asymptomatic and is diagnosed by the detection of eggs in the stool. Treatment with praziquantel results in cure in most cases.

DIPHYLLOBOTHRIASIS

Diphyllobothrium latum and other *Diphyllobothrium* species are found in the lakes, rivers, and deltas of the northern hemisphere, Central Africa, and Chile.

Etiology and Pathogenesis The adult worm, the longest tapeworm (up to 25 m), attaches to the ileal and occasionally to the jejunal mucosa by its suckers, which are located on its elongated scolex. The adult worm has 3000 to 4000 proglottids, which release approximately 1 million eggs daily into the feces. If an egg reaches water, it hatches and releases a free-swimming embryo that can be eaten by small freshwater crustaceans (*Cyclops* or *Diaptomus* species). After an infected crustacean containing a developed procercoid is swallowed by a fish, the larva migrates into the fish's flesh and grows into a plerocercoid, or sparganum larva. Humans acquire the infection by ingesting infected raw fish. Within 3 to 5 weeks, the tapeworm matures into an adult in the human intestine.

Clinical Manifestations Most *D. latum* infections are asymptomatic, although manifestations may include transient abdominal discomfort, diarrhea, vomiting, weakness, and weight loss. Occasionally, infection can cause acute abdominal pain and intestinal obstruction; in rare cases cholangitis or cholecystitis may be produced by migrating proglottids. Because the tapeworm absorbs large quantities of vitamin B_{12} and interferes with ileal B_{12}absorption, vitamin B_{12}deficiency can develop. Up to 2% of infected patients, especially the elderly, have megaloblastic anemia resembling pernicious anemia and may exhibit neurologic sequelae of B_{12}deficiency.

Diagnosis The diagnosis is made readily by the detection of the characteristic eggs in

the stool. The eggs possess a single shell with an operculum at one end and a knob at the other. Mild to moderate eosinophilia may be detected.

TREATMENT

Praziquantel (5 to 10 mg/kg once) is highly effective. Parenteral vitamin B_{12}should be given if B_{12}deficiency is manifest.

Prevention Infection can be prevented by heating fish to 54°C for 5 min or by freezing it at-18°C for 24 h. Placing fish in brine with a high salt concentration for long periods kills the eggs.

DIPYLIDIASIS

Dipylidium caninum, a common tapeworm of dogs and cats, may accidentally infect humans. Dogs, cats, and occasionally humans become infected by ingesting fleas harboring cysticercoids. Children are more likely to become infected than adults. Most infections are asymptomatic, but abdominal pain, diarrhea, anal pruritus, urticaria, eosinophilia, or passage of segments in the stool may occur. The diagnosis is made by the detection of proglottids in the stool. As in *D. latum* infection, therapy consists of praziquantel. Prevention requires anthelmintic treatment and flea control for pet dogs or cats.

SPARGANOSIS

Humans can be infected by the sparganum, or plerocercoid larva, of a diphyllobothrid tapeworm of the genus *Spirometra*. Infection can be acquired by the consumption of water containing infected *Cyclops*; by the ingestion of infected snakes, birds, or mammals; or by the application of infected flesh as poultices. The worm migrates slowly in tissues, and infection commonly presents as a subcutaneous swelling. Periorbital tissues can be involved, and ocular sparganosis may destroy the eye. Surgical excision is used to treat localized sparganosis.

COENUROSIS

This rare infection of humans by the larval stage (coenurus) of the dog tapeworm *Taenia multiceps* or *T. serialis* results in a space-occupying cystic lesion. As in cysticercosis, involvement of the central nervous system and subcutaneous tissue is most common. Both definitive diagnosis and treatment require surgical excision of the lesion. Chemotherapeutic agents generally are not effective.

(Bibliography omitted in Palm version)

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PART EIGHT -DISORDERS OF THE CARDIOVASCULAR SYSTEM

SECTION 1 -DIAGNOSIS

224. APPROACH TO THE PATIENT WITH HEART DISEASE - *Eugene Braunwald*

The symptoms caused by heart disease result most commonly from myocardial ischemia, from disturbance of the contraction and/or relaxation of the myocardium, from obstruction to blood flow, or from an abnormal cardiac rhythm or rate. Ischemia is manifest most frequently as chest discomfort, while reduction of the pumping ability of the heart commonly leads to weakness and fatigability or, when severe, produces cyanosis, hypotension, syncope, and elevated intravascular pressure behind a failing ventricle. The latter results in abnormal fluid accumulation, which in turn leads to dyspnea, orthopnea, and systemic or pulmonary edema. Obstruction to blood flow, as in valvular stenosis, can cause symptoms resembling those resulting from congestive heart failure. Cardiac arrhythmias often develop suddenly, and the resulting signs and symptoms -- palpitation, dyspnea, hypotension, presyncope and syncope -- generally occur abruptly and may disappear as rapidly as they develop. Ischemic heart disease, by far the most common form of heart disease in adults, may present with chest discomfort but also as heart failure, tachyarrhythmia, and sudden cardiac death.

Myocardial or coronary function that may be adequate at rest may be inadequate during exertion. Thus a history of chest discomfort and/or dyspnea that appears only during activity is characteristic of heart disease, while the opposite pattern, i.e., the appearance of these symptoms at rest and their remission during exertion, is rarely observed in patients with organic heart disease.

Many patients with cardiocirculatory disease also may be asymptomatic, both at rest and during exertion, but may present an abnormal physical finding, such as a heart murmur, elevated arterial pressure, or an abnormality of the electrocardiogram (ECG) or of the cardiac silhouette on the chest roentgenogram. Patients may exhibit asymptomatic ischemia on an exercise stress test. In some asymptomatic patients the first clinical event may be catastrophic -- sudden cardiac death, acute myocardial infarction, or stroke.

Diseases of the heart and circulation are so common and the laity is so well acquainted with the major symptoms resulting from these disorders that patients, and occasionally physicians, erroneously attribute many noncardiac complaints to cardiovascular disease. The combination of the widespread fear of heart disease with the deep-seated emotional connotations concerning this organ's function results in the frequent development of symptoms that mimic those of organic disease in persons with normal cardiovascular systems. The unraveling of symptoms and signs due to organic heart disease from those not directly related is an important and challenging task in such patients.

Patients in whom heart disease has been confirmed, especially those who have experienced a major cardiovascular event such as a myocardial infarction or a serious arrhythmia, are often frightened and anxious about hospital discharge and resuming normal activity, including sexual relations. Attention to these matters is vital in the care

of cardiac patients.

Dyspnea, one of the cardinal manifestations of heart failure, is not limited to patients with heart disease but is also observed in conditions as diverse as pulmonary disease, marked obesity, and anxiety (Chap. 32). Similarly, chest discomfort may result from a variety of causes other than myocardial ischemia (Chap. 13). Whether heart disease is responsible for these symptoms can frequently be determined by carrying out a careful clinical examination. Noninvasive testing using electrocardiography at rest and during exercise (Chap. 226), echocardiography (Chap. 227), roentgenography, and myocardial imaging usually provides important additional information to permit the correct interpretation of symptoms; more specialized invasive examinations (catheterization and angiography;Chap. 228) are occasionally necessary.

DIAGNOSIS

As outlined by the New York Heart Association, the elements of a complete cardiac diagnosis include consideration of the following:

1. *The underlying etiology*. Is the disease congenital, infectious, hypertensive, or ischemic in origin?

2. *The anatomic abnormalities*. Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?

3. *The physiologic disturbances*. Is an arrhythmia present? Is there evidence of congestive heart failure or of myocardial ischemia?

One example may serve to illustrate the importance of establishing a complete diagnosis. The identification of myocardial ischemia as the etiology of a patient's exertional chest discomfort is of great clinical importance. However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomic abnormalities responsible for the myocardial ischemia, e.g., coronary atherosclerosis or aortic stenosis, are identified and a judgment made as to whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia, thyrotoxicosis, or supraventricular tachycardia, play a contributory role.

The fourth element of the diagnosis involves an assessment of *functional disability*. How strenuous is the physical activity required to elicit symptoms? The functional classification provided by the New York Heart Association has been found to be useful (Table 224-1).

The establishment of a correct and complete cardiac diagnosis often commences with the history and physical examination (Chap. 225). Indeed the clinical examination remains the basis for the diagnosis of a wide variety of disorders (Table 224-2). The clinical examination may then be supplemented by four types of laboratory tests: (1)ECG(Chap. 226); (2) chest roentgenogram; (3) noninvasive graphic examinations [echocardiogram, radionuclide and imaging techniques] (Chap. 227); and occasionally

(4) specialized invasive examinations, i.e., cardiac catheterization, angiocardiography, and coronary angiography (Chap. 228).

In the diagnostic process, the results obtained from each of these several modalities should be analyzed independently of one another as well as together. Only in this way can one avoid overlooking a subtle, though important, finding. For example, anECGshould be obtained in every patient suspected of heart disease. It may provide the critical clue in establishing the correct diagnosis, e.g., the finding of a mild atrioventricular conduction disturbance in a patient with unexplained syncope, even when all other methods of examination reveal no abnormal findings, can be the clue that advanced heart block and asystole might be the cause and can dictate electrophysiologic testing. On the other hand, when combined intelligently with the results of other methods of examination, the ECG may provide essential confirmatory data. Thus, the knowledge that a patient has an apical diastolic rumbling murmur may direct particular attention to the P waves, and the recognition of electrocardiographic left atrial enlargement supports the suggestion that the murmur is caused by mitral stenosis. The diagnosis can then be confirmed by echocardiography, a technique that can also determine the severity of the obstruction and its effects on pulmonary artery pressure and on right and left ventricular function.

Family History In eliciting the history of a patient with known or suspected cardiovascular disease, particular attention should be directed to the family history. Familial clustering is common in many forms of heart disease. Mendelian transmission of single-gene defects may occur, as in hypertrophic cardiomyopathy (Chap. 238), the Marfan syndrome (Chap. 351), and sudden death associated with a prolonged QT syndrome (Chap. 230). Essential hypertension or coronary atherosclerosis are often polygenic disorders. While familial transmission may be less obvious than in the single-gene disorders, it is also helpful in assessing risk and prognosis. Familial clustering of cardiovascular diseases may occur not only on a genetic basis but also may be related to familial dietary or behavior patterns, such as excessive ingestion of salt or calories or cigarette smoking.

Assessment of Functional Impairment When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain with as much precision as possible the level of activity and the rate at which it is performed before symptoms develop. Thus, breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than similar symptoms occurring after taking a few steps on the level. Also, the degree of customary physical activity at work and during recreation should be considered. The development of two-flight dyspnea in a marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person. Similarly, the history must include a detailed consideration of the patient's therapeutic regimen. For example, the persistence or development of edema, breathlessness, and other manifestations of heart failure in a patient whose diet is rigidly restricted in sodium content and who is receiving optimal doses of diuretics is far more grave than are similar manifestations in the absence of these measures. In an effort to determine the rate of progression of symptoms, and thereby of the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could carry out 1 year earlier that he or she cannot carry out at present.

Electrocardiogram (See also Chap. 226) Although an ECG should be recorded in every patient with known or suspected heart disease, with the exception of the identification of arrhythmias and of acute myocardial infarction, it rarely permits establishment of a specific diagnosis. In the absence of other abnormal findings, electrocardiographic changes must not be overinterpreted. The range of normal electrocardiographic findings is wide, and the tracing can be affected significantly by many noncardiac factors, such as age, body habitus, and serum electrolyte concentrations.

Natural History The natural history of cardiovascular disease must be appreciated. Cardiovascular disorders often present acutely, as in a previously asymptomatic patient with extensive coronary atherosclerosis who develops an acute myocardial infarction or the previously asymptomatic patient with hypertrophic cardiomyopathy whose first clinical manifestation is syncope or even sudden death. However, in both instances, the alert physician may recognize the patient at risk of these complications long before they occur and can often take measures to prevent their occurrence. For example, the patient with acute myocardial infarction may well have had risk factors for atherosclerosis for many years. Had these been recognized, their elimination or reduction might have delayed or even prevented the infarction. Similarly, the patient with hypertrophic cardiomyopathy may have had a heart murmur for years, and a positive family history might have led to an echocardiographic examination and the recognition of the condition and appropriate therapy long before the acute manifestations.

PITFALLS IN CARDIOVASCULAR MEDICINE

Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include:

1. Failure by the *noncardiologist* to recognize important cardiac manifestations of systemic illnesses. Examples of the latter are (a) stroke (atrial fibrillation, mitral stenosis); (b) skeletal muscular dystrophies (associated with cardiomyopathy); (c) hemochromatosis (associated with myocardial infiltration and restrictive cardiomyopathy); (d) congenital deafness (associated with prolonged QT interval and serious cardiac arrhythmias); (e) Raynaud's disease (associated with primary pulmonary hypertension and coronary vasospasm); (f) connective tissue disorders, e.g., the Marfan syndrome, (aortic dilatation and aneurysm, prolapsed mitral valve); (g) hyperthyroidism (heart failure, atrial fibrillation); (h) hypothyroidism (pericardial effusion, coronary artery disease); (i) rheumatoid arthritis (pericarditis, aortic valve disease); (j) scleroderma (cor pulmonale, myocardial fibrosis, pericarditis); (k) systemic lupus erythematosus (valvulitis, myocarditis, pericarditis); and (l) sarcoidosis (arrhythmias, cardiomyopathy). In patients with these and other systemic disorders a cardiovascular examination should be carried out to identify and estimate the severity of cardiovascular involvement.

2. Failure by the cardiologist to recognize underlying systemic disorders, such as those listed above, in patients with a cardiac disorder. Patients with heart disease should be assessed for the frequent *noncardiac* manifestations of systemic disorders with cardiovascular manifestations. For example, Lyme disease should be considered in patients with unexplained fluctuating atrioventricular block. A cardiovascular abnormality

may provide the clue critical to the recognition of some systemic disorders. For instance, unexplained atrial fibrillation may provide the first clue to the diagnosis of thyrotoxicosis.

3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques for the examination of the cardiovascular system. Cardiac catheterization and coronary arteriography (Chap. 228) provide precise diagnostic information under many circumstances. For example, they aid in establishing a specific anatomic diagnosis, which, in turn, may be critical to developing a therapeutic plan in patients with known or suspected ischemic heart disease. Although a great deal of attention has been lavished on these expensive examinations, it should be recognized that they serve to *supplement*, not *supplant*, a careful examination carried out by clinical and noninvasive techniques. A coronary arteriogram should not be carried out in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed, the results often do not provide a definite answer to the question of whether a patient's complaint of chest pain is attributable to coronary arteriosclerosis. Catheterization of the left side of the heart is all too frequently employed to assess patients with valvular heart disease when echocardiographic examination would actually provide more useful information.

Despite the enormous value of these invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on existing medical facilities. Therefore, they should be carried out only if, after clinical examination and assessment by noninvasive tests, the results of the invasive examination can be expected to modify the patient's management.

TREATMENT

After a complete diagnosis has been established, a number of therapeutic options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

1. In the absence of evidence of heart disease, a clear, definitive statement to that effect should be made and the patient should *not* be asked to return at intervals for repeated examinations. If there is no evidence for disease, such continued attention may lead to the patient developing inappropriate anxiety and fixation on the heart.

2. If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart disease (Chap. 242), a plan for their reduction should be developed and the patient should be retested at intervals to assess that he or she is complying and that these risk factors are in fact being reduced.

3. Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6 to 12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function can be detected in this manner and in appropriate patients may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive risk of surgical treatment (Chap. 236).

4. It is critical to establish clear criteria for deciding on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization) in patients with ischemic heart disease (Chap. 244). Mechanical revascularization, i.e., the latter two modalities, represents a major therapeutic advance in the treatment of this most common form of heart disease in developed nations, but these techniques are probably being employed too frequently in the United States; the mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexly evoke a decision to treat the patient surgically or by percutaneous coronary intervention. Instead, coronary revascularization should be limited to those patients with ischemic heart disease who have not responded adequately to medical treatment (e.g., intractable angina) or in whom the procedure has been shown to improve the natural history (e.g., three-vessel coronary artery disease with left ventricular dysfunction.)

(Bibliography omitted in Palm version)

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225. PHYSICAL EXAMINATION OF THE CARDIOVASCULAR SYSTEM - *Robert A. O'Rourke, Eugene Braunwald*

A meticulous physical examination is an often inadequately utilized low-cost method for assessing the cardiovascular system and frequently provides important information for the appropriate selection of additional tests. First, the general physical appearance should be evaluated. The patient may appear tired because of a chronic low cardiac output; the respiratory rate may be rapid in cases of pulmonary venous congestion. Central cyanosis, often associated with clubbing of the fingers and toes, indicates right-to-left cardiac or extracardiac shunting or inadequate oxygenation of blood by the lungs. Cyanosis in the distal extremities, cool skin, and increased sweating result from vasoconstriction in patients with severe heart failure (Chap. 36). Noncardiovascular details can be equally important. For example, infective endocarditis is the likely diagnosis in patients with petechiae, Osler's nodes, and Janeway lesions (Chap. 126).

The blood pressure should be taken in both arms and with the patient supine and upright; the heart rate should be timed for 30 s. Orthostatic hypotension and tachycardia may indicate a reduced blood volume, while resting tachycardia may be due to heart failure.

Careful examination of the optic fundi is essential (Chap. 246), and the retinal vessels may show evidence of systemic hypertension, arteriosclerosis, or embolism. The latter may result from atherosclerosis in larger arteries (e.g., the carotid) or may represent a complication of valvular heart disease (e.g., endocarditis).

Palpation of the peripheral arterial pulses in the upper and lower extremities is necessary to define the adequacy of systemic blood flow and to detect the presence of occlusive arterial lesions. It is also important to examine both legs for evidence of edema, varicose veins, or thrombophlebitis (Chap. 248). The cardiovascular examination includes careful evaluation of both the carotid arterial and the jugular venous pulses, as well as deliberate precordial palpation and attentive cardiac auscultation.

ARTERIAL PRESSURE PULSE

The normal central aortic pulse wave is characterized by a fairly rapid rise to a somewhat rounded peak (Fig. 225-1). The anacrotic shoulder, present on the ascending limb, occurs at the time of peak rate of aortic flow just before maximum pressure is reached. The less steep descending limb is interrupted by a sharp downward deflection, coincident with aortic valve closure, called the *incisura*. As the pulse wave is transmitted peripherally, the initial upstroke becomes steeper, the anacrotic shoulder becomes less apparent, and the incisura is replaced by the smoother dicrotic notch. Accordingly, palpation of a peripheral arterial pulse (e.g., the radial pulse) frequently gives less information than examination of a more central pulse (e.g., the carotid pulse) regarding alterations in left ventricular ejection or aortic valve function. However, certain findings, such as the bisferiens pulse of aortic regurgitation or pulsus alternans, are more evident in peripheral arteries (Fig. 225-2). The carotid pulse is best examined with the sternocleidomastoid muscle relaxed and with the head rotated slightly toward the examiner. In palpating the brachial arterial pulse, the examiner can support the subject's

relaxed elbow with the right arm while compressing the brachial pulse with the thumb. The usual technique is to compress the artery with the thumb or forefinger until the maximum pulse is sensed. Varying degrees of pressure should then be applied while concentrating on the separate phases of the pulse wave. This method, known as *trisection*, is useful for assessing the sharpness of the upstroke, systolic peak, and diastolic slope of the arterial pulse. In most normal persons, a dicrotic wave is not palpable.

A small weak pulse, *pulsus parvus*, is common in conditions with a diminished left ventricular stroke volume, a narrow pulse pressure, and increased peripheral vascular resistance (Fig. 225-2). A *hypokinetic* pulse may be due to hypovolemia, to left ventricular failure, to restrictive pericardial disease, or to mitral valve stenosis. In aortic valve stenosis, the delayed systolic peak, *pulsus tardus*, results from obstruction to left ventricular ejection. In contrast, a large, bounding (*hyperkinetic*) pulse is usually associated with an increased left ventricular stroke volume, a wide pulse pressure, and a decrease in peripheral vascular resistance. This pattern occurs characteristically in patients with an elevated stroke volume, as in complete heart block; with hyperkinetic circulation due to anxiety, anemia, exercise, or fever; or with a rapid runoff of blood from the arterial system (as caused by a patent ductus arteriosus or peripheral arteriovenous fistula). Patients with mitral regurgitation or a ventricular septal defect may also have a bounding pulse, since vigorous left ventricular ejection produces a rapid upstroke in the arterial pulse, even though the duration of systole and the forward stroke volume may be reduced. In aortic regurgitation, the rapidly rising, bounding arterial pulse results from an increased left ventricular stroke volume and an increased rate of ventricular ejection.

The *bisferiens pulse*, which has two systolic peaks, is characteristic of aortic regurgitation (with or without accompanying stenosis) and of hypertrophic cardiomyopathy (Chap. 238). In the latter condition, the pulse wave upstroke rises rapidly and forcefully, producing the first systolic peak ("percussion wave"). A brief decline in pressure follows because of the sudden midsystolic decrease in the rate of left ventricular ejection, when severe obstruction often develops. This pressure trough is followed by a smaller and more slowly rising positive pulse wave ("tidal wave") produced by continued ventricular ejection and by reflected waves from the periphery. The *dicrotic pulse* has two palpable waves, one in systole and one in diastole. It usually denotes a very low stroke volume, particularly in patients with dilated cardiomyopathy.

Pulsus alternans is a pattern in which there is regular alteration of the pressure pulse amplitude, despite a regular rhythm (Fig. 225-2). It is due to alternating left ventricular contractile force, usually indicates severe impairment of left ventricular function, and commonly occurs in patients who also have a loud third heart sound. Pulsus alternans may also occur during or following paroxysmal tachycardia or for several beats following a premature beat in patients without heart disease. In *pulsus bigeminus*, there is also a regular alteration of pressure pulse amplitude, but it is caused by a premature ventricular contraction that follows each regular beat. In *pulsus paradoxus*, the decrease in systolic arterial pressure that normally accompanies the reduction in arterial pulse amplitude during inspiration is accentuated. In patients with pericardial tamponade (Chap. 239), airway obstruction, or superior vena cava obstruction, the decrease in systolic arterial pressure frequently exceeds the normal decrease of 10 mmHg and the peripheral pulse may disappear completely during inspiration.

Simultaneous palpation of the radial and femoral arterial pulses, which normally are virtually coincident, is important to rule out aortic coarctation, in which the latter pulse is weakened and delayed (Chap. 234).

JUGULAR VENOUS PULSE (JVP)

The two main objectives of the examination of the neck veins are inspection of their waveform and estimation of the central venous pressure (CVP). In most patients, the right internal jugular vein is best for both purposes. Usually, the pulsation of the internal jugular vein is greatest when the trunk is inclined by less than 30°. In patients with elevated venous pressure, it may be necessary to elevate the trunk further, sometimes to as much as 90°. When the neck muscles are relaxed, shining a beam of light tangentially across the skin overlying the vein exposes the pulsations of the internal jugular vein. Simultaneous palpation of the left carotid artery aids the examiner in deciding which pulsations are venous and in relating the venous pulsations to their timing in the cardiac cycle.

The normalJVPreflects phasic pressure changes in the right atrium and consists of two or sometimes three positive waves and two negative troughs (Fig. 225-1). The positive presystolic *a* wave is produced by venous distention due to right atrial contraction and is the dominant wave in the JVP, particularly during inspiration. Large *a* waves indicate that the right atrium is contracting against an increased resistance (Fig. 225-3), such as occurs with tricuspid stenosis or more commonly with increased resistance to right ventricular filling (pulmonary hypertension or pulmonic stenosis). Large *a* waves also occur during arrhythmias whenever the right atrium contracts while the tricuspid valve is closed by right ventricular systole. Such "cannon" *a* waves may occur regularly (as during junctional rhythm) or irregularly (as in atrioventricular dissociation with ventricular tachycardia or complete heart block). The *a* wave is absent in patients with atrial fibrillation, and there is an increased delay between the *a* wave and the carotid arterial pulse in patients with first-degree atrioventricular block.

The *c* wave, often observed in theJVP, is a positive wave produced by the bulging of the tricuspid valve into the right atrium during right ventricular isovolumetric systole and by the impact of the carotid artery adjacent to the jugular vein. The *x* descent is due both to atrial relaxation and to the downward displacement of the tricuspid valve during ventricular systole. The *x* descent wave during systole is often accentuated in patients with constrictive pericarditis (Fig. 225-3), but the nadir of this wave is reduced with right ventricular dilation and is often reversed in tricuspid regurgitation. The positive, late systolic *v* wave results from the increasing volume of blood in the right atrium during ventricular systole when the tricuspid valve is closed. Tricuspid regurgitation causes the *v* wave to be more prominent; when tricuspid regurgitation becomes severe, the combination of a prominent *v* wave and obliteration of the *x* descent results in a single large positive systolic wave. After the *v* wave peaks, the right atrial pressure falls because of the decreased bulging of the tricuspid valve into the right atrium as right ventricular pressure declines and the tricuspid valve opens (Fig. 225-3).

This negative descending limb -- the *y* descent of theJVP -- is produced mainly by the opening of the tricuspid valve and the subsequent rapid inflow of blood into the right

ventricle. A rapid, deep *y* descent in early diastole occurs with severe tricuspid regurgitation. A venous pulse characterized by a sharp *y* descent, a deep *y* trough, and a rapid ascent to the baseline is seen in patients with constrictive pericarditis or with severe right-sided heart failure and a high venous pressure. A slow *y* descent in the JVP suggests an obstruction to right ventricular filling, as occurs with tricuspid stenosis or right atrial myxoma.

The right internal jugular is the best vein to use for accurate estimation of theCVP. The sternal angle is used as the reference point, because the center of the right atrium lies approximately 5 cm below the sternal angle in the average patient, regardless of body position. The patient is examined at the optimal degree of trunk elevation for visualization of venous pulsations. The vertical distance between the top of the oscillating venous column and the level of the sternal angle is determined; generally it is less than 3 cm (3 cm + 5 cm= 8 cm blood). The most common cause of a high venous pressure is an elevated right ventricular diastolic pressure. In patients suspected of having right ventricular failure who have a normal CVP at rest, the abdominojugular reflux test may be helpful. The palm of the examiner's hand is placed over the abdomen, and firm pressure is applied for 10 s or more. In normal persons, this maneuver does not alter the jugular venous pressure significantly, but when right heart function is impaired, the upper level of venous pulsation usually increases. A positive abdominojugular test is best defined as an increase inJVPduring 10 s of firm midabdominal compression followed by a rapid drop in pressure of 4 cm blood on release of the compression. The most common cause of a positive test is right-sided heart failure secondary to elevated left heart filling pressures. Also, abdominal compression may elicit the JVP pattern typical of tricuspid regurgitation when the resting pulse wave is normal. *Kussmaul's sign* -- an increase rather than the normal decrease in the CVP during inspiration -- is most often caused by severe right-sided heart failure; it is a frequent finding in patients with constrictive pericarditis or right ventricular infarction.

PRECORDIAL PALPATION

The location, amplitude, duration, and direction of the cardiac impulse usually can be best appreciated with the fingertips. The normal left ventricular apex impulse is located at or medial to the left midclavicular line in the fourth or fifth intercostal space and is a tapping, early systolic outward thrust localized to a point usually less than 2.5 cm in diameter. It is due primarily to recoil of the heart as blood is ejected and should be evaluated with the patient supine and in the left lateral position. Left ventricular hypertrophy results in exaggeration of the amplitude, duration, and often size of the normal left ventricular thrust. The impulse may be displaced laterally and downward into the sixth or seventh interspace, particularly in patients with a left ventricular volume load such as occurs in cases of aortic regurgitation or dilated cardiomyopathy.

Additional abnormal features that are detectable at the left ventricular apex include marked presystolic distention of the left ventricle, which is often accompanied by a fourth heart sound in patients with an excessive left ventricular pressure load or myocardial ischemia/infarction, and a prominent early diastolic rapid-filling wave, which is often accompanied by a third heart sound in patients with left ventricular failure or mitral valve regurgitation (Fig. 225-1). A double systolic apical impulse is often palpable

in patients with hypertrophic cardiomyopathy.

Right ventricular hypertrophy often results in a sustained systolic lift at the lower left parasternal area, which starts in early systole and is synchronous with the left ventricular apical impulse.

Abnormal precordial pulsations occur during systole in patients with left ventricular dyssynergy due to ischemic heart disease or to diffuse myocardial disease from some other cause. These pulsations often occur in patients with a recent myocardial infarction and may be present in some patients only during episodes of angina. They are most commonly felt in the left midprecordium one or two interspaces above and/or 1 to 2 cm medial to the left ventricular apex. A systolic bulge occurring in the region of the apex is difficult to distinguish from the impulse of left ventricular hypertrophy.

A left parasternal lift is frequently present in patients with severe mitral regurgitation. This pulsation occurs distinctly later than the left ventricular apical impulse, is synchronous with the *v* wave in the left atrial pressure curve, and is due to anterior displacement of the right ventricle by an enlarged, expanding left atrium. A similar impulse occurs to the right of the sternum in some patients with severe tricuspid regurgitation and a giant right atrium. Pulsation of the right sternoclavicular joint may indicate a right-sided aortic arch or aneurysmal dilation of the ascending aorta. Pulmonary artery pulsation is often visible and palpable in the second left intercostal space. While it may be normal in children or thin young adults, this pulsation usually denotes pulmonary hypertension, increased pulmonary blood flow, or poststenotic pulmonary artery dilation.

Thrills are palpable, low-frequency vibrations associated with heart murmurs. The systolic murmur of mitral regurgitation may be palpated at the cardiac apex. When the palm of the hand is placed over the precordium, the thrill of aortic stenosis crosses the palm toward the right side of the neck, while the thrill of pulmonic stenosis radiates more often to the left side of the neck. The thrill due to a ventricular septal defect is usually located in the third and fourth intercostal spaces near the left sternal border.

Percussion should be performed in each patient to identify normal or abnormal position of the heart, stomach, and liver. However, in patients with a normal cardiac situs, percussion adds little to careful inspection and palpation in the recognition of cardiac enlargement.

CARDIAC AUSCULTATION

To obtain the most information from cardiac auscultation, the observer should keep in mind several principles: (1) Auscultation should be performed in a quiet room to avoid the distracting noises of normal activity. (2) For optimal auscultation, attention must be focused on the phase of the cardiac cycle during which the auscultatory event is expected to occur. (3) The timing of a heart sound or murmur can be determined accurately from its relation to other observable events in the cardiac cycle -- the carotid arterial pulse, the apical impulse, or theJVP. (4) To define the significance of a cardiac sound or murmur, it is often necessary to observe alterations in its timing or intensity during various physiologic and/or pharmacologic interventions (Table 225-1).

HEART SOUNDS

The major components of heart sounds are vibrations associated with the abrupt acceleration or deceleration of blood in the cardiovascular system. Studies using simultaneous echocardiographic-phonocardiographic recordings indicate that the first and second heart sounds are produced primarily by the closure of the atrioventricular (AV) and semilunar valves and the events that accompany these closures. The intensity of the *first heart sound* (S_1) is influenced by (1) the position of the mitral leaflets at the onset of ventricular systole; (2) the rate of rise of the left ventricular pressure pulse; (3) the presence or absence of structural disease of the mitral valve; and (4) the amount of tissue, air, or fluid between the heart and the stethoscope. S_1 is louder if diastole is shortened because of tachycardia, if atrioventricular flow is increased because of high cardiac output or prolonged because of mitral stenosis, or if atrial contraction precedes ventricular contraction by an unusually short interval, reflected in a short PR interval. The loud S_1 in mitral stenosis usually signifies that the valve is pliable and that it remains open at the onset of isovolumetric contraction because of the elevated left atrial pressure. A soft S_1 may be due to poor conduction of sound through the chest wall, a slow rise of the left ventricular pressure pulse, a long PR interval, or imperfect closure due to reduced valve substance, as in mitral regurgitation. S_1 is also soft when the anterior mitral leaflet is immobile because of rigidity and calcification, even in the presence of predominant mitral stenosis.

Splitting of the two high-pitched components of S_1 by 10 to 30 ms is a normal phenomenon (Fig. 225-1). The first component of S_1 is attributed to mitral valve closure, and the second to tricuspid valve closure. Widening of the S_1 is due most often to complete right bundle branch block and the resulting delay in onset of the right ventricular pressure pulse. Reversed splitting of the S_1, in which the mitral component follows the tricuspid component, may be present in patients with severe mitral stenosis, left atrial myxoma, and left bundle branch block.

Splitting of the *second heart sound* (S_2) into audibly distinct aortic (A_2) and pulmonic (P_2) components occurs normally during inspiration, when the augmented inflow into the right ventricle increases its stroke volume and ejection period and thus delays closure of the pulmonic valve. P_2 is coincident with the incisura of the pulmonary artery pressure curve, which is separated from the right ventricular pressure tracing by an interval termed the "hangout time." The absolute value of this interval reflects the resistance to pulmonary blood flow and the impedance characteristics of the pulmonary vascular bed. This interval is prolonged, and physiologic splitting of S_2 is accentuated, in conditions associated with right ventricular volume overload and a distensible pulmonary vascular bed. However, in patients with an increase in pulmonary vascular resistance, the hangout time is markedly reduced, and narrow splitting of S_2 is present. Splitting that persists with expiration (heard best at the pulmonic area or left sternal border) is usually abnormal when the patient is in the upright position. Such splitting may be due to many causes: delayed activation of the right ventricle (right bundle branch block); left ventricular ectopic beats; a left ventricular pacemaker; prolongation of right ventricular contraction with an increased right ventricular pressure load (pulmonary embolism or pulmonic stenosis); or delayed pulmonic valve closure because of right ventricular volume overload associated with right ventricular failure or diminished impedance of the

pulmonary vascular bed and a prolonged hangout time (atrial septal defect).

In pulmonary hypertension, P_2 is loud, and splitting of the second heart sound may be diminished, normal, or accentuated, depending on the cause of the pulmonary hypertension, the pulmonary vascular resistance, and the presence or absence of right ventricular decompensation. Early aortic valve closure, occurring with mitral regurgitation or a ventricular septal defect, may also produce splitting that persists during expiration. It may also occur with constrictive pericarditis. In patients with an atrial septal defect, the proportion of right atrial filling contributed by the left atrium and the venae cavae varies reciprocally during the respiratory cycle, so that right atrial inflow remains relatively constant. Therefore, the volume and duration of right ventricular ejection are not significantly increased by inspiration, and there is little inspiratory exaggeration of the splitting of S_2. This phenomenon, termed *fixed splitting* of the second heart sound, is of considerable diagnostic value.

A delay in aortic valve closure causing P_2 to precede A_2results in so-called reversed (paradoxic) splitting of S_2. Splitting is then maximal in expiration and decreases during inspiration with the normal delay of pulmonic valve closure. The most common causes of reversed splitting of S_2 are left bundle branch block and delayed excitation of the left ventricle from a right ventricular ectopic beat. Mechanical prolongation of left ventricular systole, resulting in reversed splitting of S_2, may also be caused by severe aortic outflow obstruction, a large aorta-to-pulmonary artery shunt, systolic hypertension, and ischemic heart disease or cardiomyopathy with left ventricular failure. P_2 is normally softer than A_2 in the second left intercostal space; a P_2 that is greater than A_2 in this area suggests pulmonary hypertension, except in patients with atrial septal defect.

The *third heart sound* (S_3) is a low-pitched sound produced in the ventricle 0.14 to 0.16 s after A_2, at the termination of rapid filling. This sound is frequent in normal children and in patients with high cardiac output. However, in patients over 40 years old, an S_3usually indicates impairment of ventricular function,AV valve regurgitation, or other conditions that increase the rate or volume of ventricular filling. The left-sided S_3 is best heard with the bell piece of the stethoscope at the left ventricular apex during expiration and with the patient in the left lateral position. The right-sided S_3 is best heard at the left sternal border or just beneath the xiphoid and is usually louder with inspiration. Often it is accompanied by the systolic murmur of functional tricuspid regurgitation. Third heart sounds often disappear with treatment of heart failure.

An S_3 that is earlier (0.10 to 0.12 s after A_2) and higher-pitched than normal (a pericardial knock) often occurs in patients with constrictive pericarditis (Chap. 239); its presence depends on the restrictive effect of the adherent pericardium, which halts diastolic filling abruptly.

The *opening snap* (OS) is a brief, high-pitched, early diastolic sound, which is usually due to stenosis of an AVvalve, most often the mitral valve. It is generally heard best at the lower left sternal border and radiates well to the base of the heart. The A_2-OS interval is inversely related to the height of the mean left atrial pressure and ranges from 0.04 to 0.12 s. In the second intercostal space, an OS is often confused with P_2. However, careful auscultation will reveal both components of S_2, followed by the OS. The OS of tricuspid stenosis occurs later in diastole than the mitral OS and is often

overlooked in patients with more prominent mitral valve disease.

The *fourth heart sound* (S_4) is a low-pitched, presystolic sound produced in the ventricle during ventricular filling; it is associated with an effective atrial contraction and is best heard with the bell piece of the stethoscope. The sound is absent in patients with atrial fibrillation. The S_4occurs when diminished ventricular compliance increases the resistance to ventricular filling, and it is frequently present in patients with systemic hypertension, aortic stenosis, hypertrophic cardiomyopathy, ischemic heart disease, and acute mitral regurgitation. Most patients with an acute myocardial infarction and sinus rhythm have an audible S_4. The fourth heart sound is frequently accompanied by visible and palpable presystolic distention of the left ventricle. It is loudest at the left ventricular apex when the patient is in the left lateral position and is accentuated by mild isotonic or isometric exercise in the supine position. The right-sided S_4 is present in patients with right ventricular hypertrophy secondary to either pulmonic stenosis or pulmonary hypertension and frequently accompanies a prominent presystolic *a* wave in theJVP.

An S_4frequently accompanies delayedAVconduction even in the absence of clinically detectable heart disease. The incidence of an audible S_4increases with increasing age. Whether an audible S_4 in adults without other evidence of cardiac disease is abnormal remains controversial.

The *ejection sound* is a sharp, high-pitched event occurring in early systole and closely following the first heart sound. Ejection sounds occur in the presence of semilunar valve stenosis and in conditions associated with dilation of the aorta or pulmonary artery. The aortic ejection sound is usually heard best at the left ventricular apex and the second right intercostal space; the pulmonary ejection sound is loudest at the upper left sternal border. The latter, unlike most other right-sided acoustical events, is heard better during expiration.

Nonejection or *midsystolic clicks*, occurring with or without a late systolic murmur, often denote prolapse of one or both leaflets of the mitral valve (Chap. 236). They also may be caused by tricuspid valve prolapse. They probably result from chordae tendineae that are functionally unequal in length on either or bothAVvalves and are heard best along the lower left sternal border and at the left ventricular apex. Systolic clicks may be single or multiple, and they may occur at any time in systole but are usually later than the systolic ejection sound.

HEART MURMURS (See alsoChap. 34)

Cardiac murmurs result from vibrations set up in the bloodstream and the surrounding heart and great vessels as a result of turbulent blood flow, the formation of eddies, and cavitation (bubble formation as a result of sudden decrease in pressure).

The intensity (loudness) of murmurs may be graded from I to VI. A grade I murmur is so faint that it can be heard only with special effort; a grade IV murmur is commonly accompanied by a thrill; and a grade VI murmur is audible with the stethoscope removed from contact with the chest. The configuration of a murmur may be crescendo, decrescendo, crescendo-decrescendo (diamond-shaped), or plateau. The precise time of onset and time of cessation of a murmur depend on the instant in the cardiac cycle at

which an adequate pressure difference between two chambers arises and disappears (Fig. 225-4).

The location on the chest wall where the murmur is best heard and the areas to which it radiates can aid in identifying the cardiac structure from which the murmur originates. For example, the murmur of aortic valve stenosis is usually loudest in the second right intercostal space and radiates to the carotid arteries. By contrast, the murmur of mitral regurgitation is most often loudest at the cardiac apex. It may radiate to the left sternal border and base of the heart when the posterior mitral leaflet is predominantly involved or to the axilla and back when the anterior leaflet is more severely affected. In the latter case, the regurgitant blood is directed toward the posterior left atrial wall.

It is often difficult to classify a cardiac murmur with certainty on the basis of its timing, configuration, location, radiation, pitch, or intensity. However, by noting changes in the characteristics of the murmur during maneuvers that alter cardiac hemodynamics, the auscultator can often identify its correct origin and significance (Table 225-1).

Accentuation of a murmur during inspiration (a maneuver that augments systemic venous return) implies that it originates on the right side of the circulation; expiratory exaggeration has less significance. Prolonged expiratory pressure against a closed glottis (i.e., the Valsalva maneuver) reduces the intensity of most murmurs by diminishing both right and left ventricular filling (i.e., ventricular preload). The systolic murmur associated with *hypertrophic cardiomyopathy* and the late systolic murmur due to *mitral valve prolapse* are exceptions and may be paradoxically accentuated during the Valsalva maneuver. Murmurs due to flow across a normal or obstructed semilunar valve increase in intensity in the cycle following a premature ventricular beat or a long RR interval in atrial fibrillation. In contrast, murmurs due toAV valve regurgitation or a ventricular septal defect do not change appreciably during the beat following a prolonged diastole. Standing, which decreases left ventricular volume, accentuates the murmur of hypertrophic cardiomyopathy and occasionally the murmur due to mitral valve prolapse. Squatting, which increases both venous return and systemic arterial resistance and thus ventricular afterload, increases most murmurs, except those due to hypertrophic cardiomyopathy and mitral regurgitation due to a prolapsed mitral valve, which often decrease. Sustained handgrip exercise, which increases systemic arterial pressure and heart rate, often accentuates the murmurs of mitral regurgitation, aortic regurgitation, and mitral stenosis but usually diminishes those due to aortic stenosis or hypertrophic cardiomyopathy. Pharmacologic interventions include inhalation of amyl nitrite, which reduces systemic arterial pressure and increases blood flow, thereby increasing the intensity of murmurs due to valvular stenosis while diminishing those due to aortic or mitral regurgitation (Table 225-1). Transient external arterial occlusion by the inflation of bilateral arm cuffs to 20 mmHg (2.66 kPa) above systolic blood pressure for 5 s usually intensifies murmurs due to left-sided regurgitant lesions; this method is applicable to almost all patients and does not require administration of any drug.

Systolic Murmurs *Holosystolic (pansystolic) murmurs* are generated when there is flow between two chambers that have widely different pressures throughout systole, such as the left ventricle and either the left atrium or the right ventricle (Fig. 225-4). The pressure gradient occurs early in contraction and lasts until relaxation is almost complete. Therefore, holosystolic murmurs begin before aortic ejection, and at the area of maximal

intensity they begin with S_1 and end after S_2. Holosystolic murmurs accompany mitral or tricuspid regurgitation, ventricular septal defect, and, under certain circumstances, aortopulmonary shunts. Although the typical high-pitched murmur of mitral regurgitation usually continues throughout systole, the shape of the murmur may vary considerably. The holosystolic murmurs of mitral regurgitation and ventricular septal defect are augmented by transient exercise and are diminished by lowering the left ventricular systolic pressure by inhalation of amyl nitrite. The murmur of tricuspid regurgitation associated with pulmonary hypertension is holosystolic and frequently increases during inspiration. Not all patients with mitral or tricuspid regurgitation or ventricular septal defect have holosystolic murmurs (Chap. 236). Often, a mild valvular regurgitant jet, detected by color flow Doppler techniques, is not associated with an audible murmur despite optimal auscultation. Such regurgitant jets usually do not indicate clinical heart disease. Trivial mitral regurgitation can be detected by Doppler in up to 45% of normal individuals; tricuspid regurgitation in up to 70%; and pulmonic regurgitation in up to 88%. Normal aortic regurgitation is encountered much less frequently, and its incidence increases with advancing age (Fig. 225-5).

Midsystolic murmurs, also called *systolic ejection murmurs*, which are often crescendo-decrescendo in shape, occur when blood is ejected across the aortic or pulmonic outflow tracts (Fig. 225-4). The murmur starts shortly after S_1, when the ventricular pressure becomes high enough to open the semilunar valve. As the velocity of ejection increases, the murmur gets louder; as ejection declines, it diminishes. The murmur ends before the ventricular pressure falls enough to permit closure of the aortic or pulmonic leaflets. When the semilunar valves are normal, an increased flow rate (as occurs in states of elevated cardiac output), ejection into a dilated vessel beyond the valve, or increased transmission of sound through a thin chest wall may be responsible for this murmur. Most benign, functional murmurs are midsystolic and originate from the pulmonary outflow tract. Valvular or subvalvular obstruction of either ventricle may also cause such a midsystolic murmur, the intensity being related to the flow rate.

The murmur of aortic stenosis is the prototype of the left-sided midsystolic murmur. The location and radiation of this murmur are influenced by the direction of the high-velocity jet within the aortic root. In *valvular aortic stenosis*, the murmur is usually maximal in the second right intercostal space, with radiation into the neck. In *supravalvular aortic stenosis*, the murmur is occasionally loudest even higher, with disproportionate radiation into the right carotid artery. In hypertrophic cardiomyopathy, the midsystolic murmur originates in the left ventricular cavity and is usually maximal at the lower left sternal edge and apex, with relatively little radiation to the carotids. When the aortic valve is immobile (calcified), the aortic closure sound (A_2) may be soft and inaudible so that the length and configuration of the murmur are difficult to determine. Midsystolic murmurs also occur in patients with mitral regurgitation or, less frequently, tricuspid regurgitation resulting from papillary muscle dysfunction. Such murmurs due to mitral regurgitation are often confused with those originating in the aorta, particularly in elderly patients.

The patient's age and the area of maximal intensity aid in determining the significance of midsystolic murmurs. Thus, in a young adult with a thin chest and a high velocity of blood flow, a faint or moderate midsystolic murmur heard only in the pulmonic area is usually without clinical significance, while a somewhat louder murmur in the aortic area may indicate congenital aortic stenosis. In elderly patients, pulmonic flow murmurs are

rare, while aortic systolic murmurs are common and may be due to aortic dilation, to a significant degree of valvular aortic stenosis, or to nonstenotic thickening of the aortic valve leaflets. Midsystolic aortic and pulmonic murmurs are intensified after amyl nitrite inhalation and during the cardiac cycle following a premature ventricular beat, while those due to mitral regurgitation are unchanged or softer. Aortic systolic murmurs are diminished by interventions that increase aortic impedance, such as transient arterial occlusion. Echocardiography or cardiac catheterization may be necessary to separate a prominent and exaggerated functional murmur from one due to congenital or acquired semilunar valve stenosis.

Early systolic murmurs begin with the first heart sound and end in midsystole. In *large ventricular septal defects with pulmonary hypertension*, the shunting at the end of systole may be small or absent, resulting in an early systolic murmur. A similar murmur may occur with very *small muscular ventricular septal defects*, the shunt being interrupted in late systole. An early systolic murmur is a feature of *tricuspid regurgitation occurring in the absence of pulmonary hypertension*. This lesion is common in narcotics abusers with infective endocarditis, in whom a tall regurgitant right atrial *v* wave reaches the level of the normal right ventricular pressure in late systole, confining the murmur to early systole. Patients with acute mitral regurgitation into a noncompliant left atrium and a large *v* wave often have a loud early systolic murmur that diminishes as the pressure gradient between the left ventricle and left atrium decreases in late systole (Chap. 236).

Late systolic murmurs are faint or moderately loud, high-pitched apical murmurs that start well after ejection and do not mask either heart sound. They are probably related to papillary muscle dysfunction caused by infarction or ischemia of these muscles or to their distortion by left ventricular dilation. They may appear only during angina but are common in patients with myocardial infarction or diffuse myocardial disease. Late systolic murmurs following midsystolic clicks are due to late systolic mitral regurgitation caused by prolapse of the mitral valve into the left atrium (Chap. 236).

Diastolic Murmurs *Early diastolic murmurs* (Fig. 225-4) begin with or shortly after S_2, as soon as the corresponding ventricular pressure falls enough below that in the aorta or pulmonary artery. The high-pitched murmurs of aortic regurgitation or of pulmonic regurgitation due to pulmonary hypertension are generally decrescendo, since there is a progressive decline in the volume or rate of regurgitation during diastole. Faint, high-pitched murmurs of aortic regurgitation are difficult to hear unless they are specifically sought by applying firm pressure with the diaphragm over the left midsternal border while the patient sits leaning forward and holds a breath in full expiration. The diastolic murmur of aortic regurgitation is enhanced by an acute elevation of the arterial pressure, such as occurs with handgrip exercise; it diminishes with a decrease in arterial pressure, as with amyl nitrite inhalation. The diastolic murmur of congenital pulmonic regurgitation without pulmonary hypertension is low- to medium-pitched. The onset of this murmur is delayed because the regurgitant flow is minimal at the onset of pulmonic valve closure when the reverse pressure gradient responsible for the regurgitation is negligible.

Middiastolic murmurs usually arise from the mitral or tricuspid valves (Fig. 225-4), occur during early ventricular filling, and are due to disproportion between valve orifice size and flow rate. Such murmurs may be quite loud (grade III), despite only slightAV valve

stenosis, when there is normal or increased blood flow. Conversely, the murmurs may be soft or even absent despite severe obstruction if the cardiac output is markedly reduced. When stenosis is marked, the diastolic murmur is prolonged, and the duration of the murmur is more reliable than its intensity as an index of the severity of valve obstruction.

The low-pitched, middiastolic murmur of mitral stenosis characteristically follows the OS. It should be specifically sought by placing the bell of the stethoscope at the site of the left ventricular impulse, which is best localized with the patient on the left side. Frequently, the murmur of mitral stenosis is present only at the left ventricular apex, and it may be increased in intensity by mild supine exercise or by inhalation of amyl nitrite. In tricuspid stenosis, the middiastolic murmur is localized to a relatively limited area along the left sternal edge and may be louder during inspiration.

Middiastolic murmurs may be generated across the mitral valve in cases of mitral regurgitation, patent ductus arteriosus, or ventricular septal defect, and across the tricuspid valve in cases of tricuspid regurgitation or atrial septal defect. These murmurs are related to the torrential flow across anAVvalve, usually follow an S_3, and tend to occur with large left-to-right shunts or severe AV valve regurgitation. A soft middiastolic murmur may sometimes be heard in patients with acute rheumatic fever (Carey-Coombs murmur). It has been attributed to inflammation of the mitral valve cusps or excessive left atrial blood flow as a consequence of mitral regurgitation.

In acute, severe aortic regurgitation, the left ventricular diastolic pressure may exceed the left atrial pressure, resulting in a middiastolic murmur due to "diastolic mitral regurgitation." In severe, chronic aortic regurgitation, a murmur is frequently present that may be either middiastolic or presystolic (Austin-Flint murmur). This murmur appears to originate at the anterior mitral valve leaflet when blood enters the left ventricle simultaneously from both the aortic root and the left atrium.

Presystolic murmurs begin during the period of ventricular filling that follows atrial contraction and therefore occur in sinus rhythm. They are usually due toAV valve stenosis and have the same quality as the middiastolic filling rumble, but they are usually crescendo, reaching peak intensity at the time of a loud S_1. The presystolic murmur corresponds to the AV valve gradient, which may be minimal until the moment of right or left atrial contraction. It is the presystolic murmur that is most characteristic of tricuspid stenosis and sinus rhythm. A right or left *atrial myxoma* may occasionally cause either middiastolic or presystolic murmurs that resemble the murmurs of mitral or tricuspid stenosis.

Continuous Murmurs These begin in systole, peak near S_2, and continue into all or part of diastole. These murmurs result from continuous flow due to a communication between high- and low-pressure areas that persists through the end of systole and the beginning of diastole. A *patent ductus arteriosus* causes a continuous murmur as long as the pressure in the pulmonary artery is much below that in the aorta. The murmur is intensified by elevation of the systemic arterial pressure and is reduced by amyl nitrite inhalation. When pulmonary hypertension is present, the diastolic portion may disappear, leaving the murmur confined to systole. A continuous murmur is uncommon in cases of aortopulmonary septal defect, which usually is associated with severe

pulmonary hypertension. Surgically produced connections and the subclavian-pulmonary artery anastomosis result in murmurs similar to that of a patent ductus.

Continuous murmurs may result from congenital or acquired *systemic arteriovenous fistula*, *coronary arteriovenous fistula*, anomalous origin of the left coronary artery from the pulmonary artery, and communications between the *sinus of Valsalva and the right side of the heart*. Continuous murmurs may also occur in patients with a small atrial septal defect with a high left atrial pressure. Murmurs associated with *pulmonary arteriovenous fistulas* may be continuous but are usually only systolic. Continuous murmurs may also be due to disturbances of flow pattern in constricted systemic (e.g., renal) or pulmonary arteries when marked pressure differences between the two sides of the narrow segment persist; a continuous murmur in the back may be present in *coarctation of the aorta*; *pulmonary embolism* may cause continuous murmurs in partially occluded vessels.

In nonconstricted arteries, continuous murmurs may be due to rapid flow through a tortuous bed. Such murmurs typically occur within the bronchial arterial collateral circulation in cyanotic patients with severe pulmonary outflow obstruction. The "mammary souffle," an innocent murmur heard over the breasts during late pregnancy and in the early postpartum period, may be systolic or continuous. The innocent cervical venous hum is a continuous murmur usually audible over the medial aspect of the right supraclavicular fossa with the patient upright. The hum is usually louder during diastole and can be abolished instantaneously by digital compression of the ipsilateral internal jugular vein. Transmission of a loud venous hum to the area below the clavicles may result in a mistaken diagnosis of patent ductus arteriosus.

Pericardial Friction Rub These adventitious sounds may have presystolic, systolic, and early diastolic scratchy components, may be confused with a murmur or extracardiac sound when heard only in systole. It is best appreciated with the patient upright and leaning forward and may be accentuated during inspiration.

The evaluation of the patient with a heart murmur may vary greatly depending on many of the considerations discussed above. These include the intensity of the cardiac murmur, its timing in the cardiac cycle, its location and radiation, and its response to various physiologic maneuvers. Also of importance are the presence or absence of cardiac and noncardiac symptoms and whether other cardiac or noncardiac physical findings suggest that the cardiac murmur is clinically significant. The skill and confidence of the cardiac auscultator, the relative costs of various diagnostic approaches, and the accuracy and reliability of additional tests in the laboratory where they are performed are also important factors. One systematic approach to the patient with a heart murmur is depicted inFig. 34-3. This algorithm is particularly applicable to children and adults under age 40.

(Bibliography omitted in Palm version)

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226. ELECTROCARDIOGRAPHY - *Ary L. Goldberger*

The electrocardiogram (ECG or EKG) is a graphic recording of electric potentials generated by the heart. The signals are detected by means of metal electrodes attached to the extremities and chest wall and are then amplified and recorded by the electrocardiograph. ECG *leads* actually display the instantaneous *differences* in potential between these electrodes.

The clinical utility of theECGderives from its immediate availability as a noninvasive, inexpensive, and highly versatile test. In addition to its use in detecting arrhythmias, conduction disturbances, and myocardial ischemia, electrocardiography may reveal other findings related to life-threatening metabolic disturbances (e.g., hyperkalemia) or increased susceptibility to sudden cardiac death (e.g., QT prolongation syndromes). The advent of coronary thrombolysis or angioplasty in the early therapy of acute myocardial infarction (Chap. 243) has refocused particular attention on the sensitivity and specificity of ECG signs of myocardial ischemia.

ELECTROPHYSIOLOGY (See alsoChaps. 229 and230)

Depolarization of the heart is the initiating event for cardiac contraction. The electric currents that spread through the heart are produced by three components: cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself. TheECG, however, records only the depolarization (stimulation) and repolarization (recovery) potentials generated by the atrial and ventricular myocardium. Under resting conditions, myocardial cells are *polarized*; that is, they carry an electric charge on their surface due to transmembrane ion concentration differences. The charge measured across atrial and ventricular cell membranes is about 90 mV, with the inside negative relative to the outside. When these cells are stimulated above a critical threshold potential, they rapidly depolarize and transiently reverse their membrane polarity. This depolarization process spreads in a wavelike manner through the atria and ventricles. The return of myocardial fibers to their original resting state occurs during repolarization.

The depolarization stimulus for the normal heartbeat originates in the sinoatrial (SA) *node* (Fig. 226-1) or *sinus node*, a collection of *pacemaker* cells. These cells fire spontaneously; that is, they exhibit *automaticity*. The first phase of cardiac electrical activation is the spread of the depolarization wave through the right and left atria, followed by atrial contraction. Next, the impulse stimulates pacemaker and specialized conduction tissues in the atrioventricular (AV) nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His bifurcates into two main branches, the right and left bundles, which rapidly transmit depolarization wavefronts to the right and left ventricular myocardium by way of Purkinje fibers. The main left bundle bifurcates into two primary subdivisions, a left anterior fascicle and a left posterior fascicle. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering ventricular contraction.

Since the cardiac depolarization and repolarization waves have direction and magnitude, they can be represented by vectors. *Vectorcardiograms* that measure and display these instantaneous potentials are no longer used much in clinical practice. However, the general principles of vector analysis remain fundamental to understanding

the genesis of normal and pathologicECGwaveforms. Vector analysis illustrates a central concept of electrocardiography -- that the ECG records the complex spatial and temporal summation of electrical potentials from multiple myocardial fibers conducted to the surface of the body. This principle accounts for inherent limitations in both ECG *sensitivity* (activity from certain cardiac regions may be canceled out or may be too weak to be recorded) and *specificity* (the same vectorial sum can result from either a selective gain or a loss of forces in opposite directions).

ECG WAVEFORMS AND INTERVALS

TheECGwaveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization (Fig. 226-2). The QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization is usually too low in amplitude to be detected, but it may become apparent in such conditions as acute pericarditis or atrial infarction.

The QRS-T waveforms of the surface (extracellular)ECGcorrespond in a general way with the different phases of simultaneously obtained ventricular *action potentials*, the intracellular recordings from single myocardial fibers (Fig. 226-3) (Chap. 229). The rapid upstroke (phase 0) of the action potential corresponds to the onset of QRS. The plateau (phase 2) corresponds to the isoelectric ST segment, and active repolarization (phase 3) to the inscription of the T wave. Factors that decrease the slope of phase 0 by impairing the influx of Na^+(e.g., drugs such as quinidine or procainamide, or hyperkalemia) tend to increase QRS duration. Conditions that prolong phase 2 (amiodarone, hypocalcemia) increase the QT interval. In contrast, shortening of ventricular repolarization (phase 2), as by digitalis or hypercalcemia, abbreviates the ST segment.

The electrocardiogram is ordinarily recorded on special graph paper which is divided into 1-mm^2gridlike boxes (Fig. 226-4). Since theECGpaper speed is generally 25 mm/s, the smallest (1 mm) horizontal divisions correspond to 0.04 s (40 ms), with heavier lines at intervals of 0.20 s (200 ms). Vertically, the ECG graph measures the amplitude of a given wave or deflection (1 mV = 10 mm with standard calibration; the voltage criteria for hypertrophy mentioned below are given in millimeters). There are four major ECG intervals: R-R, PR, QRS, and QT (Fig. 226-2). The heart rate (beats per minute) can be readily computed from the interbeat (R-R) interval by dividing the number of large (0.20 s) time units between consecutive R waves into 300 or the number of small (0.04 s) units into 1500. The PR interval measures the time (normally 120 to 200 ms) between atrial and ventricular depolarization, which includes the physiologic delay imposed by stimulation of cells in theAVjunction area. The QRS interval (normally 100 ms or less) reflects the duration of ventricular depolarization. The QT interval includes both ventricular depolarization and repolarization times and varies inversely with the heart rate. A rate-related ("corrected") QT interval, QT_c, can be calculated as and normally is£0.44s.

The QRS complex is subdivided into specific deflections or waves. If the initial QRS deflection in a given lead is negative, it is termed a *Q wave*; the first positive deflection

is termed an *R wave*. A negative deflection after an R wave is an *S wave*. Subsequent positive or negative waves are labeled R¢ and S¢, respectively. Lowercase letters (qrs) are used for waves of relatively small amplitude. An entirely negative QRS complex is termed a *QS wave*.

ECG LEADS

The 12 conventionalECGleads record the difference in potential between electrodes placed on the surface of the body. These leads are divided into two groups: six extremity (limb) leads and six chest (precordial) leads. The extremity leads record potentials transmitted onto the *frontal plane* (Fig. 226-5*A*), and the chest leads record potentials transmitted onto the *horizontal plane* (Fig. 226-5*B*). The six extremity leads are further subdivided into three *bipolar* leads (I, II, and III) and three *unipolar* leads (aVR, aVL, and aVF). Each bipolar lead measures the difference in potential between electrodes at two extremities: lead I= left arm-right arm voltages, lead II= left leg-right arm, and lead III= left leg-left arm. The unipolar leads measure the voltage (V) at one locus relative to an electrode (called the *central terminal* or *indifferent electrode*) that has approximately zero potential. Thus, aVR = right arm, aVL= left arm, and aVF = left leg (foot). The lowercase *a* indicates that these unipolar potentials are electrically augmented by 50 percent. The right leg electrode functions as a ground. The spatial orientation and polarity of the six frontal plane leads is represented on the hexaxial diagram (Fig. 226-6).

The six chest leads (Fig. 226-7) are unipolar recordings obtained by electrodes in the following positions: lead V_1, fourth intercostal space, just to the right of the sternum; lead V_2, fourth intercostal space, just to the left of the sternum; lead V_3, midway between V_2 and V_4; lead V_4, midclavicular line, fifth intercostal space; lead V_5, anterior axillary line, same level as V_4; and lead V_6, midaxillary line, same level as V_4 and V_5.

Together, the frontal and horizontal plane electrodes provide a three-dimensional representation of cardiac electrical activity. Each lead can be likened to a different camera angle "looking" at the same events -- atrial and ventricular depolarization and repolarization -- from different spatial orientations. The conventional 12-leadECG can be supplemented with additional leads under special circumstances. For example, right precordial leads V_3R, V_4R, etc. are useful in detecting evidence of acute right ventricular ischemia. Esophageal leads may reveal atrial activity not detectable on the surface ECG. Bedside telemetry units and ambulatory ECG (Holter) recordings usually employ only one or two modified leads, respectively.**Intracardiac electrocardiography and electrophysiologic testing are discussed in Chaps. 229 and 230.*

TheECGleads are configured so that a positive (upright) deflection is recorded in a lead if a wave of depolarization spreads toward the positive pole of that lead, and a negative deflection if the wave spreads toward the negative pole. If the mean orientation of the depolarization vector is at right angles to a given lead axis, a biphasic (equally positive and negative) deflection will be recorded.

GENESIS OF THE NORMAL ECG

P WAVE

The normal atrial depolarization vector is oriented downward and toward the subject's left, reflecting the spread of depolarization from the sinus node to the right and then the left atrial myocardium. Since this vector points toward the positive pole of lead II and toward the negative pole of lead aVR, the normal P wave will be positive in lead II and negative in lead aVR. By contrast, activation of the atria from an ectopic pacemaker in the lower part of either atrium or in theAVjunction region may produce retrograde P waves (negative in lead II, positive in lead aVR).

QRS COMPLEX

Normal ventricular depolarization proceeds as a rapid, continuous spread of activation wavefronts. This complex process can be divided into two major, sequential phases, and each phase can be represented by a mean vector (Fig. 226-8). The first phase is depolarization of the interventricular septum from the left to the right (vector 1). The second results from the simultaneous depolarization of the main mass of the right and left ventricles; it is normally dominated by the more massive left ventricle, so that vector 2 points leftward and posteriorly. Therefore, a right precordial lead (V_1) will record this biphasic depolarization process with a small positive deflection (septal r wave) followed by a larger negative deflection (S wave). A left precordial lead, e.g., V_6, will record the same sequence with a small negative deflection (septal q wave) followed by a relatively tall positive deflection (R wave). Intermediate leads show a relative increase in R-wave amplitude (normal R-wave progression) and a decrease in S-wave amplitude progressing across the chest from the right to left. The precordial lead where the R and S waves are of approximately equal amplitude is referred to as the *transition zone* (usually V_3 or V_4) (Fig. 226-9).

The QRS pattern in the extremity leads may vary considerably from one normal subject to another depending on the *electrical axis* of the QRS, which describes the mean orientation of the QRS vector with reference to the six frontal plane leads. Normally, the QRS axis ranges from -30° to + 100°(Fig. 226-6). An axis more negative than- 30° is referred to as *left axis deviation*, while an axis more positive than + 100° is referred to as *right axis deviation*. Left axis deviation may occur as a normal variant but is more commonly associated with left ventricular hypertrophy, a block in the anterior fascicle of the left bundle system (left anterior fascicular block or hemiblock), or inferior myocardial infarction. Right axis deviation also may occur as a normal variant (particularly in children and young adults), as a spurious finding due to reversal of the left and right arm electrodes, or in conditions such as right ventricular overload (acute or chronic), infarction of the lateral wall of the left ventricle, dextrocardia, left pneumothorax, or left posterior fascicular block.

T WAVE AND U WAVE

Normally, the mean T-wave vector is oriented roughly concordant with the mean QRS vector. Since depolarization and repolarization are electrically opposite processes, this normal QRS-T-wave vector concordance indicates that repolarization must normally proceed in the reverse direction from depolarization (i.e., from ventricular epicardium to endocardium). The normal U wave is a small, rounded deflection (£1 mm) that follows the T wave and usually has the same polarity as the T wave. An abnormal increase in

U-wave amplitude is most commonly due to drugs (e.g., quinidine, procainamide, disopyramide) or hypokalemia. Very prominent U waves are a marker of increased susceptibility to the *torsades de pointes* type of ventricular tachycardia (Chap. 230). Inversion of the U wave in the precordial leads is abnormal and may be a subtle sign of ischemia.

MAJOR ECG ABNORMALITIES

CARDIAC ENLARGEMENT AND HYPERTROPHY

Right atrial overload (acute or chronic) may lead to an increase in P-wave amplitude (³2.5 mm) (Fig. 226-10). Left atrial overload typically produces a biphasic P wave in V_1 with a broad negative component or a broad (³120 ms), often notched P wave in one or more limb leads (Fig. 226-10). This pattern also may occur with left atrial conduction delays in the absence of actual atrial enlargement, leading to the more general designation of *left atrial abnormality*.

Right ventricular hypertrophy due to a pressure load (as from pulmonic valve stenosis or pulmonary artery hypertension) is characterized by a relatively tall R wave in lead V_1 (R³ S wave), usually with right axis deviation (Fig. 226-11); alternatively, there may be a qR pattern in V_1 or V_3R. ST depression and T-wave inversion in the right to midprecordial leads are also often present. This so-called ventricular strain pattern is attributed to repolarization abnormalities in hypertrophied muscle. Right ventricular hypertrophy due to ostium secundum-type atrial septal defects, with the accompanying right ventricular volume overload, is commonly associated with an incomplete or complete right bundle branch block pattern with a rightward QRS axis.

Acute cor pulmonale due to pulmonary embolism (Chap. 261) for example, may be associated with a normalECG or a variety of abnormalities. Sinus tachycardia is the most common arrhythmia, although other tachyarrhythmias, such as atrial fibrillation or flutter, may occur. The QRS axis may shift to the right, sometimes in concert with the so-called $S_1Q_3T_3$pattern (prominence of the S wave in lead I, Q wave in lead III, with T-wave inversion in lead III). Acute right ventricular dilation also may be associated with poor R-wave progression and T-wave inversions in V_1 to V_4(right ventricular "strain") simulating acute anterior infarction. A right ventricular conduction disturbance may appear.

Chronic cor pulmonale due to obstructive lung disease (Chap. 237) usually does not produce the classicECGpatterns of right ventricular hypertrophy noted above. Instead of tall right precordial R waves, chronic lung disease more typically is associated with small R waves in right to midprecordial leads (poor R-wave progression) due in part to downward displacement of the diaphragm and the heart. Low-voltage complexes are commonly present, owing to hyperaeration of the lungs.

A number of different voltage criteria for *left ventricular hypertrophy* (Fig. 226-11) have been proposed on the basis of the presence of tall left precordial R waves and deep right precordial S waves [e.g., SV_1 + (RV_5 or RV_6)³ 35 mm; or (RV_5 or RV_6)³ 25 mm]. Repolarization abnormalities (ST depression with T-wave inversions) also may appear (left ventricular "strain" pattern) in leads with prominent R waves. However, prominent

precordial voltages may occur as a normal variant, especially in athletic or thin-chested individuals. Left ventricular hypertrophy may increase limb lead voltage (e.g., RaVL ³ 11 to 13 mm, RaVF³ 20 mm; R_I + S_{III}³ 25 mm) with or without increased precordial voltage. The presence of left atrial abnormality increases the likelihood of underlying left ventricular hypertrophy in cases with borderline voltage criteria. Left ventricular hypertrophy often progresses to incomplete or complete left bundle branch block. The sensitivity of conventional voltage criteria for left ventricular hypertrophy is decreased in obese persons and in women.ECGevidence for left ventricular hypertrophy is a major noninvasive marker of increased risk of cardiovascular morbidity and mortality, including sudden cardiac death. However, because of false-positive and false-negative diagnoses, the ECG is of limited utility in diagnosing atrial or ventricular enlargement. More definitive information is provided by echocardiography (Chap. 227).

BUNDLE BRANCH BLOCKS

Intrinsic impairment of conduction in either the right or left bundle system (intraventricular conduction disturbances) leads to prolongation of the QRS interval. With complete bundle branch blocks the QRS interval is³ 120 ms in duration; with incomplete blocks the QRS interval is between 100 and 120 ms. The QRS vector is usually oriented in the direction of the myocardial region where depolarization is delayed (Fig. 226-12). Thus, with right bundle branch block, the terminal QRS vector is oriented anteriorly and to the right (rSR¢ in V_1 and qRS in V_6, typically). Left bundle branch block alters both early and later phases of ventricular depolarization. The major QRS vector is directed to the left and posteriorly. In addition, the normal early left-to-right pattern of septal activation is disrupted such that septal depolarization proceeds from right to left as well. As a result, left bundle branch block generates wide, predominantly negative (QS) complexes in lead V_1 and entirely positive (R) complexes in lead V_6. A pattern identical to that of left bundle branch block, preceded by a sharp spike, is seen in most cases of electronic right ventricular pacing because of the relative delay in left ventricular activation.

Bundle branch block may occur in a variety of conditions. In subjects without structural heart disease, right bundle branch block is seen more commonly than left bundle branch block. Right bundle branch block also occurs with heart disease, both congenital (e.g., atrial septal defect) and acquired (e.g., valvular, ischemic). Left bundle branch block is often a marker of one of four underlying conditions: ischemic heart disease, long-standing hypertension, severe aortic valve disease, and cardiomyopathy. Bundle branch blocks may be chronic or intermittent. A bundle branch block may be rate-related; for example, often it occurs when the heart rate exceeds some critical value.

Bundle branch blocks and depolarization abnormalities secondary to artificial pacemakers not only affect ventricular depolarization (QRS) but are also characteristically associated with *secondary repolarization* (ST-T) abnormalities. With bundle branch blocks, the T-wave is typically opposite in polarity to the last deflection of the QRS (Fig. 226-12). This discordance of the QRS-T-wave vectors is caused by the altered sequence of repolarization that occurs secondary to altered depolarization. In contrast, *primary repolarization* abnormalities are independent of QRS changes and are related instead to actual alterations in the electrical properties of the myocardial fibers

themselves (for example, in the resting membrane potential or action potential duration), not just to changes in the sequence of repolarization. Ischemia, electrolyte imbalance, and drugs such as digitalis all cause such primary ST-T-wave changes. Primary and secondary T-wave changes may coexist. For example, T-wave inversions in the right precordial leads with left bundle branch block or in the left precordial leads with right bundle branch block may be important markers of underlying ischemia or other abnormalities.

Partial blocks ("hemiblocks") in the left bundle system (left anterior or posterior fascicular blocks) generally do not prolong the QRS duration substantially but instead are associated with shifts in the frontal plane QRS axis (leftward or rightward, respectively). More complex combinations of fascicular and bundle branch blocks may occur involving the left and right bundle system. Examples of *bifascicular block* include right bundle branch block and left posterior fascicular block, right bundle branch block with left anterior fascicular block, and complete left bundle branch block. Chronic bifascicular block in an asymptomatic individual is associated with a relatively low risk of progression to high-degreeAV heart block. In contrast, new bifascicular block with acute anterior myocardial infarction carries a much greater risk of complete heart block. Alternation of right and left bundle branch block is a sign of *trifascicular disease*. However, the presence of a prolonged PR interval and bifascicular block does not necessarily indicate trifascicular involvement, since this combination may arise with AV node disease and bifascicular block. Intraventricular conduction delays also can be caused by extrinsic (toxic) factors that slow ventricular conduction, particularly hyperkalemia or drugs (type 1 antiarrhythmic agents, tricyclic antidepressants, phenothiazines).

Prolongation of QRS duration does not necessarily indicate a conduction delay but may be due to *preexcitation* of the ventricles via a bypass tract, as in the Wolff-Parkinson-White (WPW) syndrome (Chap. 230) and related variants. The diagnostic triad of WPW consists of a wide QRS complex associated with a relatively short PR interval and slurring of the initial part of the QRS (delta wave), the latter effect due to aberrant activation of ventricular myocardium. The presence of a bypass tract predisposes to reentrant supraventricular tachyarrhythmias (Chap. 230).

MYOCARDIAL ISCHEMIA AND INFARCTION (See alsoChap. 243)

TheECG is a cornerstone in the diagnosis of acute and chronic ischemic heart disease. The findings depend on several key factors: the nature of the process [reversible (i.e., ischemia) versus irreversible (i.e., infarction)], the duration (acute versus chronic), extent (transmural versus subendocardial), and localization (anterior versus inferoposterior), as well as the presence of other underlying abnormalities (ventricular hypertrophy, conduction defects).

Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between these regions. These so-called currents of injury are represented on the surfaceECG by deviation of the ST segment (Fig. 226-13). When the acute ischemia is *transmural*, the

ST vector is usually shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the *subendocardium*, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying (e.g., anterior precordial) leads show ST-segment depression (with ST elevation in lead aVR). Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. From a clinical viewpoint, the division of acute myocardial infarction into ST segment elevation and non-ST elevation (NSTEMI) types is useful since the efficacy of acute reperfusion therapy is limited to the former group (Chap. 243).

TheECGleads are more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior wall ischemia is reflected by ST elevations or increased T-wave positivity (Fig. 226-14) in one or more of the precordial leads (V_1 to V_6) and leads I and aVL. Anteroseptal ischemia produces these changes in leads V_1 to V_3, apical or lateral ischemia in leads V_4 to V_6. Transmural inferior wall ischemia produces changes in leads II, III, and aVF. Posterior wall ischemia may be indirectly recognized by *reciprocal* ST depressions in leads V_1 to V_3. Prominent reciprocal ST depressions in these leads also occur with certain inferior wall infarcts, particularly those with posterior or lateral wall extension. Right ventricular ischemia usually produces ST elevations in right-sided chest leads (Fig. 226-7). When ischemic ST elevations occur as the earliest sign of acute infarction, they are typically followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. (T-wave inversions due to evolving or chronic ischemia correlate with prolongation of repolarization and are often associated with QT lengthening.) Reversible transmural ischemia, for example, due to coronary vasospasm (Prinzmetal's variant angina), may cause transient ST-segment elevations without development of Q waves. Depending on the severity and duration of such ischemia, the ST elevations may either resolve completely in minutes or be followed by T-wave inversions that persist for hours or even days. Patients with ischemic chest pain who present with deep T-wave inversions in multiple precordial leads (e.g., V_1 to V_4) with or without cardiac enzyme elevations typically have severe obstruction in the left anterior descending coronary artery system (Fig. 226-15). In contrast, patients whose baseline ECG already shows abnormal T-wave inversions may develop T-wave normalization (pseudonormalization) during episodes of acute transmural ischemia.

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or frank abnormal Q waves in the anterior or inferior leads (Fig. 226-16). Previously, abnormal Q waves were considered to be markers of transmural myocardial infarction, while subendocardial infarcts were thought not to produce Q waves. However, carefulECG-pathology correlative studies have indicated that transmural infarcts may occur without Q waves and that subendocardial (nontransmural) infarcts may sometimes be associated with Q waves. Therefore, infarcts are more appropriately classified as "Q-wave" or "non-Q-wave." The major acute ECG changes in syndromes of ischemic heart disease are schematically summarized inFig. 226-17. Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V_1 and V_2without diagnostic Q waves in any of

the conventional leads. Atrial infarction may be associated with PR-segment deviations due to an atrial current of injury, changes in P-wave morphology, or atrial arrhythmias. In the weeks and months following infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG following Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm.

ECGchanges due to ischemia may occur spontaneously or may be provoked by various exercise protocols (stress electrocardiography) (Chap. 244). In patients with severe ischemic heart disease, exercise testing is most likely to elicit signs of subendocardial ischemia (horizontal or downsloping ST depression in multiple leads). ST-segment elevation during exercise is most often observed after a Q-wave infarct. This repolarization change does not necessarily indicate active ischemia but correlates strongly with the presence of an underlying ventricular wall motion abnormality. However, in patients *without* prior infarction, transient ST-segment elevation with exercise is a reliable sign of transmural ischemia.

TheECG has important limitations in both sensitivity and specificity in the diagnosis of ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG *throughout* the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes, therefore, should always prompt a careful search for other noncoronary causes of chest pain (Chap. 13). Furthermore, the diagnostic changes of acute or evolving ischemia are often masked by the presence of left bundle branch block, electronic ventricular pacemaker patterns, andWPWpreexcitation. On the other hand, clinicians may overdiagnose ischemia or infarction based on the presence of ST-segment elevations or depressions, T-wave inversions, tall positive T waves, or Q waves *not* related to ischemic heart disease (pseudoinfarct patterns). For example, ST-segment elevations simulating ischemia may occur with acute pericarditis (Fig. 226-18) or myocarditis, or as a normal variant ("early repolarization" pattern). Similarly, tall, positive T waves do not invariably represent hyperacute ischemic changes but also may be caused by normal variants, hyperkalemia, cerebrovascular injury, and left ventricular volume overload due to mitral or aortic regurgitation, among other causes. ST-segment elevations and tall, positive T waves are common findings in leads V_1 and V_2 in left bundle branch block or left ventricular hypertrophy in the absence of ischemia. The differential diagnosis of Q waves (Table 226-1) includes physiologic or positional variants, ventricular hypertrophy, acute or chronic noncoronary myocardial injury, hypertrophic cardiomyopathy, and ventricular conduction disorders. Digitalis, ventricular hypertrophy, hypokalemia, and a variety of other factors may cause ST-segment depression mimicking subendocardial ischemia. Prominent T-wave inversion may occur with ventricular hypertrophy, cardiomyopathy, myocarditis, and cerebrovascular injury (particularly intracranial bleeds;Fig. 226-19), among many other conditions.

METABOLIC FACTORS AND DRUG EFFECTS

A variety of metabolic and pharmacologic agents alter theECG and, in particular, cause changes in repolarization (ST-T-U) and sometimes QRS prolongation. Certain

life-threatening electrolyte disturbances may be diagnosed initially and monitored from the ECG. *Hyperkalemia* produces a sequence of changes usually beginning with narrowing and peaking (tenting) of the T waves. Further elevation of extracellular K^+ leads to AVconduction disturbances, diminution in P-wave amplitude, and widening of the QRS interval. Severe hyperkalemia eventually causes cardiac arrest with a slow sinusoidal type of mechanism ("sine-wave" pattern) followed by asystole. *Hypokalemia* (Fig. 226-19) prolongs ventricular repolarization, often with prominent U waves. Prolongation of the QT interval (Fig. 226-19) is also seen with drugs that increase the duration of the ventricular action potential -- type 1A antiarrhythmic agents and related drugs (e.g., quinidine, disopyramide, procainamide, tricyclic antidepressants, phenothiazines) and type III agents (amiodarone, sotalol). Marked QT prolongation, sometimes with deep, wide T-wave inversions, may occur with intracranial bleeds, particularly subarachnoid hemorrhage ("CVA T-wave" pattern) (Fig. 226-19). Systemic *hypothermia* (Fig. 226-19) also prolongs repolarization, usually with a distinctive convex elevation of the J point (Osborn wave). *Hypocalcemia* typically prolongs the QT interval (ST portion), while *hypercalcemia* shortens it (Fig. 226-20). Digitalis glycosides also shorten the QT interval, often with a characteristic "scooping" of the ST-T-wave complex (*digitalis effect*).

Many other factors are associated withECGchanges, particularly alterations in ventricular repolarization. T-wave flattening, minimal T-wave inversions or slight ST-segment depression ("nonspecific ST-T-wave changes") may occur with a variety of electrolyte and acid-base disturbances, a variety of infectious processes, central nervous system disorders, endocrine abnormalities, many drugs, ischemia, hypoxia, and virtually any type of cardiopulmonary abnormality. While subtle ST-T-wave changes may be markers of ischemia, transient nonspecific repolarization changes also may occur following a meal or with postural (orthostatic) change, hyperventilation, or exercise in healthy individuals.

ELECTRICAL ALTERNANS

Electrical alternans -- a beat-to-beat alternation in one or more components of theECGsignal -- is a common type of nonlinear cardiovascular response to a variety of perturbations. For example, total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign of pericardial effusion, often with cardiac tamponade. The mechanism relates to a periodic swinging motion of the heart in the effusion at a frequency exactly one-half the heart rate. ST-T alternans is a sign of electrical instability and may precede ventricular fibrillation.

CLINICAL INTERPRETATION OF THE ECG

Accurate analysis ofECGs requires thoroughness and care. The patient's age, gender, and clinical status should always be taken into account. For example, T-wave inversions in leads V_1 to V_3 are more likely to represent a normal variant in a healthy young adult woman ("persistent juvenile T-wave pattern") than in an elderly man with chest discomfort. Similarly, the likelihood that ST-segment depression during exercise testing represents ischemia depends partly on the prior probability of coronary artery disease.

Many mistakes inECGinterpretation are errors of omission. Therefore, a systematic

approach is desirable. The following 14 points should be analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts); (2) heart rate; (3) rhythm; (4) PR interval; (5) QRS interval; (6) QT interval; (7) P waves; (8) QRS voltages; (9) mean QRS electrical axis; (10) precordial R-wave progression; (11) abnormal Q waves; (12) ST segments; (13) T waves; (14) U waves.

Only after analyzing all these points should the interpretation be formulated. Where appropriate, important clinical correlates or inferences should be mentioned. For example, prolonged ventricular repolarization with prominent U waves should suggest hypokalemia or drug toxicity (e.g., due to quinidine or procainamide) (Fig. 226-19). The combination of left atrial abnormality (enlargement) and signs of right ventricular hypertrophy suggests mitral stenosis. Low voltage with sinus tachycardia raises the possibility of pericardial tamponade or chronic obstructive lung disease. Sinus tachycardia with QRS and QT (U) prolongation suggests tricyclic antidepressant overdose (Fig. 226-19). Comparison with previousECGs is essential.**The diagnosis and management of specific cardiac arrhythmias and conduction disturbances are discussed in Chaps. 229 and 230.*

COMPUTERIZED ELECTROCARDIOGRAPHY

ComputerizedECGsystems are increasingly used. Digital systems provide for convenient storage and immediate retrieval of thousands of ECG records. In recent years, computer programs for ECG analysis have become more reliable. However, despite these advances, computer interpretation of ECGs has important limitations. Incomplete or inaccurate readings are most likely with arrhythmias and complex abnormalities. Therefore, computerized interpretation (including measurements of basic ECG intervals) should not be accepted without careful physician review.

(Bibliography omitted in Palm version)

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227. NONINVASIVE CARDIAC IMAGING: ECHOCARDIOGRAPHY AND NUCLEAR CARDIOLOGY - *Rick A. Nishimura*, *Raymond J. Gibbons*, *A. Jamil Tajik*

Cardiovascular imaging has significantly enhanced the practice of cardiology over the past few decades. Two-dimensional echocardiography is able to visualize the heart directly in real time using ultrasound, providing instantaneous assessment of the myocardium, valves, pericardium, and great vessels. Doppler echocardiography measures the velocity of moving red blood cells and has become a noninvasive alternative to cardiac catheterization for assessment of hemodynamics. Transesophageal echocardiography has provided a new window for high-resolution imaging of posterior structures of the heart, particularly the left atrium, mitral valve, and aorta. Nuclear cardiology uses isotopes to assess myocardial perfusion and function and has contributed greatly to the evaluation of patients with ischemic heart disease. This**chapter**provides an overview of the basic concepts of both echocardiography and nuclear cardiology and the clinical indications for each procedure.

ECHOCARDIOGRAPHY

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Basic Principles Two-dimensional echocardiography uses the principle of ultrasound reflection off cardiac structures to produce images of the heart (Table 227-1). The imaging is performed from multiple acoustic windows with different transducer rotations so that the entire heart and great vessels can be displayed in real time and in various two-dimensional planes. Most information from a study is obtained from a visual analysis of the two-dimensional images. Some laboratories use a concomitant M-mode study (one-dimensional echocardiogram) derived from the two-dimensional image for objective measurements of chamber size and function. For a transthoracic echocardiogram, the imaging is performed with a hand-held transducer placed directly on the chest wall. In selected patients, a transesophageal echocardiogram may be performed, in which an ultrasound transducer is mounted on the tip of an endoscope placed in the esophagus and directed towards the cardiac structures, so that high-resolution images of the posterior structures are obtained.

The frequency of the ultrasound used in clinical practice is usually between 2.5 and 5.0 MHz. The images produced depend on the acoustic reflection of the ultrasound off the various structures. Ultrasound passes readily through liquid, such as blood or pericardial fluid, and these are displayed as black on the two-dimensional image. When ultrasound is reflected off more solid structures, such as the myocardium and valves, there is a gray scale display. Structures such as calcium produce intense acoustic reflection and are displayed as bright white on the two-dimensional image. In a standard echocardiographic examination, the images are obtained from parasternal, apical, subcostal, and suprasternal windows. Multiple transducer rotations and angulations from each window are used to ensure that all parts of the cardiac structures are imaged. Most echocardiographic studies are recorded on videotape for off-line analysis, but direct digital acquisition units are enhancing the ability for storage and retrieval of images.

Current echocardiographic machines are portable, which allows them to be wheeled

directly to the patient's bedside. Thus, a major advantage of echocardiography over other imaging modalities is the ability to obtain instantaneous images of the cardiac structures for immediate interpretation, even in emergency or trauma units or in critical care settings.

A limitation of a two-dimensional echocardiogram performed via a transthoracic approach is the inability to obtain high-quality images in all patients, especially those with a thick chest wall or severe lung disease. Ultrasound waves are poorly transmitted through lung parenchyma. In patients with inadequate transthoracic echocardiographic images, transesophageal echocardiography can be performed.

The diagnostic accuracy of an echocardiogram is highly dependent upon both the operator of the echocardiographic equipment and the interpreter of the study. There are many important technical aspects to obtaining and interpreting the two-dimensional images, requiring training, experience, and expertise.

Chamber Size and Function Two-dimensional echocardiography is an ideal imaging modality for assessing left ventricular size and function (Fig. 227-1). A qualitative assessment of the cavity size of the ventricle and systolic function can be made directly from the two-dimensional image by experienced observers (Fig. 227-2). Quantitative assessment of left ventricular size and function can be made by M-mode echocardiography (measuring systolic and diastolic dimensions of the short axis of the left ventricle) or quantitative two-dimensional echocardiography. With quantitative two-dimensional echocardiography, endocardial outlines of the left ventricular cavity are traced in systole and diastole and the left ventricular cavity areas are then fitted to computer models of the left ventricle to obtain systolic and diastolic volumes, making it more cumbersome and less reproducible than the M-mode method. However, the M-mode method can be used only in patients with symmetrically contracting ventricles, as the M-mode samples only the septum and free wall at the mid-ventricle level. The presence or absence of regional wall motion abnormalities can be visually assessed by examining endocardial motion as well as wall thickening. M-mode and two-dimensional echocardiography are useful in the diagnosis of left ventricular hypertrophy, seen as an increase in wall thickness. Other chamber sizes are assessed by visual analysis, including the left atrium and right-sided chambers. There is no method for quantitative analysis of right ventricular size and function by two-dimensional echocardiography, due to the complex geometry of the right ventricle.

Valve Abnormalities (See also Chap. 236) Valve morphology and motion can be visualized by two-dimensional echocardiography (Figs. 227-1 and 227-2). Leaflet thickness and mobility, valve calcification, and the appearance of subvalvular and supravalvular structures can be assessed. Valve stenosis is reliably diagnosed by the thickening and decreased mobility of the valve. Two-dimensional echocardiography is the "gold standard" for the diagnosis of mitral stenosis, which produces typical tethering and diastolic doming. The severity of the stenosis can be obtained from a direct planimeter measurement of the mitral valve orifice from the short axis view. The presence and etiology of stenosis of the semilunar valves can be made by two-dimensional echocardiography (Plate I-1). Estimating the severity of the stenosis by two-dimensional echocardiography alone is less reliable and requires Doppler echocardiography. The diagnosis of valvular regurgitation must be made by Doppler

echocardiography, but two-dimensional echocardiography is valuable for determining the etiology of the regurgitation. Annular dilatation, prolapse, flail leaflets, vegetation, and rheumatic involvement can be diagnosed and the left ventricular response to volume overload can be assessed by two-dimensional echocardiography.

Pericardial Disease (See also Chap. 239) Two-dimensional echocardiography is the imaging modality of choice for the detection of pericardial effusion, which is easily visualized as a black echo-lucent ovoid structure surrounding the heart. In the hemodynamically unstable patient with pericardial tamponade, typical echo findings of right ventricular collapse, right atrial collapse, and a dilated inferior vena cava are seen (seeFig. 239-1). In patients with subclinical tamponade, these two-dimensional echocardiographic features may not be present, but the diagnosis of elevated pericardial pressure can be made by Doppler findings of variations of inflow velocities with respiration (seeFigs. 239-2 and239-4). Echocardiographically guided pericardiocentesis has now become a standard of care. A two-dimensional echocardiogram can directly visualize the location of the pericardial fluid in relationship to the entry point, and this technique has led to a low complication rate. Increased thickness of the pericardium is difficult to assess by two-dimensional echocardiography. Subtle clues to pericardial constriction can be seen on two-dimensional echocardiography from enhanced ventricular interaction, but Doppler imaging is required for confirmation of this diagnosis.

Intracardiac Masses (See also Chap. 240) Intracardiac masses can be visualized on two-dimensional echocardiography, provided that image quality is adequate. Solid masses appear as echo-dense structures, which can be located inside the cardiac chambers or infiltrating into the myocardium or pericardium (see Fig. 240-1). Although an echocardiographic examination cannot provide pathologic confirmation of the etiology of a mass, there are several instances in which the diagnosis of the mass can be suspected from its appearance, mobility, and the concomitant abnormalities seen. *Left ventricular thrombus* appears as an echo-dense structure, usually in the apical region associated with regional wall motion abnormalities. The appearance and mobility of the thrombus are predictive of embolic events. *Atrial myxoma* can be diagnosed by the appearance of a well-circumscribed mobile mass with attachments to the atrial septum. Prominent benign structures, such as *lipomatous infiltration of the atrial septum* and a *calcified mitral annulus*, may appear as cardiac masses. The high-resolution images provided by transesophageal echocardiography may be required for further delineation of myocardial masses.

Aortic Disease (See alsoChap. 247) Two-dimensional echocardiography can provide information on diseases of the aorta. The proximal ascending aorta, the arch, and the distal descending aorta can usually be visualized via the transthoracic approach. For patients in whom a dilated aorta is well visualized, two-dimensional echocardiography can be used for serial follow-up. Aortic dissection can be diagnosed when an intimal flap is visualized on a transthoracic echocardiogram. However, the definitive diagnosis of an aortic dissection usually requires a transesophageal echocardiogram (Plate I-2).

DOPPLER ECHOCARDIOGRAPHY

Basic Principles Doppler echocardiography uses ultrasound reflecting off moving red

blood cells to measure the velocity of blood flow across valves, within cardiac chambers, and through the great vessels. Normal and abnormal blood flow patterns can be assessed noninvasively. Color flow Doppler imaging (Plates I-1 and I-2) displays the blood velocities in real time superimposed upon a two-dimensional echocardiographic image. The different colors indicate the direction of blood flow (blue towards and red away from the transducer), with green color superimposed when there is turbulent flow. Thus regurgitant lesions and shunts may be assessed by color flow Doppler. Pulsed-wave Doppler measures the blood flow velocity in a specific location on the two-dimensional echocardiographic image and displays the velocities in a spectral pattern using time as the *x*-axis. Continuous-wave Doppler echocardiography can measure high velocities of blood flow directed along the line of the Doppler beam, such as occur in the presence of valve stenosis, valve regurgitation, or intracardiac shunts. These high velocities can be used to determine intracardiac pressure gradients by a modified Bernoulli equation:

In this equation, the contribution from viscous friction and flow acceleration to the change in pressure is assumed to be negligible. The derived pressure gradient can be used to determine intracardiac pressures and stenosis severity.

Valve Gradients (See also Chap. 236) In the presence of valvular stenosis, there is an increase in the velocity of blood flow across the stenotic valve. A continuous-wave Doppler beam can be placed into this jet of blood, and the measured velocity used to determine an instantaneous gradient across the valve by applying the modified Bernoulli equation. Integration of this velocity over time provides an accurate measurement of the mean gradient across the valve. If the Doppler beam is directed parallel to the jet, the Doppler-derived valve gradient is accurate and reproducible and correlates with that obtained from cardiac catheterization. Since the valve gradient is dependent upon transvalvular flow, a valve area should be derived noninvasively. An accurate assessment of the mean gradient and valve area can be obtained in most patients, provided that the Doppler beam is parallel to the stenotic jet. The Doppler examination is highly operator-dependent, especially in patients with aortic stenosis. If the Doppler beam is not parallel to the stenotic jet, there may be a significant underestimation of the valve gradient. In patients with mitral stenosis, it is technically easier to align the Doppler beam with the stenotic jet; thus the mean transmitral gradient is usually accurate and reproducible. A Doppler-derived transmitral gradient may be more reliable than that obtained by conventional cardiac catheterization, given the inherent errors that may occur with a pulmonary artery wedge pressure measurement.

Valvular Regurgitation (See also Chap. 236) Valvular regurgitation is diagnosed by Doppler echocardiography when there is an abnormal retrograde flow across the valve. Color flow imaging is the Doppler method used most frequently to detect valve regurgitation by visualization of a high-velocity turbulent jet in the chamber proximal to the regurgitant valve. The sensitivity of Doppler echocardiography for the detection of regurgitant lesions is high, and even trivial or mild regurgitation in the absence of clinical auscultatory evidence of a regurgitant murmur may be detected. The size and extent of the color flow jet into the receiving cardiac chamber provide a qualitative estimate of the severity of regurgitation, but there are many limitations to using color jet size alone.

Indirect clues for the severity of valvular regurgitation are available from other Doppler interrogation sites (e.g., intensity of a continuous-wave signal, volume of forward flow across a regurgitant valve). Methods for quantitation of regurgitation severity are now available, such as the measurement of the proximal isovelocity surface area, and these may be employed for determining effective orifice area and regurgitant volumes. As with other quantitative Doppler measurements, these methods are operator-dependent, and reliable data require an experienced high-volume laboratory.

Intracardiac Pressures These can be calculated from the peak continuous-wave Doppler signal of a regurgitant lesion. The Bernoulli equation is applied to the peak velocity to obtain the pressure gradient between two cardiac chambers. This is commonly applied to a tricuspid regurgitant jet, from which the systolic pressure gradient between the right atrium and right ventricle can be calculated. Adding an assumed right atrial pressure to this gradient will give a derived right ventricular systolic pressure. Change in pressure over time during isovolumic contraction can be derived from a mitral regurgitation signal. This measurement provides an index of systolic contractility.

Cardiac Output Volume flow rates can be reliably measured noninvasively from Doppler echocardiography. Using the hydrodynamic principle of flow through a rigid tube, the volume of flow can be calculated from the area of an orifice through which blood flows multiplied by the time of the velocity. The most accurate site for this measurement is through the left ventricular outflow tract. The product of the outflow area and velocity provides a beat-to-beat measurement of stroke volume, which, when multiplied by heart rate, provides a measurement of cardiac output.

Diastolic Filling (See also Chap. 231) Doppler echocardiography allows noninvasive evaluation of ventricular diastolic filling. The transmitral velocity curves reflect the relative pressure gradients between the left atrium and left ventricle throughout the diastolic filling period. They are influenced by the rate of ventricular relaxation, the driving force across the valve, and the compliance of the left ventricle. There is a progression of diastolic dysfunction in disease states, which can be assessed by Doppler flow velocity curves (Fig. 227-3). In the early phase of diastolic dysfunction there is primarily an abnormality of relaxation, with decreased early transmitral flow and a compensatory increase in flow during atrial contraction. As disease progresses, there is a higher left atrial pressure and reduced compliance of the left ventricle, resulting in a higher early transmitral velocity and shortening of the deceleration of flow in early diastole, termed *restriction to filling*. These transmitral flow curves can be used to estimate ventricular filling pressures and to determine prognosis in certain disease entities. The addition of Doppler interrogation of pulmonary venous flow as well as right-sided chamber flow provides further information concerning the diastolic properties.

Congenital Heart Disease (See also Chap. 234) Doppler echocardiography has been useful in the evaluation of patients with congenital heart disease. Congenital stenotic or regurgitant valve lesions can be assessed. The detection and semiquantitation of intracardiac shunts is possible by Doppler echocardiography. Patency of surgical shunts and conduits can be determined.

STRESS ECHOCARDIOGRAPHY (See also Chap. 244)

Two-dimensional and Doppler echocardiography are usually performed in the resting state. Further information can be obtained by reimaging during either exercise or pharmacologic stress. The primary indications for stress echocardiography are to confirm the suspicion of coronary artery disease and estimate its severity. Doppler stress testing provides additional information for the patient with valvular heart disease.

The response of the myocardium to ischemia consists of a cascade of events. A decrease in systolic contraction of the ischemic area, termed a *regional wall motion abnormality*, occurs before symptoms or electrocardiographic changes. During a stress echocardiogram, two-dimensional echocardiographic images at rest and during stress are digitized and displayed in a side-by-side format so that induced regional wall motion abnormalities may be detected. Changes in overall systolic function as well as end-systolic volume are also assessed. New regional wall motion abnormalities, a decline in ejection fraction, and an increase in end-systolic volume with stress are all indicators of myocardial ischemia (Fig. 227-4).

Stress testing is usually done with exercise protocols using either upright treadmill or bicycle exercise. The echocardiographic imaging is done at baseline and then immediately after exercise. In patients who are not able to exercise, pharmacologic testing can be performed by infusing dobutamine, which increases myocardial oxygen demand. Dobutamine echocardiography has also been used to assess myocardial viability in patients with poor systolic function and concomitant coronary artery disease. In this type of study, dobutamine is given at a low dose of 5 to 10 ug/kg per minute. In the presence of viable myocardium, an increase in the systolic contraction of the myocardium is evident.

There are limitations to stress echocardiography. It is important that the images be obtained as soon as possible after exercise is stopped since regional wall motion abnormalities may dissipate rapidly with time. Optimal image quality is essential for proper interpretation, and this depends on not only patient habitus but also the ability of the sonographer to obtain the image. Interpretation of the images is highly operator-dependent, and thus this technique requires an experienced echocardiographer.

Doppler echocardiography can be used at rest and during exercise in patients with valvular heart disease to determine the hemodynamic response to stress. Gradients across stenotic valves can be measured at rest and immediately after exercise, which provides information previously obtained by right heart catheterization during exercise. Pulmonary pressures can be obtained from the tricuspid regurgitation velocities at rest and during exercise.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

This technique has provided a new window on the heart. Because of the close proximity of the esophagus to the heart, high-resolution images of posterior structures are consistently obtained. Transesophageal echocardiography should be performed when further information is required after comprehensive two-dimensional and Doppler

transthoracic echocardiograms. Diseases of the aorta, such as aortic dissection, can be readily diagnosed and quantitated by transesophageal echocardiography (Plate I-2;Chap. 247). Defining the source of embolism is a common indication for transesophageal echocardiography, as abnormalities such as atrial thrombi, patent foramen ovale, and aortic debris can be detected. Other masses, particularly those in the atria, can be visualized. The presence of vegetations for the diagnosis of infective endocarditis and its complications can be assessed by transesophageal echocardiography (Chap. 126). The evaluation of suspected abnormalities of a mitral prosthesis is an indication for transesophageal echocardiography, as the posterior imaging window will avoid the problems of acoustic reflection caused by the prosthetic valve seen with transthoracic echocardiography. Transesophageal echocardiography can be used during cardiac surgery to guide various operations, such as mitral valve repair and septal myectomy. When limited information is obtained from a transthoracic echocardiogram due to poor imaging windows, transesophageal echocardiography can be useful.

ADVANCES IN ECHOCARDIOGRAPHY

There are several areas of technological advances in the field of echocardiography. Digital conversion of images allows zoom functions and endless loop playback and facilitates storage and retrieval. Harmonic imaging is a technologic advance that may significantly improve image quality, particularly in patients with poor acoustic windows. Echo contrast agents containing microbubbles cause reflection of ultrasound waves and produce bright echo-dense images. Newer contrast agents have been developed that traverse the pulmonary circulation, entering the left-sided chambers from an intravenous injection. Two-dimensional echocardiographic imaging during the appearance of echo contrast in the left ventricle enhances definition of the endocardial border. The appearance of contrast directly in the myocardium may be useful for examining myocardial blood flow. Three-dimensional reconstruction of ultrasound images is an exciting new area of investigation that will add further to the utility of echocardiography.

NUCLEAR CARDIOLOGY

BASIC PRINCIPLES OF NUCLEAR CARDIOLOGY

All nuclear cardiology studies depend upon the injection into the patient of an isotope that emits photons, generally gamma rays generated during radioactive decay when the nucleus of an isotope changes from one energy level to a lower one. Radionuclide imaging uses a special camera that images these photons. A common problem with all nuclear studies is that photons are emitted in all directions from the point of origin, and scattering, attenuation, and absorption of the photons can occur. The higher the energy of the isotope, the less chance for scatter or absorption.

The two most commonly used isotopes are technetium 99m (^{99m}Tc) and thallium 201 (^{201}Tl). Technetium is used in both myocardial perfusion studies and radionuclide angiography and is formed on site from molybdenum 99 (^{99}Mo). The parent compound has a half-life of 66 h and thus is easily transported.^{99m}Tc, which is a metastable compound, is constantly formed from^{99}Mo in the on-site generator. During the decay of^{99m}Tc to^{99}Tc, photons are emitted with a characteristic 140-keV photopeak and a

half-life of 6 h.^{201}Tl, on the other hand, needs to be generated in a cyclotron facility and transported as a finished product, with a half-life of 73 h. The thallium isotope decay process is more complex than that of technetium, with most photons in the 80-keV range. Due to its higher energy and shorter half-life, technetium is a more desirable imaging agent.

ASSESSMENT OF VENTRICULAR FUNCTION

Equilibrium radionuclide angiography, also known as *multiple-gated blood pool imaging*, is useful for the noninvasive assessment of ventricular function. It involves the imaging of^{99m}Tc-labeled albumin or red cells that are uniformly distributed throughout the blood volume. Resting images of the blood pool of isotopes within the cardiac chambers are obtained by electrocardiographic gating through multiple cycles, so that sufficient counts can be detected to obtain an image. This requires that the heart rate be reasonably constant without significant arrhythmia. Resting images are usually obtained in the anterior, lateral, and left anterior oblique views. Each image lasts approximately 2 to 4 min.

Ejection fraction is determined by a count-based program from equilibrium radionuclide angiography; this does not require any assumptions regarding the geometry of the ventricle. It provides an accurate, reproducible method for assessment of left ventricular function. Regional wall motion analysis can be done by visual qualitative assessment, although there are programs for quantitative analysis. Left ventricular volume can also be assessed by a count-based method, using a regression equation. Other clinical variables that can be obtained include size and function of the right ventricle, size of atrial chambers and great vessels, and diastolic filling parameters. The severity of valvular regurgitant lesions can be assessed by measurement of a regurgitant fraction, which compares right ventricular stroke volume with left ventricular stroke volume.

First-pass radionuclide angiography is an alternative method for the noninvasive assessment of ventricular function. In contrast to equilibrium radionuclide angiography, first-pass radionuclide angiography involves the recording of the movement of a bolus of radionuclide during its "first pass" through the central circulation. This does not require labeling of red blood cells.^{99m}Tc is utilized because of its low cost and short half-life. During this testing, the passage of the radioisotope through the right atrium, right ventricle, pulmonary circulation, left atrium, left ventricle, and aorta is recorded with a high count (usually multicrystal) camera. The high count rates allow temporal definition of the passage of the bolus. The change in counts of a sample placed over a ventricle reflects its function. One major advantage of first-pass angiography is the short acquisition time required, as an injected bolus will complete its passage within 30 s. In contrast to equilibrium radionuclide angiography, the right and left sides of the heart can be scanned separately. The disadvantage of first-pass radionuclide angiography compared to equilibrium testing is its poorer resolution of ventricular wall motion. It is also inaccurate in instances where the injected bolus becomes delayed in its transit, such as with severe tricuspid regurgitation or pulmonary hypertension.

Ejection fraction and regional wall motion may also be assessed using gating of single-photon emission computed tomographic (SPECT) myocardial perfusion images using technetium-labeled perfusion agents (see below).

ASSESSMENT OF MYOCARDIAL PERFUSION

Myocardial perfusion imaging by nuclear techniques is now widely applied for the evaluation of ischemic heart disease. Injection of radioisotopes at rest and during stress is performed to produce images of myocardial regional uptake proportional to regional blood flow. With maximal exercise, myocardial blood flow is increased up to fivefold above the resting condition. In the presence of a fixed coronary stenosis, there is an inability to increase myocardial perfusion in the territory supplied by the stenosis, creating a flow differential and inhomogeneous distribution of the isotope (see Fig. 244-2). In patients who are unable to exercise, pharmacologic agents are used to increase blood flow and create similar inhomogeneities. The preferred pharmacologic agents are adenosine or dipyridamole, which increase blood flow to a similar degree as exercise. In patients with bronchospastic lung disease, which is a contraindication to the use of adenosine or dipyridamole, dobutamine may be used as an alternative, although it does not increase blood flow to the same extent.

^{201}Tl is a potassium analogue and is avidly taken up by viable myocardial cells. The degree of uptake is related directly to the coronary blood flow. An initial injection is usually performed at peak exercise, and hypoperfused myocardium will have less thallium uptake than a region of normal perfusion (see Fig. 244-2). Over the next several hours, a complex process occurs that is known as "redistribution." There is a continuous input of thallium into the myocardium from a large reservoir of thallium in the blood pool. At the same time, thallium continuously washes out of portions of the myocardium at a rate that is dependent on local myocardial perfusion. The final result is that a region of ischemia that initially appears as an area of reduced uptake becomes apparently normal over time; this redistribution is seen on delayed imaging. In regions of fibrosis (infarction), there will be no redistribution on delayed imaging. A "reinjection" of an additional small amount of thallium before acquisition of the delayed images enhances the detection of ischemia. The presence of redistribution in areas of hypokinesia has been associated with recovery of left ventricular function after revascularization.

Other findings on thallium imaging may be of considerable clinical importance. Increased lung uptake of thallium may be seen immediately after stress and assessed either quantitatively or qualitatively. This finding reflects increased pulmonary capillary wedge pressure during stress. It occurs in the presence of severe coronary artery disease and/or left ventricular dysfunction. It provides important adverse prognostic information that is incremental to other clinical, stress, and coronary angiographic variables. Thallium images may also show evidence of transient poststress left ventricular dilatation. This finding is also associated with severe coronary artery disease and/or left ventricular dysfunction as well as with an adverse prognosis.

^{99m}Tc-labeled compounds have a higher photon energy and shorter half-life than ^{201}Tl, permitting the injection of larger doses. As a result, these compounds generally provide higher quality scans with fewer artifacts. Three technetium-labeled agents have been approved for general use: teboroxime, tetrofosmin, and sestamibi. The latter is the best studied of these agents and is currently used most frequently. Like thallium, sestamibi distributes to the myocardium in relation to blood flow, and its uptake requires a viable myocardial cell and an intact cell membrane. It is transported through the cytoplasm and

bound to the mitochondria in a nearly irreversible fashion. Compared to thallium, there is far less redistribution. As a result, the agent must generally be injected twice -- once at rest and once during stress.

Myocardial Perfusion Imaging Protocols (Plate I-1) The use of ^{201}Tl usually involves one of three protocols. The first protocol (stress-redistribution-delayed imaging) involves stress imaging, followed by redistribution imaging 3 or 4 h later (see Fig. 244-2). If fixed defects are present, delayed imaging is performed at a later time (usually 24 h) to detect additional redistribution. The second protocol (stress-redistribution-reinjection) also involves stress images and redistribution images 3 or 4 h later. In those patients with fixed defects on redistribution imaging, reinjection of a small amount of thallium is then performed. Repeat imaging is performed approximately 30 min later to identify a difference in myocardial uptake consistent with ischemia. In the third protocol (stress-reinjection-delayed imaging) patients are reinjected with a small amount of thallium before performing delayed imaging at 3 or 4 h. In those patients who have fixed defects on these reinjection images, more delayed imaging is then performed (usually at 24 h) in order to detect redistribution of both the initial stress dose as well as the reinjection dose. All three protocols therefore involve the use of stress images and delayed images in all patients, with a third set of images in a small subset of patients in order to improve the detection of thallium redistribution.

Stress imaging with sestamibi may utilize a 2-day protocol with different days for the injections of sestamibi at rest and during stress. Either the stress image or the rest image may be performed first. The protocol may also be carried out in one day. When the rest study is performed first a low dose is used, followed by a stress study using a larger injected dose. Alternatively, the order of these two studies may be reversed.

COMPARISON OF THALLIUM AND SESTAMIBI

Both ^{201}Tl and ^{99m}Tc sestamibi provide clinically useful myocardial perfusion images in the majority of patients. The choice between the two is often dictated by local experience and economics. However, in selected patients, there may be factors that suggest a clear advantage for one or the other. The relative advantages of both agents are listed in Table 227-2.

NUCLEAR CARDIOLOGY IN CLINICAL DECISION MAKING

Stress-myocardial-perfusion imaging with either ^{201}Tl or ^{99m}Tc sestamibi plays a pivotal role in both the diagnosis and risk stratification of patients with established or suspected coronary artery disease.

For the diagnosis of coronary artery disease, stress-myocardial-perfusion imaging is an appropriate initial test (as opposed to a treadmill exercise electrocardiogram) in patients with left bundle branch block, an electronically paced ventricular rhythm,>1 mm of ST segment depression at rest, or prior coronary artery revascularization, or in patients who are unable to exercise to a level high enough to give meaningful results. Stress-myocardial-perfusion imaging is also performed as a second test to clarify the significance of an equivocal treadmill exercise electrocardiogram.

For risk stratification, stress perfusion imaging can identify the extent, severity, and location of ischemia. These findings are often pivotal in defining the need for coronary angiography and coronary revascularization. Normal stress-myocardial-perfusion scans are highly predictive of both the absence of significant coronary artery disease and a low risk of cardiac death (less than 1% per year); coronary angiography is usually not required. Patients with markedly abnormal myocardial perfusion scans (large stress-induced defects, multiple stress-induced defects of moderate size, large fixed defect with left ventricular dilatation or increased ^{201}Tl lung uptake) are at high risk (>3 percent annual mortality rate). In such patients, coronary angiography and possible revascularization are appropriate.

POSITRON EMISSION TOMOGRAPHY (PET)

The underlying physics of PET scanning is quite different from that involved in the standard radionuclide techniques described above. The annihilation of the positron leads to the simultaneous emission of two very high energy (511 keV) photons in opposite directions. These can then be imaged by a series of detectors placed in a ring around the patient. The very high energy of the photons results in far less scatter and attenuation than with conventional nuclear cardiology techniques. The sophistication of the required equipment and the associated expense have generally limited the availability of this technique. PET cameras are considerably more expensive than conventional nuclear cardiology cameras. The radiopharmaceuticals involved require a cyclotron for production and generally have half-lives that are so short that transportation beyond the immediate local region is not feasible.

Positron emitters can be employed to study both myocardial blood flow and myocardial metabolism. Nitrogen-13 ammonia, oxygen-15 water, and rubidium-82 have all been employed to assess myocardial blood flow. They permit measurement of absolute regional blood flows, in contrast to the relative blood flows that are assessed with ^{201}Tl or ^{99m}Tc sestamibi. This advantage has been utilized for research purposes but has not yet been exploited clinically. Myocardial metabolism is most often assessed using fluorine-18 deoxyglucose. This agent permits the detection and quantification of exogenous glucose utilization in areas of hypoperfused myocardium.

The clinical application of PET scanning that has been most well studied is the assessment of myocardial viability. The pattern of enhanced fluorodeoxyglucose uptake in regions of decreased perfusion (termed *glucose/blood flow "mismatch"*) indicates the presence of ischemic myocardium that has preferentially shifted its metabolic substrate towards glucose rather than fatty acid or lactate. This pattern identifies regions of ischemic or hibernating myocardium that are likely to improve in function after revascularization (Chap. 244).

Careful studies have consistently shown the ability of PET to identify ischemic or hibernating myocardium in 10 to 20% of regions that would be classified as fibrotic (infarcted) by ^{201}Tl or ^{99m}Tc sestamibi. For that reason, this technique is generally regarded as the "gold standard" for the assessment of myocardial viability. However, because of its greater cost, national clinical practice guidelines have suggested that its usage be restricted to the specific situations where it is most beneficial.

Within the past few years, specially modified conventional gamma cameras have been employed to image fluorodeoxyglucose in an attempt to avoid the expense related to cameras dedicated toPET. The limited evidence available suggests that this approach is inferior to standard PET.

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228. DIAGNOSTIC CARDIAC CATHETERIZATION AND ANGIOGRAPHY - *Donald S. Baim, William Grossman*

Despite progressive improvements in noninvasive techniques, cardiac catheterization remains a key clinical tool for assessing the anatomy and physiology of the heart and its associated vasculature. It involves the insertion of small (diameter, 2 to 3 mm), hollow plastic tubes or catheters into a peripheral artery or vein under local anesthesia, and passage of their tips into the heart for pressure measurement or for the injection of a liquid radiographic contrast agent. The findings characterize the extent and severity of cardiac disease and thereby help in deciding on the most appropriate plan for medical, surgical, or catheter-based treatment. While most patients with coronary artery disease (CAD) or valvular disease can be managed using only clinical and noninvasive test data, more than 1.5 million cardiac catheterization and angiographic procedures are performed each year for diagnostic or interventional purposes, or both. This**chapter**focuses on the uses of cardiac catheterization as a diagnostic tool.**For further discussion of catheter-based interventions, see Chap. 245.*

INDICATIONS, CONTRAINDICATIONS, AND COMPLICATIONS

Indications Given the expense and small, but real, risks of cardiac catheterization, it is not performed routinely whenever cardiac disease is diagnosed or suspected. Instead, cardiac catheterization is recommended only when there is a need to confirm the presence of a clinically suspected condition, define its anatomic and physiologic severity, and determine whether important associated conditions are present. This need most commonly arises when a patient is experiencing limiting or escalating symptoms of cardiac dysfunction (Chap. 232) or myocardial ischemia (Chap. 244) or when objective measures (such as exercise testing or echocardiography) suggest that the patient has a high risk of progressing to rapid functional deterioration, myocardial infarction, or other adverse events. Under these circumstances, catheterization is often a prelude to treatment by cardiac surgery or a catheter-based intervention. In the past, cardiac catheterization was considered mandatory in *all* patients being considered for cardiac surgery. Today, many patients with congenital or valvular heart disease can undergo surgical correction based solely on clinical and noninvasive test data; however, cardiac catheterization and coronary arteriography remain the only techniques that can define coronary anatomy with sufficient precision to support decisions regarding coronary surgery or catheter-based interventions in patients withCAD. In patients with other forms of heart disease (e.g., dilated cardiomyopathy, valvular heart disease), cardiac catheterization can provide hemodynamic characterization essential for the design of an appropriate medical regimen as well as for an assessment of prognosis.

Contraindications When there is a clinical "need to know," there are very few absolute contraindications in a patient who understands and accepts the associated risks. Some relative contraindications to cardiac catheterization, however, are listed inTable 228-1. Most center on factors that increase the risk of the procedure above the baseline mortality risk of roughly 1 in 1000 for clinically stable patients. This risk is increased more than tenfold in patients with severe symptoms, certain types of coronary anatomy, valve disease, left ventricular dysfunction, or severe noncardiac disease, as outlined inTable 228-2.

Complications Beyond the mortality risk, cardiac catheterization carries a 1 in 1000 risk of stroke or myocardial infarction. Other problems, such as transient tachy- or bradyarrhythmias or bruising or bleeding at the catheter insertion site, occur in fewer than 1% of patients and respond to drug therapy, countershock, or vascular surgical repair, without long-term sequelae. Although serious, problems such as cardiac perforation or arterial dissection are very rare in the modern era of cardiac catheterization.

Some patients, however, are intolerant of the iodinated contrast agents used for angiography, which may produce transient deterioration in renal function (particularly in patients with baseline renal dysfunction or proteinuria who are not adequately prehydrated) or *allergic reactions* ranging from urticaria to frank anaphylaxis in sensitive patients. These allergic reactions can be suppressed by pretreatment with glucocorticoids (prednisone, 20 to 40 mg every 6 h), conventional antihistamines (e.g., diphenhydramine, 25 mg every 6 h), and H_2antagonists (cimetidine, 300 mg every 6 h), starting 18 to 24 h prior to the procedure. Despite these precautions, occasional individuals still develop anaphylactic reactions during radiographic contrast angiography, and intravenous epinephrine must be at hand to treat such instances. Alternatively, one of the newer nonionic contrast agents may be used with less risk of a severe allergic reaction. Unlike the original high-osmolar agents, the newer low-osmolar contrast agents (including true nonionic contrast agents and the ionic dimer ioxaglate) have a lesser myocardial depressant effect and produce fewer side effects (hypotension, nausea, bradycardia, or a sensation of marked warmth following injection) than earlier high-osmolar agents. They are, however, somewhat more expensive than traditional high-osmolar ionic agents, so that many catheterization laboratories reserve their use for patients who are at higher risk for contrast-related problems.

TECHNIQUES

Cardiac catheterization is performed with the patient in the fasting state and awake but sedated. Although cardiac catheterization used to be performed exclusively as an inpatient procedure, current practice is to perform most elective procedures on an outpatient basis, with the patient discharged 4 to 6 h after the procedure is completed. Typical preprocedure sedatives include diazepam (Valium, 5 to 10 mg orally) or midazolam (Versed, 1 mg intravenously). It is also customary to give the antihistamine diphenhydramine (Benadryl, 25 to 50 mg orally) before the procedure in the hope of suppressing minor allergic reactions to iodinated contrast. Since cardiac catheterization is a sterile procedure, prophylactic antibiotics are not necessary. To minimize the risks of bleeding at the local catheter insertion site, patients who have been anticoagulated chronically with warfarin should have this agent discontinued at least 48 h prior to the procedure, so that the INR falls below 2.

Most (>95%) cardiac catheterizations are performed by the percutaneous femoral technique, in which a needle puncture is performed in the femoral artery (for left heart catheterization) and the femoral vein (for right heart catheterization). A flexible guidewire is inserted through this needle, allowing placement of a vascular access sheath through which the desired catheters can be advanced. This percutaneous technique has been modified for other sites, including the brachial and even the radial artery. The brachial or radial approach has an advantage in the patient with peripheral vascular disease

involving the abdominal aorta and iliac or femoral arteries or in whom immediate postprocedure ambulation is desired, but it involves some limitations in the range of devices that can be used if the diagnostic procedure evolves into a catheter-based intervention. With these alternatives, the original cut-down, or Sones, technique of cardiac catheterization by direct exposure of the brachial artery and vein in the antecubital fossa is rarely used.

Cardiac catheterization may include a variety of different measurements of pressure and flow (hemodynamics) as well as a variety of different contrast injections recorded as x-ray movies (angiography). The exact types of testing performed in any given procedure depend on the nature of the clinical problem being evaluated. In patients withCAD, the procedure may include only left ventriculography and coronary angiography, while in patients with valvular heart disease, full left and right heart hemodynamic studies may be performed.

RIGHT HEART CATHETERIZATION

Measurement of the pressures in the right side of the heart was once a routine part of each cardiac catheterization, but it is now used in fewer than 25% of procedures because it adds little to the evaluation of the patient withCAD. It is still useful, however, when significant left and/or right ventricular dysfunction, valve disease, myopericardial disease, or intracardiac shunting is suspected. The right heart catheterization procedure is similar to the placement of a Swan-Ganz catheter at the bedside in the intensive care unit, except that it is performed under fluoroscopic guidance. A balloon flotation catheter is advanced from a suitable vein (femoral, brachial, subclavian, or internal jugular) into the superior vena cava, where blood is sampled for oximetry. The catheter is then positioned in the right atrium, where pressure is measured. The balloon is inflated with air (or carbon dioxide, if intracardiac shunting is supected) and advanced sequentially into the right ventricle, pulmonary artery, and pulmonary artery wedge position. Pressure is recorded at each of these locations, with normal values for pressures measured during cardiac catheterization summarized in Table 228-3. After the pulmonary wedge pressure (which approximates left atrial pressure) is recorded, the balloon is deflated so that pulmonary artery pressure can be monitored and blood samples obtained for oximetry. Comparison of oxygen saturations in the superior and inferior vena cava, the chambers of the right heart, and pulmonary artery permits assessment of the presence of a left-to-right shunt at the atrial, ventricular, or pulmonary artery level, which will be manifested as an increase ("step-up") in oxygen saturation of blood as it traverses these vessels and chambers.

Measurement of Cardiac Output Measurements of the pulmonary artery and aortic oxygen content and oxygen consumption allow calculation of the cardiac output by the Fick principle, which states that

In order to compare individuals of different body weights and sizes, O_2consumption and cardiac output (Q) are commonly divided by body surface area. Normal values for O_2consumption and cardiac output are given inTable 228-3. What is calculated by dividing O_2consumption by the arteriovenous O_2difference across the lungs (estimated

pulmonary venous- pulmonary arterial O_2content) is actually the pulmonary blood flow (Q_p). In patients with left-to-right shunt at the atrial, ventricular, or pulmonary artery levels, pulmonary blood flow will exceed systemic blood flow. In such cases, systemic blood flow (Q_s) is calculated by dividing O_2consumption by the systemic arteriovenous O_2difference. The latter is calculated as the systemic arterial blood O_2content minus the mixed venous blood O_2content as estimated using blood from the chamber immediately proximal to the level of the shunt. The Fick method is most dependable when the cardiac output is low and the arteriovenous oxygen difference is large.

Another approach to the measurement of cardiac output during right heart catheterization is the thermodilution technique, in which a thermistor is mounted on the tip of a balloon flotation catheter and positioned in the pulmonary artery. Cold dextrose solution or saline is injected via a proximal port on the catheter into the vena cava or right atrium, and the change in temperature monitored at the thermistor is integrated electronically. This integral is inversely proportional to the volume flow rate past the thermistor, and if the temperatures of the injectate and pulmonary artery blood are measured, cardiac output (actually, pulmonary blood flow) can be calculated. In contrast to the Fick method, the indicator-dilution method is least reliable when the cardiac output is low.

LEFT HEART CATHETERIZATION

Whether performed using the femoral, brachial, or radial approach, the left heart catheter is advanced under fluoroscopic guidance into the central aorta, where pressure is measured and recorded. Next, the catheter is advanced in retrograde fashion across the aortic valve into the left ventricle, where pressure is measured. If a right heart catheter is in place, this is an appropriate time for simultaneous measurement and recording of left heart, right heart, and peripheral arterial pressures together with a determination of cardiac output by either thermodilution or the Fick principle. These measures allow assessment of possible pressure gradients across the mitral and aortic valves, and catheter pullback on the right side permits assessment of possible gradients across the pulmonic and tricuspid valves. Simultaneous measurement of pressures and cardiac output provides the data for calculation of systemic and pulmonary vascular resistances. The resistance to blood flow through the systemic vascular bed is

where *SVR* is systemic vascular resistance [(dyn×s)/cm_5], *MAP* and *RA* are mean aortic and right atrial pressures (mmHg), 80 is a constant for converting to metric units, and *SBF* is systemic blood flow (L/min). Resistance to blood flow through the pulmonary vascular bed is

where *PVR* is pulmonary vascular resistance [(dyn×s)/cm_5]; *PA*, *PCW*, and *LA* are pulmonary artery, pulmonary capillary wedge, and left atrial mean pressures, respectively (mmHg); and *PBF* is pulmonary blood flow (L/min). Normal values for pulmonary and systemic vascular resistances are given in Table 228-3.

When valvular stenosis is present, the measurements of the upstream and downstream pressures and flow allow calculation of the valve orifice using the Gorlin formula.

where *A* is the valve orifice area (cm^2), *flow* is the blood flow (mL/s) across the stenotic valve;D*P* is the mean pressure gradient (mmHg) during the period of blood flow; and *K* is a constant (44.3 for the aortic valve and 37.7 for the mitral valve).

As seen inFig. 228-1, normal left ventricular and aortic pressures are essentially equal during systole, while normal left atrial (pulmonary capillary wedge) and left ventricular pressures are equal during diastole in the normal heart. The presence of a systolic pressure gradient between the left ventricle and aorta indicates obstruction at the level of the aortic valve (e.g., calcific *aortic stenosis*) or at subaortic level (e.g., *hypertrophic obstructive cardiomyopathy*). Similarly, the presence of a diastolic pressure gradient between the left atrium (or pulmonary capillary wedge pressure) and the left ventricle generally indicates *mitral stenosis*, although it may also be seen in rare conditions such as cor triatriatum and left atrial myoxoma. An example of a large diastolic pressure gradient in a patient with mitral stenosis is seen inFig. 228-2. As seen inFig. 228-3, patients with significant mitral regurgitation may have a prominent *v* wave in the pulmonary capillary wedge pressure, which often increases substantially during modest exercise. Severe *aortic regurgitation* produces a widening of the aortic pulse pressure, with equilibration of aortic and left ventricular pressures in diastole (Fig. 228-4). Right-sided pressures exhibit a characteristic deformity in the presence of valvular heart disease affecting the tricuspid or pulmonic valves. In patients with severe *tricuspid regurgitation*, the right atrial pressure resembles the right ventricular pressure closely in appearance. Mean right atrial pressure and right ventricular end-diastolic pressure are both elevated in tricuspid regurgitation. In *tricuspid stenosis*, there is a pressure gradient between the right atrium and ventricle during diastole.

Abnormalities in pressure waveforms may also be suggestive of conditions such as *cardiac tamponade* or *pericardial constriction* (Chap. 239). In both conditions there is equalization of left and right ventricular diastolic pressures. However, in constrictive pericarditis, nearly all ventricular filling occurs shortly after mitral and tricuspid valve opening; after this period of rapid filling, ventricular volumes cannot increase further owing to the constricting pericardium. This abnormality produces an abrupt early ventricular diastolic pressure rise with a mid- and late-ventricular pressure plateau, giving the so-called square root sign (Fig. 228-5). In contrast, in tamponade there is equalization of diastolic pressures with a gradual increase throughout diastole.

Congestive heart failure due to myocardial contractile dysfunction is associated with characteristic alterations in the ventricular pressure waveforms seen at cardiac catheterization. Neither the rise nor the decline in isovolumic pressure is as steep as in the normal heart. The reduced slopes of pressure rise and decline are associated with an abbreviated ejection period, giving the left ventricular pressure tracing a triangular appearance (Fig. 228-6). Also, the pressure decline does not continue to zero, so the minimal left ventricular pressure may be elevated. This hemodynamic finding correlates with an increased ventricular end-systolic volume, which is a sign of depressed contractile function of the left ventricular myocardium.

CARDIAC ANGIOGRAPHY

LEFT VENTRICULOGRAPHY

Following the measurement of cardiac pressures, the angiographic portion of the cardiac catheterization usually begins with left ventriculography -- the injection of radiographic contrast material directly into the left ventricular cavity. A power injector is used to inject 30 to 45 mL of radiographic contrast material into the left ventricular chamber at a rate of 10 to 12 mL/s. The resulting radiographic images are recorded, and the left ventricular silhouette is defined at end-diastole and end-systole. This permits calculation of the left ventricular chamber volumes and ejection fraction, as well as qualitative assessment of regional wall motion abnormalities. The normal left ventricle ejects 50 to 80% of its end-diastolic volume with each beat; i.e., its *ejection fraction* is 0.50 to 0.80. In adults, normal values for left ventricular volumes are, for end-diastolic volume, 72± 15 mL/m^2(mean ± standard deviation) and, for end-systolic volume, 20 ± 8 mL/m^2. Regional abnormalities of wall motion are illustrated inFig. 228-7 and include diminished inward motion of a myocardial segment (*hypokinesis*), absence of inward movement of a myocardial segment (*akinesis*), and paradoxical systolic expansion of a regional myocardial segment (*dyskinesis*).

Left ventriculography is usually performed in the right anterior oblique projection, which allows assessment of the mitral and aortic valves. Mitral regurgitation is easily visualized as the leakage of radiographic contrast material back into the left atrium during left ventricular systole. Its severity can be estimated qualitatively using a grading system of 1+ (mild; radiographic contrast material clears with each beat and never opacifies the entire left atrium) to 4+ (severe; opacification of the entire left atrium occurs within one beat, and contrast material can be seen refluxing into the pulmonary veins).

Left ventriculography performed in the *left* anterior oblique projection permits detection of abnormal communications, such as a ventricular septal defect (Chap. 234). In the most common form of hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis;Chap. 238), left ventriculography in this projection shows anterior motion of the anterior leaflet of the mitral valve during systole and bulging of the interventricular septum into the left ventricular cavity, especially in the subaortic region. Mural thrombi within the left ventricular chamber may be well visualized during left ventriculography; they occur most commonly in the left ventricular apex.

AORTOGRAPHY

Rapid injection of radiographic contrast material into the ascending aorta allows detection of abnormalities that involve the aorta and aortic valve. When suspected clinically, aortography permits detection and qualitative assessment of the severity of abnormalities such as aortic regurgitation, which is graded using a 1+ to 4+ scale, as for mitral regurgitation. Abnormal communications between the aorta and right side of the heart, such as a patent ductus arteriosus or ruptured aneurysm of a sinus of Valsalva, may be visualized. Aortography can permit identification of aortic aneurysm and of aortic dissection (Chap. 247) by visualizing an intimal flap within the aortic lumen.

CORONARY ANGIOGRAPHY

This common procedure involves the selective injection of a radiographic contrast agent into the coronary arteries. Placement of the catheter tip into the right and left coronary arteries is carried out under fluoroscopic guidance, and contrast agent is injected by hand during recording of the radiographic image. Each coronary artery is usually viewed in several projections to permit assessment of the severity of stenosis and to minimize the overlap of adjacent vessels. In addition to the detection of coronary artery stenoses, coronary angiography is useful for the detection of congenital abnormalities of the coronary circulation, coronary arteriovenous fistulas, and patency of coronary artery bypass grafts. Examples of normal and abnormal coronary anatomy are shown in Figs. 228-8 and 228-9. The location, severity, and morphology of the stenotic lesions can be analyzed in great detail, and the resulting information is essential to planning either bypass surgery or catheter-based intervention (Fig. 228-10). This is usually done by visual estimation of percent diameter stenosis of each lesion relative to the "uninvolved" adjacent reference segment, with stenosis > 50% taken as being hemodynamically significant (interfering with maximal increases in perfusion of the subserved myocardial territory during stress).

POSTPROCEDURE CARE

The average cardiac catheterization procedure takes between 30 and 45 min. Intravenous heparin (2000 to 3000 IU) may or may not be given at the time of catheter insertion. At the completion of the procedure, heparin may be reversed with intravenous protamine or allowed to wear off until the activated clotting time falls below 160 s. At that time, the vascular sheaths are removed and hemostasis is achieved by applying local pressure over the puncture site for 10 to 15 min. Patients then remain at bed rest for 4 to 6 h before ambulating and being discharged to home. A variety of devices for sealing the arterial puncture site can allow a shorter period of bed rest and earlier ambulation. Patients with suitable anatomy may return at a later date for either catheter-based intervention or bypass surgery, although it is now common practice to perform a catheter-based intervention during the same procedure as the diagnostic cardiac catheterization, if appropriate.

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SECTION 2 -DISORDERS OF RHYTHM

229. THE BRADYARRHYTHMIAS: DISORDERS OF SINUS NODE FUNCTION AND AV CONDUCTION DISTURBANCES - *Mark E. Josephson, Peter Zimetbaum*

ANATOMY OF THE CONDUCTING SYSTEM

Under normal conditions, the pacemaker function of the heart resides in the sinoatrial (SA) node, which lies at the junction of the right atrium and superior vena cava. The SA node is approximately 1.5 cm long and 2 to 3 mm wide and is supplied by the sinus node artery, which arises from either the right coronary artery (60%) or the left circumflex coronary artery (40%). Once the impulse exits the sinus node and perinodal tissue, it traverses the atrium until it reaches the atrioventricular (AV) node. The blood supply of the AV node is derived from the posterior descending coronary artery (90%). The AV node lies at the base of the interatrial septum just above the tricuspid annulus and anterior to the coronary sinus. The electrophysiologic properties of the AV node result in slow conduction, which is responsible for the normal delay in AV conduction, i.e., the PR interval.

The bundle of His emerges from the AVnode, enters the fibrous skeleton of the heart, and courses anteriorly across the membranous interventricular septum. It has a dual blood supply from the AV nodal artery and a branch of the anterior descending coronary artery. The branching (distal) portion of the bundle of His gives rise to a broad sheet of fibers that course over the left side of the interventricular septum to form the left bundle branch and a narrow cable-like structure on the right side that forms the right bundle branch. The arborization of both the right and left bundle branches gives rise to the distal His-Purkinje system, which ultimately extends throughout the endocardium of the right and left ventricles.

TheSA node, atrium, andAV node are significantly influenced by autonomic tone. Vagal influences depress automaticity of the SA node, depress conduction, and prolong refractoriness in the tissue surrounding the SA node; inhomogeneously decrease atrial refractoriness and slow atrial conduction; and prolong AV nodal conduction and refractoriness. Sympathetic influences exert the opposite effect.

ELECTROPHYSIOLOGIC PRINCIPLES

In the resting state, the interior of most cardiac cells, with the exception of theSA andAVnodes, is approximately -80 to-90 mV, negative with respect to a reference extracellular electrode. The resting membrane potential is determined primarily by the concentration gradient of potassium across the cell membrane. Activation of cardiac cells results from movement of ions across the cell membrane, causing a transient depolarization known as the *action potential*. The ionic species responsible for the action potential varies among the cardiac tissues, and the configuration of the action potential is therefore unique to each tissue (Fig. 229-1).

The action potential of the His-Purkinje system and ventricular myocardium has five phases (Fig. 229-2). The rapid depolarizing current (phase 0) is mainly determined by an influx of sodium into myocardial cells followed by a secondary (slower) influx of

calcium, which produces a slow inward current. The repolarization phases of the action potential (phases 1 to 3) are primarily related to outward flux of potassium. The resting membrane potential is phase 4.

The bradyarrhythmias result from abnormalities either of impulse formation, i.e., automaticity, or of conduction. *Automaticity*, which is normally observed in the sinus node, the specialized fibers of the His-Purkinje system, and some specialized atrial fibers, is the property of a cardiac cell that causes it to depolarize spontaneously during phase 4 of the action potential, leading to the generation of an impulse. To exhibit automaticity, the resting membrane potential must decrease spontaneously until threshold potential is reached and an all-or-none regenerative response occurs. The ionic currents producing spontaneous diastolic depolarization appear to involve the inward current of either sodium or calcium and a decreasing outward potassium current. The velocity of *conduction*, i.e., impulse propagation through cardiac tissues, depends on the magnitude of inward current, which is directly related to the rate of rise and amplitude of phase 0 of the action potential. The more positive the threshold potential and the slower the rate of depolarization toward threshold, the slower is the rate of rise of phase 0 of the action potential and the slower is the conduction velocity. Disease states or drugs may result in lower rates of rise of phase 0 at any given membrane potential. Passive membrane properties (e.g., intracellular resistance and intercellular coupling) can also affect impulse propagation. Propagation is more rapid parallel to fiber orientation than transverse to it, a property termed *anisotropic conduction*.

Refractoriness is a property of cardiac cells that defines the period of recovery that cells require after being discharged before they can be reexcited by a stimulus. The *absolute refractory period* is defined by that portion of the action potential during which no stimulus, regardless of its strength, can evoke another response. The *effective refractory period* is that part of the action potential during which a stimulus can evoke only a local, nonpropagated response. The *relative refractory period* extends from the end of the effective refractory period to the time that the tissue is fully recovered. During this time, a stimulus of greater than threshold strength is required to evoke a response, which is propagated more slowly than normal. In the normal His-Purkinje system or ventricular myocytes, excitability is recovered following completion of the action potential, and evoked responses have characteristics similar to the spontaneous normal response. In theAV node, recovery of excitability occurs well after completion of the action potential.

INTRACARDIAC RECORDINGS OF THE SPECIALIZED CONDUCTING SYSTEM

Electrode catheters allow the recording of activation of portions of the specialized conducting system, including the bundle of His. To obtain a recording from the bundle of His, the electrode catheter is positioned across the tricuspid valve (Fig. 229-3). The interval from local atrial depolarization in the His bundle recording to the onset of depolarization of the His bundle deflection is called the *AH interval* (normal= 60 to 125 ms) and represents an indirect method of assessingAV nodal conduction time. The interval from the beginning of the His bundle deflection to the earliest onset of ventricular activation, as measured from any of multiple-surface electrocardiogram (ECG) leads or the intracardiac ventricular electrogram, is called the *HV interval* (normal= 35 to 55 ms) and represents conduction time through the His-Purkinje system.

Electrode catheters can be positioned in the area of the sinus node to record high right atrial activity. Left atrial activity may be recorded directly via a catheter placed across a patent foramen ovale or indirectly using a catheter inserted into the coronary sinus. The atrial activation sequence may be "mapped," and sites of intra- and interatrial conduction abnormalities may be ascertained.

SINUS NODE DYSFUNCTION

TheSA node is normally the dominant cardiac pacemaker because its intrinsic discharge rate is the highest of all potential cardiac pacemakers. Its responsiveness to alterations in autonomic nervous system tone is responsible for the normal acceleration of heart rate during exercise and the slowing that occurs during rest and sleep. Increases in sinus rate normally result from an increase in sympathetic tone acting via b-adrenergic receptors and/or a decrease in parasympathetic tone acting via muscarinic receptors. Slowing of the heart rate is normally due to opposite alterations. In adults, the normal sinus rate under basal conditions is 60 to 100 beats per minute. *Sinus bradycardia* is said to exist when the sinus rate is less than 60 beats per minute, and *sinus tachycardia* when it exceeds 100 beats per minute. However, there is wide variation among individuals, and rates less than 60 beats per minute do not necessarily indicate pathologic states. For example, trained athletes often exhibit resting rates under 50 beats per minute due to increases in vagal tone. Normal elderly individuals may also show marked sinus bradycardia at rest.

ETIOLOGY

SAnode dysfunction is most often found in the elderly as an isolated phenomenon. Although interruption of the blood supply to the SA node may produce dysfunction, the correlation between obstruction of the sinus node artery and clinical evidence of SA node dysfunction is poor. Specific disease states associated with SA node dysfunction include senile amyloidosis and other conditions associated with infiltration of the atrial myocardium. Sinus bradycardia is associated with hypothyroidism, advanced liver disease, hypothermia, typhoid fever, and brucellosis; it occurs during episodes of hypervagotonia (vasovagal syncope), severe hypoxia, hypercapnia, acidemia, and acute hypertension. However, most cases of SA node dysfunction are due to idiopathic degeneration or are secondary to pharmacologic agents.

MANIFESTATIONS

Although marked (£50 beats per minute) sinus bradycardia may cause fatigue and other symptoms due to inadequate cardiac output, more commonly sinus node dysfunction is manifest as paroxysmal dizziness, presyncope, or syncope. These symptoms usually result from abrupt, prolonged sinus pauses caused by failure of sinus impulse formation (sinus arrest) or block of conduction of sinus impulses to the surrounding atrial tissue (sinus exit block). In either case, theECGmanifestation is a prolonged period (>3 s) of atrial asystole. In some patients,SA node dysfunction is accompanied by abnormalities inAVconduction. In addition to the absence of atrial activity, lower pacemakers fail to emerge during the sinus pauses, resulting in periods of ventricular asystole and syncope. Occasionally, SA node dysfunction is manifested by an inadequate acceleration in sinus rate in response to a stress such as exercise or fever. In some

patients, SA node dysfunction may become manifest only in the presence of certain cardioactive drugs: cardiac glycosides,b-adrenergic blocking drugs, calcium channel blockers, amiodarone, and other antiarrhythmic agents. These agents, which do not usually cause sinus node dysfunction in normal people, may unmask evidence of sinus node dysfunction in susceptible individuals.

The *sick sinus syndrome* refers to a combination of symptoms (dizziness, confusion, fatigue, syncope, and congestive heart failure) caused bySA node dysfunction and manifested by marked sinus bradycardia, sinoatrial block, or sinus arrest. Because these symptoms are nonspecific, and becauseECGmanifestations of sinus node dysfunction are often intermittent, it may be difficult to prove that such symptoms are actually caused by SA node dysfunction.

Atrial tachyarrhythmias such as atrial fibrillation, atrial flutter, or atrial tachycardia may be accompanied bySA node dysfunction. The *bradycardia-tachycardia syndrome* refers to paroxysmal atrial arrhythmia that upon termination is followed by prolonged sinus pauses (Fig. 229-4) or in which there are alternating periods of tachyarrhythmia and bradyarrhythmia. Syncope or presyncope may result from failure of the sinus node to recover function following suppression of automaticity by atrial tachyarrhythmia.

DIAGNOSIS

First-degree sinoatrial exit block denotes a prolonged conduction time from theSA node to the surrounding atrial tissue. It cannot be recognized on a standard (surface)ECG but requires invasive intracardiac recordings, which can detect this condition indirectly, by measuring the sinus response to atrial premature beats, or directly, by recording SA node electrograms. *Second-degree sinoatrial exit block* denotes the intermittent failure of conduction of sinus impulses to the surrounding atrial tissue; it is manifested as the intermittent absence of P waves (Fig. 229-5). *Third-degree*, or *complete, sinoatrial block* is characterized by a lack of atrial activity or by the presence of an ectopic subsidiary atrial pacemaker. On the standard ECG it cannot be distinguished from sinus arrest, but direct intracardiac recordings of SA node activity permit this distinction. The *bradycardia-tachycardia syndrome* is manifested on the standard ECG as tachyarrhythmias (Fig. 229-4). Most often these are atrial flutter or fibrillation, although any tachycardia during which the atria are activated may cause overdrive suppression of the sinus node resulting in clinical appearance of this syndrome.

The most important step in the diagnosis is to correlate symptoms withECGevidence ofSA node dysfunction. While ambulatory ECG (Holter) monitoring remains a mainstay in evaluating sinus node function, most episodes of syncope are paroxysmal and unpredictable. Single and even multiple 24-h Holter monitor recordings may fail to include a symptomatic episode.

Caution must be taken in interpreting the Holter monitor results. For instance, a pause during sleep is often a normal finding associated with heightened vagal tone. This should not be interpreted as sinus node dysfunction requiring pacemaker implantation.

Continuous-loop event records represent a more specific diagnostic tool. These devices may be worn for prolonged periods of time and allow close correlation between

electrocardiographic findings and symptoms. They do require the patient's ability to activate the monitor at the time of symptoms. More recently, an implantable event recorder, which can be interrogated like a pacemaker, has been developed for patients with rare events.

The response to carotid sinus pressure and pharmacologic autonomic "denervation" of the heart may be helpful. Carotid sinus pressure can be particularly useful in patients in whom paroxysmal dizziness or syncope is compatible with the hypersensitive carotid sinus syndrome (Chap. 21). In such patients, the response can be dramatic, and sinus pauses in excess of 5 s may occur. Although pauses in excess of 3 s are considered abnormal, in elderly patients such pauses are common and do not necessarily signify a diagnostic response. This is a major limitation of the use of carotid sinus pressure as a diagnostic test in the elderly. The other noninvasive test ofSA node function involves the use of pharmacologic agents to manipulate the autonomic nervous system and assess the balance of parasympathetic and sympathetic activity on the sinus node. Physiologic or pharmacologic maneuvers that are vagomimetic (Valsalva maneuver or phenylephrine-induced hypertension), vagolytic (atropine), sympathomimetic (isoproterenol or hypotension by nitroprusside), or sympatholytic (b-adrenergic blocking agents) can be utilized, singly and in combination. These studies are designed to test the response of the sinus node to autonomic stimulation and inhibition and thereby characterize the status of autonomic regulation of the sinus node. Abnormalities of the autonomic control of sinus function are particularly common in patients in whom asymptomatic sinus bradycardia is documented.

Intrinsic Heart Rate This is a manifestation of the primary activity of theSA node, and its determination requires chemical autonomic blockade of the heart with a combination of atropine and a beta blocker. Normal values of intrinsic heart rate (in beats per minute) are calculated by the formula 118.1- (0.57 ´ age). The use of autonomic blockade can separate patients with asymptomatic sinus bradycardia into a group with primary sinus node dysfunction (slow intrinsic heart rate) and a group with autonomic imbalance (normal intrinsic heart rate). Autonomic blockade is particularly useful when combined with invasive assessment of sinus node function. Autonomic blockade may depress conduction in patients with intrinsic disease of the conduction system and should be carried out only in a setting where arrhythmias can be monitored and treated rapidly.

EVALUATION

The invasive electrophysiologic investigation ofSA node dysfunction should be undertaken in patients who have had symptoms compatible with SA node dysfunction and in whom no documentation of the arrhythmia responsible for these symptoms has been obtained by prolonged Holter monitoring. Asymptomatic patients with sinus bradycardia need *not* be tested, since no therapy is indicated. Similarly, symptomatic patients withECGdocumentation of asystole, sinoatrial block or arrest, or the bradycardia-tachycardia syndrome do not require electrophysiologic tests for diagnosis. However, in symptomatic patients without documentation of an arrhythmia, electrophysiologic assessment of SA node function can yield information that may be used to guide appropriate therapy.

The results of electrophysiologic tests of sinus node function must be interpreted with

caution.SA node dysfunction coexists frequently with other disorders such asAVconduction disturbances, which may cause symptoms such as syncope. Electrophysiologic evaluation of patients with symptoms such as undiagnosed syncope must not stop with the demonstration of abnormalities of SA node dysfunction or carotid sinus hypersensitivity. Instead, complete evaluation, including His bundle recordings and programmed atrial and ventricular stimulation (Chap. 230), is necessary to search for additional electrophysiologic abnormalities that could be responsible for symptoms.

TREATMENT

Permanent pacemakers (p. 1290) are the mainstay of therapy for patients with symptomaticSA node dysfunction. Patients with intermittent paroxysms of bradycardia or sinus arrest and with the cardioinhibitory form of the hypersensitive carotid sinus syndrome are usually adequately treated by demand ventricular pacemakers. These devices are reliable, relatively inexpensive, and suffice to prevent episodic symptoms due to abrupt bradycardia. Whether dual-chamber pacing offers any advantages to ventricular pacing in such circumstances remains uncertain. Patients with symptomatic chronic sinus bradycardia or frequent prolonged episodes of sinus node dysfunction do better with dual-chamber pacemakers that preserve the normalAVactivation sequence. Although theoretically an atrial demand pacemaker should be adequate for patients with SA node dysfunction, the frequent accompaniment of dysfunction in other portions of the cardiac conduction system usually mandates placement of a pacemaker capable of ventricular pacing. Recent studies suggest that AV sequential pacing may also be useful in preventing atrial fibrillation, an important component of the bradycardia-tachycardia syndrome.

AV CONDUCTION DISTURBANCES

The specialized cardiac conducting system normally ensures synchronous conduction of each sinus impulse from the atria to the ventricles. Abnormalities of conduction of the sinus impulse to the ventricles may portend the development of heart block, which can ultimately lead to syncope or cardiac arrest. In order to evaluate the clinical significance of conduction abnormalities, the physician must assess (1) the site of conduction disturbance, (2) the risk of progression to complete block, and (3) the probability that a subsidiary escape rhythm arising distal to the site of block will be electrophysiologically and hemodynamically stable. This latter point is perhaps the most important, since the rate and stability of the escape pacemaker determine what symptoms result from heart block. The escape pacemaker followingAV nodal block is usually in the His bundle, which generally has a stable rate of 40 to 60 beats per minute and is associated with a QRS complex of normal duration (in the absence of a preexisting intraventricular conduction defect). This contrasts with escape rhythms arising in the distal His-Purkinje system, which have lower intrinsic rates (25 to 45 beats per minute), manifest wide QRS complexes with prolonged duration, and are unstable. Thus, the most important issue is to assess the risk of infra- or intra-His block (which always mandates a pacemaker) or AV nodal block in which the frequency of the escape pacemaker is not sufficient to meet hemodynamic requirements (Table 229-1). Although prolonged QRS complexes are invariable when the distal His-Purkinje pacemakers form the escape mechanism, wide QRS complexes can also coexist with AV nodal block and a His bundle rhythm. Therefore, QRS morphology alone may not be adequate to identify the site of block.

ETIOLOGY

TheAV node is supplied by the parasympathetic and sympathetic nervous systems and is sensitive to variations in autonomic tone. Chronic slowing of AV nodal conduction may be seen in highly trained athletes who have hypervagotonia at rest. A variety of diseases and drugs can also influence AV nodal conduction. These include acute processes such as myocardial infarction (particularly inferior), coronary spasm (usually of the right coronary artery), digitalis intoxication, excesses of beta and/or calcium blockers, acute infections such as viral myocarditis, acute rheumatic fever, infectious mononucleosis, and miscellaneous disorders such as Lyme disease, sarcoidosis, amyloidosis, and neoplasms, particularly cardiac mesotheliomas. AV nodal block may also be congenital.

Two degenerative diseases are commonly responsible for damage to the specialized conducting system and produceAV block usually associated with bundle branch block (Chap. 226). In *Lev's disease*, there is calcification and sclerosis of the fibrous cardiac skeleton, which frequently involves the aortic and mitral valves, the central fibrous body, and the summit of the ventricular septum. *Lenegre's disease* appears to be a primary sclerodegenerative disease within the conducting system itself with no involvement of the myocardium or the fibrous skeleton of the heart. These two diseases are probably the most common causes of isolated chronic heart block in adults. Hypertension and aortic and/or mitral stenosis are specific disorders that either accelerate the degeneration of the conducting system or have a direct effect by calcification and fibrosis involving the conducting system.

First-degree AV block, more properly termed *prolonged AV conduction*, is classically characterized by a PR interval >0.20 s, but use of this value may be misleading in terms of clinical significance. Since the PR interval is determined by atrial,AVnodal, and His-Purkinje activation, delay in any one or more of these structures can contribute to a prolonged PR interval. In the presence of a QRS complex of normal duration, a PR interval >0.24 s almost invariably is due to a delay within the AV node. If the QRS is prolonged, delays may be present at any of the levels mentioned above. Delay within the His-Purkinje system is always accompanied by a prolonged QRS duration but can occur with a relatively normal PR interval (Fig. 229-6). However, as indicated below, it is only with intracardiac recordings that the exact site of delay can be determined.

Second-degree heart block (intermittentAVblock) is present when some atrial impulses fail to conduct to the ventricles. Mobitz type I second-degree AV block (AV Wenckebach block) is characterized by progressive PR interval prolongation prior to block of an atrial impulse (Fig. 229-7*A*). The pause that follows is less than fully compensatory (i.e., is less than two normal sinus intervals), and the PR interval of the first conducted impulse is shorter than the last conducted atrial impulse prior to the blocked P wave. Usually the difference between the longest and shortest PR intervals exceeds 100 ms. This type of block is almost always localized to the AV node and associated with a normal QRS duration, although bundle branch block may be present. It is seen most often as a transient abnormality with inferior wall infarction or with drug intoxication, particularly digitalis, beta blockers, and occasionally calcium channel antagonists. This type of block can also be observed in normal individuals with heightened vagal tone. Although Mobitz

type I block can progress to complete heart block, this is uncommon, except in the setting of acute inferior wall myocardial infarction. Even when it does, however, the heart block is usually well tolerated because the escape pacemaker usually arises in the proximal His bundle and provides a stable rhythm. As a result, the presence of Mobitz type I second-degree AV block rarely mandates aggressive therapy. Therapeutic decisions depend on the ventricular response and the symptoms of the patient. If the ventricular rate is adequate and the patient is asymptomatic, observation is sufficient.

In Mobitz type II second-degreeAVblock, conduction fails suddenly and unexpectedly without a preceding change in PR intervals (Fig. 229-7*B*). It is generally due to disease of the His-Purkinje system and is most often associated with a prolonged QRS duration. When Mobitz type II block occurs with a normal QRS duration, an intra-His site of block should be expected (Fig. 229-7*C*). It is important to recognize this type of block because it has a high incidence of progression to complete heart block with an unstable, slow, lower escape pacemaker. Therefore, pacemaker implantation is necessary in this condition. Mobitz type II block may occur in the setting of anteroseptal infarction or in the primary or secondary sclerodegenerative or calcific disorders of the fibrous skeleton of the heart. In so-called high-degree AV block there are periods of two or more consecutively blocked P waves, but intermittent conduction can be demonstrated. Block is usually in the His-Purkinje system, but simultaneous block in the AV node may also be present. Regardless of the site of origin of the escape rhythm, if it is slow and the patient is symptomatic, a cardiac pacemaker is mandatory.

Third-degree AV block is present when no atrial impulse propagates to the ventricles. If the QRS complex of the escape rhythm is of normal duration, occurs at a rate of 40 to 55 beats per minute, and increases with atropine or exercise,AV nodal block is probable. Congenital complete AV block is usually localized to the AV node. If the block is within the His bundle, the escape pacemaker is usually less responsive to these perturbations. If the escape rhythm of the QRS is wide and associated with rates £40 beats per minute, block is usually localized in, or distal to, the His bundle and mandates a pacemaker, since the escape rhythm in this setting is unreliable (Fig. 229-8). Some patients with infra-His bundle block are capable of retrograde conduction. In such patients, a "pacemaker syndrome" (see below) may develop if a simple ventricular pacemaker is used. Dual-chamber pacemakers eliminate this potential problem.

AV DISSOCIATION

AV dissociation exists whenever the atria and ventricles are under the control of two separate pacemakers and, while present in complete AV block, can occur in the absence of a primary conduction disturbance. AV dissociation unrelated to heart block may occur under two circumstances: First, it may develop with an AV junctional rhythm in response to severe sinus bradycardia. When the sinus rate and the escape rate are similar and the P waves occur just before, in, or following the QRS complex, *isorhythmic AV dissociation* is said to be present. Treatment usually consists of removal of the offending cause of sinus bradycardia (i.e., discontinuation of digitalis, beta blockers, or calcium antagonists), accelerating the sinus node by vagolytic agents, or insertion of a pacemaker if the escape rhythm is slow and results in symptoms. Second, AV dissociation can be caused by an enhanced lower (junctional or ventricular) pacemaker that competes with normal sinus rhythm and frequently exceeds it. This has been called

interference AV dissociation because the rapid lower pacemaker results in bombardment of the AV node in a retrograde fashion, rendering it refractory to the normal sinus impulses. Thus failure of antegrade conduction is a physiologic response in this circumstance. Interference dissociation commonly occurs during ventricular tachycardia, accelerated junctional or ventricular rhythms seen with digitalis intoxication, myocardial ischemia and/or infarction, or local irritation following cardiac surgery. The accelerated rhythm should be treated with either antiarrhythmic drugs (Chap. 230), removal of an offending drug, or correction of the metabolic abnormality or ischemia.

INTRACARDIAC ELECTROCARDIOGRAPHIC RECORDINGS IN DIAGNOSIS AND MANAGEMENT

The main therapeutic decision in patients withAVconduction disturbance is whether or not a permanent pacemaker is required, and a number of circumstances exist in which His bundle electrocardiography can be a useful diagnostic tool upon which to base this decision. It is unquestionable that patients with *symptomatic* second- or third-degree AV block should be paced, and therefore, these patients do not require electrophysiologic study. However, intracardiacECGrecordings can be useful in at least the following four groups of patients:

1. *Patients with syncope and bundle branch or bifascicular block without documentation ofAVblock*. In such patients, the demonstration of marked infra-His bundle conduction disturbances, i.e., a prolonged HV interval (>100 ms), may usually be taken as an indication of the need for the insertion of the permanent pacemaker. Complete electrophysiologic evaluation, including atrial and ventricular programmed stimulation, is indicated to help identify other possible cardiac etiologies for the syncope. Since the incidence of significant advanced AV block is low in *asymptomatic* patients who have bifascicular block, electrophysiologic evaluation or permanent pacemakers are not cost-effective. In this group, observation appears most reasonable.

2. *Patients with 2:1 AV conduction*. Intracardiac recordings are necessary to ascertain the site of the conduction disturbance because the typicalECGfeatures of Mobitz type I or Mobitz type II block cannot be discerned during a 2:1 pattern ofAVconduction on the surface ECG. Intracardiac recordings may demonstrate that AV nodal block, intra-His bundle block, infra-His bundle block, or combinations of block may be responsible (Figs. 229-7 and229-8). A surface ECG finding that suggests an infra-His bundle lesion is the presence of alternating bundle branch block associated with changing PR intervals. Intracardiac recordings in such patients confirm that the block is almost always in the His-Purkinje system. Increasing block with exercise or following atropine suggests intra- or infra-His block (Table 229-2). The finding of infra- or intra-His bundle block in patients with asymptomatic second-degree AV block mandates pacemaker therapy because of the high likelihood of the development of symptomatic high-grade AV block and syncope.

3. *Patients with Wenckebach block in the presence of bundle branch block*. This situation, particularly when the maximal change in PR interval is£ 50 ms, can suggest intra- or infra-His Wenckebach block, in which case a pacemaker is mandated. Intracardiac recordings are necessary to make this diagnosis.

4. *Asymptomatic patients with third-degreeAVblock*. In such patients, electrophysiologic studies may be useful in assessing the stability of the junctional pacemaker. Pacing is indicated when the His bundle escape pacemaker is shown to be unstable by an inadequate response to exercise, atropine, or isoproterenol or by a prolonged junctional recovery time following ventricular pacing.

GENETIC CONSIDERATIONS

A number of congenital and familial syndromes involving the cardiac conduction system have been described. An example of a congenital condition that is transmitted but not genetic is congenital complete heart block associated with material systemic lupus erythematosus. This disorder is associated with maternal IgG autoantibodies to several ribonucleoproteins that are transplacentally transmitted to the fetus and damage the fetalAV node. The fetal conduction disease is generally clinically evident by the second trimester and is associated with significant fetal mortality and neonatal requirement of cardiac pacing.

The embryonic development of the cardiac septa and conduction system occur together, and clinical disorders have been described, including the Holt-Oram syndrome, an autosomal dominant disorder including upper limb dysplasia and atrial septal defect, often with conduction disturbances in theAV node. Studies of families with a high incidence of congenital heart disease, including ostium secundum atrial septal defect and conduction disorders in the AV node, have identified the gene NKX2-5 on chromosome 5q35 as important in the regulation of septation and in the development and function of the AV node. A familial syndrome of progressive complete heart block has also long been recognized. The gene for this disorder has been mapped to a region on chromosome 19q13. Familial disorders ofSA node function have also been described, but specific details of abnormal genetic sites are not available.

TREATMENT

Pharmacologic Therapy Pharmacologic therapy is usually reserved for acute situations. Atropine (0.5 to 2.0 mg intravenously) and isoproterenol (1 to 4 ug/min intravenously) are useful in increasing heart rate and decreasing symptoms in patients with sinus bradycardia orAV block localized to the AV node. They have an insignificant effect on lower pacemakers. In patients with neurovascular syncope, beta blockers and disopyramide have been suggested as methods to depress left ventricular function and decrease mechanoreceptor-related reflexes. Mineralocorticoids, ephedrine, and theophylline have also been reported to be of benefit to occasional patients. Unfortunately, no controlled study has shown that any of these pharmacologic modalities works in a predictable fashion in all patients. Further work on delineating different mechanisms in different patient groups may allow us to apply pharmacologic agents more appropriately. Long-term therapy of bradyarrhythmias is best accomplished by pacemakers.

Pacemakers External energy sources can be used to stimulate the heart when disorders in impulse formation and/or transmission lead to symptomatic bradyarrhythmias (Fig. 229-CD1). Pacer stimuli can be applied to the atria and/or ventricles. Indications for pacemaker insertion are listed in theGuidelines.

Temporary Pacing This is usually instituted to provide immediate stabilization prior to permanent pacemaker placement or to provide pacemaker support when a bradycardia is precipitated by what is presumed to be a transient event such as ischemia or drug toxicity. Temporary pacing is usually achieved by the transvenous insertion of an electrode catheter with the catheter positioned in the right ventricular apex and attached to an external generator. This procedure is associated with a small risk of cardiac perforation, infection at the insertion site, and thromboembolism; the risk of the latter two complications increases markedly if the pacing wire is left in place for more than 48 h. The development of an entirely external transthoracic cardiac pacing system may preclude the need for transvenous pacing in selected patients. However, occasional failure of ventricular capture and significant discomfort related to the large current required for effective transthoracic ventricular stimulation preclude the uniform use of this approach.

Permanent Pacing This mode of pacing is instituted for persistent or intermittent symptomatic bradycardia not related to a self-limiting precipitating factor or for documented infranodal second- or third-degreeAVblock. Permanent pacing leads are usually inserted transvenously through the subclavian or cephalic vein with the leads positioned in the right atrial appendage for atrial pacing and the right ventricular apex for ventricular pacing. The leads are then attached to the pulse generator, which is inserted into a subcutaneous pocket below the clavicle. Epicardial lead placement is used when (1) transvenous access cannot be obtained; (2) the chest is already open, i.e., in the course of a cardiac operation; and (3) adequate endocardial lead placement cannot be achieved. Most pacemaker generators are powered by lithium batteries. The life expectancy of the generator is related to (1) voltage output required for capture, (2) requirement for incessant or intermittent pacing, and (3) number of cardiac chambers paced. Life expectancy of the simple ventricular demand pacemaker can exceed 10 years.

Pacing Code A code consisting of three to five letters has been developed for describing pacemaker type and function (Table 229-3). The first letter indicates the chamber(s) paced and is designated *V* for ventricular pacing, *A* for atrial pacing, or *D* for dual-chamber (both atrial and ventricular) pacing. The second letter indicates the chamber in which electrical activity is sensed and is also indicated by *A*, *V*, or *D*. An additional designation, *O*, has been used when pacemaker discharge is not dependent on a sensed electrical activity. The third letter refers to the response to a sensed electric signal. The letter *O* represents no response to an underlying electric signal, usually related to the absence of associated sensing function; *I* represents inhibition of pacing function; *T* represents triggering of pacing function; and *D* indicates a dual response, i.e., spontaneous atrial and ventricular activity inhibiting atrial and ventricular pacing and atrial activity triggering a ventricular response. Additional fourth and fifth letters of the pacing code have been recommended to indicate whether the pacemaker is programmable and has rate modulation (fourth) and whether special antitachycardia functions are available (i.e., antitachycardia pacing, *T*, and delivery of high- or low-energy shocks). In the fourth category, *M* represents multiprogrammability and *R* represents rate response ("physiologic") pacing. It follows from the described code that the standard VVIR (ventricular demand pacemaker) paces the ventricle, senses the ventricle, is inhibited by sensed spontaneous ventricular activity, and has rate

modulation, while the DDDR pulse generator is capable of sensing and pacing both the atria and ventricles and has a dual response to the sensed atrial and ventricular activity as described above (Fig. 229-9). Both pacemakers have rate modulation (*R*). "Physiologic" pacemakers use sensors (muscular activity, respiratory rate, temperature, O_2saturation, QT interval, etc.) as methods to allow the pacemaker to increase the heart rate in response to physiologic demands, i.e., exercise. These pacemakers are essential when chronotropic incompetence is present and an increase in heart rate is required to enhance physiologic performance. Studies have shown that such "physiologic" pacemakers improve exercise tolerance and relieve symptoms to a greater degree than fixed-rate pacemakers.

Selection of the appropriate pacemaker and pacing mode depends on the clinical condition and the type of bradyarrhythmia being treated. The two most common pacing mode selections are DDD and VVI. DDD providesAVsequential pacing, which is ideally suited for the relatively young and active patient who has intact sinus node function or intermittent dysfunction and high-grade persistent or intermittent AV block. The DDD mode will allow for physiologic atrial sensed and ventricular paced rates and improve exercise tolerance. AV synchrony and dual-chamber pacing may also be desirable in patients with borderline hemodynamic reserve who are dependent on atrial contribution to cardiac output and in those patients who develop the pacemaker syndrome (see below) in response to ventricular demand pacing.

Rate-responsive DDD (i.e., DDDR) pacing is indicated when chronotropic incompetence is present in a patient who requiresAVsynchrony. The DDD pacing mode is contraindicated in chronic atrial fibrillation or flutter, because rapid and irregular ventricular pacing will occur to the upper rate limit. In some cases this will produce a more rapid ventricular rate than the patient's own rate in the absence of a pacemaker. DDD pacemakers must either automatically switch (i.e., mode-switching function) or be reprogrammed to the VVI mode. Almost all such pacemakers are now combined with some form of rate responsiveness so that when the device functions in the VVI mode, it also will respond to physiologic demands (VVIR).

Chronotropic insufficiency (i.e., the inability of the sinus rate to accelerate) is a contraindication for a DDD pacemaker, since such a pacemaker will act as a "fixed-rate" pacemaker at the programmed lower rate. In these situations, a rate-adaptive or "physiologic" pacemaker is indicated (VVIR or DDDR). In patients with impaired sinus node function or chronic atrial fibrillation, a sensor-driven, rate-adaptive pacemaker must be implanted. As mentioned earlier, these pacemakers automatically adjust ventricular pacing rates to a sensed indicator of exertion. The DDD pacing mode may also be contraindicated in patients with intermittent or persistent ventriculoatrial conduction, who may develop pacemaker-mediated tachycardia (see below).

Programmability of Pacemakers This allows for modification of pacing function after implantation and for adaptation to changes in clinical needs. Pacemaker programming is accomplished by activation of the programming head positioned over the implanted pulse generator after making the desired changes in programmable parameters (Table 229-3). A radio frequency system is routinely used to communicate the program to the pacemaker. A high degree of sophistication is required to recognize the presence and causes of pacemaker malfunction and their treatment.

Complications Adverse effects of permanent pacing are usually associated with failure or malfunction of the pacing system. These problems are usually secondary to over- or undersensing, output failure, and/or lead fracture or displacement. Two other problems may occur. The *pacemaker syndrome* consists of fatigue, dizziness, syncope, and distressing pulsations in the neck and chest and can be associated with adverse hemodynamic effects. The pathophysiologic contributors to the pacemaker syndrome include (1) loss of atrial contribution to ventricular systole; (2) vasodepressor reflex initiated by cannon *a* waves, which are caused by atrial contractions against a closed tricuspid valve and observed in the jugular venous pulse (Chap. 225); and (3) systemic and pulmonary venous regurgitation due to atrial contraction against a closedAVvalve. The symptoms associated with the pacemaker syndrome can be prevented by maintaining AV synchrony by dual-chamber pacing or, in the case of a ventricular demand pacemaker, by programming an escape rate 15 to 20 beats per minute below that of the paced rate (i.e., hysteresis). As a result of this programming, sinus activity and thus atrial contraction will be less likely to occur at the same time as ventricular pacing and ventricular contraction. The second major problem peculiar to dual-chamber pacemakers is the development of *pacemaker-mediated tachycardia*. In this instance, retrograde depolarization of the atria, resulting from a premature ventricular depolarization or a paced ventricular complex, is sensed and leads to subsequent triggering of ventricular pacing. This, in turn, can result in repetition of the phenomenon of ventriculoatrial conduction with the development of an endless-loop, pacemaker-mediated tachycardia. It may be corrected by reprogramming the atrial refractory period.

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230. THE TACHYARRHYTHMIAS - *Mark E. Josephson, Peter Zimetbaum*

MECHANISMS OF TACHYARRHYTHMIAS

Tachyarrhythmias may be divided into disorders of impulse propagation and disorders of impulse formation.

REENTRY

Disorders of impulse propagation (reentry) are generally considered to be the most common mechanism of sustained paroxysmal tachyarrhythmia. The requirements for initiating reentry include (1) electrophysiologic inhomogeneity (i.e., differences in conduction and/or refractoriness) in two or more regions of the heart connected with each other to form a potentially closed loop; (2) unidirectional block in one pathway; (3) slow conduction over an alternative pathway, allowing time for the initially blocked pathway to recover excitability; and (4) reexcitation of the initially blocked pathway to complete a loop of activation (Fig. 230-1). Repetitive circulation of the impulse over this loop can produce a sustained tachyarrhythmia. While anatomic obstacles may underlie reentry and provide an inexcitable center around which the impulse can circulate, they are not essential. Reentrant arrhythmias can be reproducibly initiated and terminated by premature complexes and rapid stimulation. The response of these arrhythmias to stimulation can help distinguish them from arrhythmias caused by triggered activity.

ENHANCED AUTOMATICITY

Disorders of impulse formation can be subdivided into tachyarrhythmias caused by enhanced automaticity and those caused by triggered activity. In addition to the sinus node, automatic pacemaker activity can be observed in specialized atrial fibers, fibers of the atrioventricular (AV) junction, and Purkinje fibers (Chap. 229). Myocardial cells do not normally possess pacemaker activity. Enhancement of normal automaticity in latent pacemaker fibers or the development of abnormal automaticity due to partial depolarization of the resting membrane occurs as a consequence of a variety of pathophysiologic states, which include (1) increased endogenous or exogenous catecholamines, (2) electrolyte disturbances (e.g., hyperkalemia), (3) hypoxia or ischemia, (4) mechanical effects (e.g., stretch), and (5) drugs (e.g., digitalis). Tachycardia caused by automaticity cannot be started or stopped by pacing.

TRIGGERED ACTIVITY

Rhythms due to triggered activity are events that do not occur spontaneously but require a change in cardiac electrical frequency as a trigger. Triggered activity may be caused by early afterdepolarizations, which occur during phases 2 and 3 of the action potential, or delayed afterdepolarizations, which occur following completion of phase 3 of the action potential (Fig. 229-2). Triggered activity has been observed in atrial, ventricular, and His-Purkinje tissue under conditions such as increased local catecholamine concentration, hyperkalemia, hypercalcemia, and digitalis intoxication (delayed afterdepolarizations) or during bradycardia, hypokalemia, or other situations prolonging action potential duration (early afterdepolarizations). All of these conditions produce an accumulation of intracellular calcium. With increasing amplitude of the

afterdepolarizations, threshold can be reached and repetitive activity produced. The exact role of triggered activity in spontaneous clinical arrhythmias is unknown, but tachyarrhythmias associated with digitalis intoxication, accelerated idioventricular rhythm in acute infarction and/or reperfusion, and exercise-induced ventricular tachycardia (VT) are believed to be caused by triggered activity due to delayed afterdepolarizations. *Torsade de pointes* ("twisting of the points"; polymorphic VT associated with long QT intervals) may be caused by triggered activity due to early afterdepolarizations, although reentry may also be operative.

The use of electrophysiologic studies, i.e., intracardiac recordings and programmed stimulation, has greatly expanded the understanding of the mechanisms of tachyarrhythmias. In addition to helping diagnose arrhythmias, these techniques may be of value in determining the most appropriate types of therapy because they allow the physician to observe the hemodynamic and symptomatic consequences of the arrhythmia in the presence or absence of therapy. Electrophysiologic studies of tachycardias require the positioning of multiple electrode catheters at critical areas within the heart. These electrodes must be capable of both stimulating and recording from multiple sites in the atria and/or ventricles.

PREMATURE COMPLEXES

ATRIAL PREMATURE COMPLEXES (APC)

APCscan be found on 24-h Holter monitoring in over 60% of normal adults. APCs are usually asymptomatic and benign, although at times they may be associated with palpitations. In susceptible patients, they can initiate paroxysmal supraventricular tachycardias. APCs may originate from any location in either atrium, and they are recognized on the electrocardiogram (ECG) as early P waves with a morphology that differs from the sinus P wave (Fig. 230-2). While APCs usually conduct to the ventricles when they occur late in the cardiac cycle, early APCs may reach theAVconduction system while it is still in its relative refractory period, resulting in a conduction delay manifested by prolonged PR interval following the premature P wave (Fig. 230-2). Very early APCs may even block in the AV node if this structure is encountered during its effective refractory period. APCs, whether conducted or not, are usually followed by a pause before a return to sinus activity. Most commonly, an APC enters and resets the sinus node, so the sum of the pre- and postextrasystolic PP intervals is less than the sum of two sinus PP intervals (Fig. 230-2). In this case, the pause is said to be less than fully compensatory. The QRS complex following most APCs is normal, although early APCs may be followed by aberrantly conducted QRS complexes due to the premature complex falling within the relative refractory period of the His-Purkinje system.

Since mostAPCs are asymptomatic, treatment is not required. When they cause palpitations or trigger paroxysmal supraventricular tachycardias (see below), treatment may be useful. Factors that precipitate APCs, such as alcohol, tobacco, or adrenergic stimulants, should be identified and eliminated; in their absence, mild sedation or the use of a beta blocker may be tried.

AVJUNCTIONAL COMPLEXES

The site of origin of these complexes is thought to be in the bundle of His, since the normal AV node in vivo possesses no automaticity. AV junctional complexes are less common than either atrial or ventricular premature complexes and are more often associated with cardiac disease or digitalis intoxication. Junctional premature impulses can conduct both antegradely to the ventricles and retrogradely to the atrium and, on rare occasions, may fail to conduct in either direction. Premature AV junctional complexes can be recognized by normal-appearing QRS complexes that are not preceded by a P wave. Retrograde P waves (inverted in leads II, III, and aVF) may be observed after the QRS complex.

While often asymptomatic, junctional premature complexes may be associated with palpitations and cause cannon *a* waves, which may result in distressing pulsations in the neck. When symptomatic, they should be treated likeAPCs.

VENTRICULAR PREMATURE COMPLEXES (VPCS)

These are among the most common arrhythmias and occur in patients with and without heart disease. Of adult males, ³60% will exhibit VPCs during a 24-h Holter monitoring. In patients without heart disease, VPCs have not been shown to be associated with any increased incidence in mortality or morbidity. VPCs may occur in up to 80% of patients with previous myocardial infarction, and in this setting, if frequent (>10 per hour) and/or complex (occurring in couplets), they have been associated with increased mortality. However, cardiac mortality in such patients usually occurs in association with significantly impaired ventricular function. While frequent and complex ventricular ectopy is an independent risk factor, it is not as strong a risk factor as is impaired ventricular function. Moreover, even though ventricular tachycardia and/or fibrillation may be the basis for the sudden death in these patients, this does not a priori establish a cause-and-effect relation between spontaneous ectopy and life-threatening ventricular tachycardia or fibrillation. Very early cycle (R-on-T) VPCs have been stated by some to increase the risk of sudden death. Although this has been observed during acute ischemia and in the setting of QT prolongation, frequently,VT or fibrillation is precipitated by VPCs that occur after the T wave of the prior beat.

VPCsare recognized by wide (usually >0.14 s), bizarre QRS complexes that are not preceded by P waves (Fig. 230-3*A*). They may bear a relatively fixed relationship to the preceding sinus complex (i.e., fixed coupled VPCs). When fixed coupling is not present and the interval between VPCs has a common denominator, *ventricular parasystole* is said to be present (Fig. 230-4). Under these circumstances, the VPCs are a manifestation of abnormal automaticity of a protected ventricular focus. Because this focus is not penetrated by sinus impulses, it is not reset by them, and the interectopic intervals remain relatively fixed (£120 ms variation of mean RR cycle length).

VPCsmay occur singly; in patterns of bigeminy, in which every sinus beat is followed by a VPC; in trigeminy, in which two sinus beats are followed by a VPC; in quadrigeminy, etc. Two successive VPCs are termed *pairs* or *couplets*, while three or more consecutive VPCs are termed *ventricular tachycardia* when the rate exceeds 100 beats per minute (Fig. 230-3*B*). VPCs may have similar morphologies (monomorphic, or uniform) or different morphologies (polymorphic, or multiformed).

Most commonly,VPCs are not conducted retrogradely to the atrium to reset the sinoatrial node. Thus they produce a fully compensatory pause; i.e., the interval between conducted sinus beats that bracket the VPC equals two basic RR intervals. Ventricular impulses may also manifest retrograde conduction to the atrium and cause inverted P waves in leads II, III, and aVF. This retrograde atrial activation can reset the sinus node, and the pause that results may therefore be less than compensatory. In many instances, the VPC will not be associated with retrograde ventriculoatrial (VA) conduction but may block retrogradely in theAV node. This renders the AV node refractory to the subsequent sinus beat and causes slowed conduction (i.e., prolonged PR interval) or block of the next sinus P wave. This prolonged PR interval is said to be a manifestation of concealed retrograde conduction of the ventricular impulse into the AV node. A VPC that does not produce any manifestation of retrograde concealed conduction and fails to influence the oncoming sinus impulse is termed an *interpolated VPC*.

VPCscan cause palpitations or neck pulsations secondary to either the occurrence of cannon *a* waves or the increased force of contraction due to postextrasystolic potentiation of ventricular contractility. Patients with frequent VPCs or bigeminy may rarely develop syncope or lightheadedness because the VPCs do not result in an adequate stroke volume and the cardiac output is reduced by the "halving" of the heart rate.

TREATMENT

In the absence of cardiac disease, isolated asymptomaticVPCs, regardless of configuration and frequency, need no treatment. When arrhythmias are symptomatic, the symptoms should first be addressed by either allaying the patient's anxiety or, if this is not successful, reducing the frequency of the VPCs with antiarrhythmic agents. b-Adrenergic blockers may be successful in managing VPCs that occur primarily in the daytime or under stressful situations and in specific settings such as mitral valve prolapse and thyrotoxicosis. While other antiarrhythmic agents may be tried should this be unsuccessful, their risk may outweigh any benefits. In patients with cardiac disease, frequent VPCs are associated with an increased risk of sudden and nonsudden cardiac death, and many physicians have attempted to eliminate or reduce the frequency of these VPCs in an attempt to reduce this risk. However, the cause-and-effect relationship of the VPCs to fatal events has never been established. The ability of pharmacologic antiarrhythmic therapy guided by continuousECGmonitoring to reduce the risk of sudden death in postmyocardial infarction patients with frequent (³6 per minute) VPCs was tested by the Cardiac Arrhythmia Suppression Trial (CAST). This study compared mortality in patients whose ectopy was suppressed by one of three agents (encainide, flecainide, or moricizine) and then randomized to treat with either the "effective" drug or placebo. After a mean follow-up of 2 years, the study was discontinued because both the sudden death and overall mortality rate were significantly increased in patients receiving antiarrhythmic agents. This study has shown that in patients having the characteristics of the study population, abolition of ventricular ectopy by pharmacologic therapy cannot be used as a marker to define reduction of the risk of sudden death after myocardial infarction and, in fact, may increase mortality. Recent studies have evaluated the use of electrophysiologic testing and implantable cardioverter/defibrillator (ICD) placement in the management of patients at high risk for sudden death (i.e., those

with left ventricular ejection fractions<40% and nonsustainedVT). These studies have found that induction of a sustained ventricular arrhythmia through programmed electrical stimulation selects a group of these patients whose prognosis is improved with implantation of a defibrillator. These studies have found no correlation between the rate, morphology, or duration of nonsustained episodes of VT and the likelihood of having a sustained ventricular arrhythmia.

Antiarrhythmic agents can also produce the lethal arrhythmias that they are given to prevent (proarrhythmic effects). Thus therapy directed towardVPCs in the setting of chronic cardiac disease may result in an inappropriate and costly use of agents without proven efficacy and with potential side effects in many patients. The high incidence of side effects and the frequent exacerbation of arrhythmias caused by all antiarrhythmic drugs make it mandatory to monitor patients being treated with such agents.

In acute myocardial infarction, the greatest incidence of primary ventricular fibrillation occurs within the first 24 h (Chap. 243). Temporary prophylactic antiarrhythmic therapy with lidocaine or procainamide was formerly recommended for all patients with acute infarction, regardless of the presence or degree of spontaneous ectopy. However, failure to improve overall survival and drug toxicity have led most physicians to recommend prophylactic antiarrhythmic therapy only to young patients with complicated infarctions, where a favorable risk-benefit ratio may be obtained. Other studies have shown that intravenous beta blockers may also reduce the incidence of primary ventricular fibrillation.

TACHYCARDIAS

Tachycardias refer to arrhythmias with three or more complexes at rates exceeding 100 beats per minute; they occur more often in structurally diseased than in normal hearts. Those paroxysmal tachycardias that are initiated byAPCs orVPCs are considered to be due to reentry, except some of the digitalis-induced tachyarrhythmias, which are probably due to triggered activity (see below).

If the patient is hemodynamically stable, an attempt should be made to determine the mechanism and origin of the tachycardia, since this will usually lead to an appropriate therapeutic decision. Information to be obtained from theECGincludes (1) the presence, frequency, morphology, and regularity of P waves and QRS complexes; (2) the relationship between atrial and ventricular activity; (3) a comparison of the QRS morphology during sinus rhythm and during the tachycardia; and (4) the response to carotid sinus massage or other vagal maneuvers. It is useful first to compare a 12-lead ECG during the tachycardia with one recorded during sinus rhythm. One can also utilize the electrodes situated at the end of a flexible pacing catheter inserted into the esophagus behind the left atrium to record atrial activity.

Observation of the jugular venous pulse can provide clues to the presence of atrial activity and its relationship to ventricular ectopy. Intermittent cannon *a* waves suggestAVdissociation, while persistent cannon a waves suggest 1:1VAconduction. Flutter waves may be seen or no atrial activity may be apparent, as in the presence of atrial flutter and fibrillation, respectively. The arterial pulse may also manifest AV dissociation or atrial fibrillation by demonstrating variations in amplitude. A first heart

sound of variable intensity during a regular rhythm also suggests AV dissociation or atrial fibrillation (AF).

Carotid sinus pressure should only be applied while the patient is electrocardiographically monitored with resuscitative equipment available to manage the rare episode of asystole and/or ventricular fibrillation associated with this procedure. Carotid sinus massage should not be performed in patients with carotid arterial bruits. The patient should be positioned flat with the neck extended. Massage of one carotid bulb at a time should be performed by applying firm pressure just underneath the angle of the jaw for up to 5 s. Alternative vagomimetic maneuvers include the Valsalva maneuver, immersion of the face in cold water, and administration of 5 to 10 mg edrophonium.

SINUS TACHYCARDIA

In the adult, sinus tachycardia is said to be present when the heart rate exceeds 100 beats per minute (bpm): sinus tachycardia rarely exceeds 200 bpm and is not a primary arrhythmia; instead, it represents a physiologic response to a variety of stresses, such as fever, volume depletion, anxiety, exercise, thyrotoxicosis, hypoxemia, hypotension, or congestive heart failure. Sinus tachycardia has a gradual onset and offset. TheECGdemonstrates P waves with sinus contour preceding each QRS complex. Carotid sinus pressure usually produces modest slowing with a gradual return to the previous rate upon cessation. This contrasts with the response of paroxysmal supraventricular tachycardias, which may slow slightly and terminate abruptly.

TREATMENT

Sinus tachycardia should not be treated as a primary arrhythmia, since it is almost always a physiologic response to a demand placed on the heart. As such, the therapy should be directed to the primary disorder. This may involve institution of digitalis and/or diuretics for heart failure and oxygen for hypoxemia, treatment of thyrotoxicosis, volume repletion, aspirin for fever, or tranquilizers for emotional upset.

ATRIAL FIBRILLATION

AFis a common arrhythmia that may occur in paroxysmal and persistent forms. It may be seen in normal subjects, particularly during emotional stress or following surgery, exercise, acute alcoholic intoxication, or a prominent surge of vagal tone (i.e., vasovagal response). It may also occur in patients with heart or lung disease who develop acute hypoxia, hypercapnia, or metabolic or hemodynamic derangements. Persistent AF usually occurs in patients with cardiovascular disease, most commonly rheumatic heart disease, nonrheumatic mitral valve disease, hypertensive cardiovascular disease, chronic lung disease, atrial septal defect, and a variety of miscellaneous cardiac abnormalities. AF may be the presenting finding in thyrotoxicosis. So-called lone AF, which occurs in patients without underlying heart disease, often represents the tachycardia phase of the tachycardia-bradycardia syndrome.

The morbidity associated withAF is related to (1) excessive ventricular rate, which in turn may lead to hypotension, pulmonary congestion, or angina pectoris in susceptible

individuals; (2) the pause following cessation of AF, which can cause syncope; (3) systemic embolization, which occurs most commonly in patients with rheumatic heart disease (Table 230-1); (4) loss of the contribution of atrial contraction to cardiac output, which may cause fatigue; and (5) anxiety secondary to palpitations. In patients with severe cardiac dysfunction, particularly those with hypertrophied, noncompliant ventricles, the combination of the loss of the atrial contribution to ventricular filling and the abbreviated filling period due to the rapid ventricular rate in AF can produce marked hemodynamic instability, resulting in hypotension, syncope, or heart failure. In patients with mitral stenosis, in whom ventricular filling time is critical, development of AF with a rapid ventricular rate may precipitate pulmonary edema (Chap. 236). AF may also cause a cardiomyopathy related to persistent rapid rates (so-called tachycardia-induced cardiomyopathy).

AFis characterized by disorganized atrial activity without discrete P waves on the surfaceECG(Fig. 230-5*A*). Atrial activation is manifested by an undulating baseline or by more sharply inscribed atrial deflections of varying amplitude and frequency ranging from 350 to 600 beats per minute. The ventricular response is irregularly irregular. This results from the large number of atrial impulses that penetrate theAV node, making it partially refractory to subsequent impulses. This effect of nonconducted atrial impulses to influence the response to subsequent atrial impulses is termed *concealed conduction*. As a result, the ventricular response is relatively slow, considering the actual atrial rate. AF may convert to atrial flutter, especially in response to antiarrhythmic drugs like quinidine or flecainide. If AF converts to atrial flutter, which has a slower atrial rate, the effect of concealed conduction may be diminished, and a paradoxic increase in the ventricular response may occur. The main factor determining the rate of the ventricular response is the functional refractory period of the AV node or the most rapid paced rate at which 1:1 conduction through the AV node can be observed.

If, in the presence ofAF, the ventricular rhythm becomes regular and slow (e.g., 30 to 60 bpm), complete heart block is suggested, and if the ventricular rhythm is regular and rapid (e.g.,^{3}100 bpm), a tachycardia arising in theAVjunction or ventricle should be suspected. Digitalis intoxication is a common cause of both phenomena.

Patients withAFexhibit a loss of *a* waves in the jugular venous pulse and variable pulse pressures in the carotid arterial pulse. The first heart sound usually varies in intensity. On echocardiography, the left atrium is frequently enlarged, and in patients in whom the left atrial diameter exceeds 4.5 cm, it may be difficult to convert AF to sinus rhythm and/or maintain the latter, despite therapy.

TREATMENT

In acuteAF, a precipitating factor such as fever, pneumonia, alcoholic intoxication, thyrotoxicosis, pulmonary emboli, congestive heart failure, or pericarditis should be sought. When such a factor is present, therapy should be directed toward the primary abnormality. If the patient's clinical status is severely compromised, electrical cardioversion is the treatment of choice. In the absence of severe cardiovascular compromise, slowing of ventricular rate becomes the initial therapeutic goal. This may be most rapidly accomplished withb-adrenergic blockers and/or calcium channel antagonists. Both prolong the refractory period of theAV node and slow conduction

within it. When catecholamine levels or sympathetic nervous system tone is likely to be elevated, beta blockers may be favored. Digitalis preparations are less effective, take longer to act, and are associated with more toxicity. Conversion to sinus rhythm may then be attempted. Prior to cardioversion, precautions must be taken to reduce the risk of systemic embolization. Patients should be anticoagulated to an INR of at least 1.8 for the prior 3 consecutive weeks or have had AF for<48 h. Alternatively, for those patients with AF for >48 h who are not anticoagulated, a transesophageal echocardiogram can exclude the presence of left atrial thrombus and allow safe cardioversion. Following cardioversion, anticoagulation must be maintained for at least 4 weeks until atrial mechanical function returns to normal.

Antiarrhythmic medications in either oral or intravenous form may be employed but are only modestly effective in restoring sinus rhythm. When antiarrhythmic agents such as the quinidine-like drugs (type 1A) or the flecainide-like agents (type 1C) are used (Table 230-2), it is important to increaseAV node refractoriness prior to administering such drugs because their vagolytic effect and/or their ability to convertAF to atrial flutter may reduce the concealed conduction in the AV node and lead to an excessively rapid ventricular response. b-Adrenergic blockers are especially useful in this regard.

Direct-current electrical cardioversion is a highly effective method to restore sinus rhythm, either as a primary method of therapy or following the failure of antiarrhythmic medications. Electrical cardioversion is accomplished through the delivery of at least 200 W× s of energy between electrodes placed to the right of the sternum and the cardiac apex or to the left of the scapula. If external cardioversion is unsuccessful, internal cardioversion with energy delivered between two catheters inside the heart or one inside and a patch outside the heart may prove effective.

It is unlikely that patients with chronicAF will convert to and remain in sinus rhythm in the presence of long-standing rheumatic heart disease and/or when the atria are markedly enlarged. It is also unlikely for patients with recurrent, paroxysmal lone AF to be converted to and maintained in sinus rhythm.

The goal of therapy in patients in whomAFcannot be converted to sinus rhythm is control of the ventricular response. This can usually be accomplished by digitalis, beta blockers, or calcium channel blockers singly or in combination. In occasional patients, the ventricular response cannot be controlled by pharmacologic therapy alone. In such patients, the creation of complete heart block by radiofrequency catheter ablation of theAVjunction followed by permanent pacemaker implantation is appropriate. Surgical or direct-current catheter ablation of the AV junction is rarely required to achieve AV block.

If sinus rhythm is restored electrically or pharmacologically, quinidine or related agents as well as the class IC agents (e.g., flecainide), sotalol, or amiodarone may be used to prevent recurrence. In patients in whom cardioversion is unsuccessful or in whomAF has recurred or is likely to recur despite antiarrhythmic therapy, it is probably wisest to allow the patient to remain inAF and to control the ventricular response with calcium antagonists,b-adrenergic blockers, or digitalis glycosides. Since such patients are always at risk of systemic embolization, particularly in the presence of organic heart disease, chronic anticoagulation must be considered (Table 230-3). Chronic

anticoagulation is particularly important in the elderly, where the attributable risk of AF for stroke approaches 30%. Several studies have now demonstrated conclusively that the incidence of embolization in patients with AF not associated with valvular heart disease is reduced by chronic anticoagulation with warfarin-like agents. Aspirin also may be effective for this purpose in patients who are not at high risk for stroke. Although anticoagulation may be associated with hemorrhagic complications, the risk is largely associated with INRs above the recommended range of 1.8 to 3.0. Recommendations for the selection of antiarrhythmic medications to prevent the recurrence of AF are shown inFig. 230-6.

Ablation therapy for cure ofAF is an active area of investigation. This therapy is particularly attractive for the small subset of patients who have a focal atrial tachycardia that degenerates into AF. These automatic foci are often located in the pulmonary veins, and a targeted ablation in these areas may be curative. While ablation of these foci is possible, the procedure can result in pulmonary vein stenosis, pulmonary hypertension, and stroke. Further technologic advances are necessary before this procedure can be more widely and safely performed. A more morbid approach involves making multiple lesions in the right and left atria (MAZE procedure) to compartmentalize the electrical conductance of these chambers and disallow the propagation of fibrillatory waves. The morbidity, mortality, and success rate of such catheter-based procedures renders them experimental at this time.

ATRIAL FLUTTER

This arrhythmia occurs most often in patients with organic heart disease. Flutter may be paroxysmal, in which case there is usually a precipitating factor, such as pericarditis or acute respiratory failure, or it may be persistent. Atrial flutter (as well asAF) is very common during the first week following open-heart surgery. Atrial flutter is usually less long-lived than is AF, although on occasion it may persist for months to years. Most commonly, if it lasts for more than a week, atrial flutter will convert to AF. Systemic embolization is less common in atrial flutter than in AF.

Atrial flutter is characterized by an atrial rate between 250 and 350 bpm. Typically, the ventricular rate is half the atrial rate, i.e., approximately 150 bpm. If the atrial rate is slowed to<220 beats per minute by antiarrhythmic agents such as quinidine, which also possess vagolytic properties, the ventricular rate may rise suddenly because of the development of 1:1AVconduction. Classically, flutter waves are seen as regular sawtooth-like atrial activity, most prominent in the inferior leads (Fig. 230-5*B*). When the ventricular response is regular and not a simple fraction of the atrial rate, complete AV block is present, which may be a manifestation of digitalis toxicity. Activation mapping suggests that atrial flutter is a form of atrial reentry localized to the right atrium.

TREATMENT

The most effective treatment of atrial flutter is direct-current cardioversion, which can be accomplished at low energy (25 to 50 W× s) under mild sedation. Higher energies (100 to 200 W × s) are often used because they are less likely to causeAF, which not infrequently occurs following lower energy delivery. Although atrial flutter is associated with a slightly lower risk of embolization than AF, the same precautions should be

followed in regard to anticoagulation as are used with AF. In patients who develop atrial flutter following open-heart surgery or recurrent flutter in the setting of acute myocardial infarction, particularly if they are being treated with digitalis, atrial pacing (using temporary pacing wires implanted at the time of operation or a pacing lead inserted into the atrium pervenously) at rates of 115 to 130% of the atrial flutter rate can usually convert the atrial flutter to sinus rhythm. Atrial pacing may also result in the conversion of atrial flutter to AF, which allows for easier control of the ventricular response. If immediate conversion of atrial flutter is not mandated by the patient's clinical status, the ventricular response should first be slowed by blocking theAV node with a beta blocker, calcium antagonist, or digitalis. Digitalis is the least effective and occasionally converts atrial flutter into AF. Once AV nodal conduction is slowed with any of these drugs, an attempt to convert flutter to sinus rhythm using a class I (A or C) agent or amiodarone should be made. Increasing doses of the drug selected are administered until the rhythm converts or side effects occur. Ibutilide is a new antiarrhythmic agent that is administered intravenously and appears to be particularly effective for conversion of atrial flutter to sinus rhythm.

Quinidine, other Class IA drugs, flecainide, propafenone, sotalol, and amiodarone (Table 230-4) may be useful in preventing recurrences of atrial flutter. Radiofrequency ablation is a highly effective treatment for patients with the most typical forms of atrial flutter, which are due to reentry around the tricuspid valve in a counterclockwise or clockwise fashion. The coronary sinus and inferior vena cava cause the wavefront of activation to pass between them and the tricuspid valve. Ablation of the narrowed isthmus using radiofrequency energy can cure flutter in >85% of cases.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS (PSVT)

In most cases, functional differences in conduction and refractoriness in theAV node or the presence of an AV bypass tract provide the substrate for the development of PSVT (previously termed *paroxysmal atrial tachycardia*). Electrophysiologic studies have demonstrated that reentry is responsible for the vast majority of cases of PSVT (Fig. 230-7). Reentry has been localized to the sinus node, atrium, AV node, or a macroreentrant circuit involving conduction in the antegrade direction through the AV node and retrograde through an AV bypass tract. Such a bypass tract may also conduct antegradely, in which case the Wolff-Parkinson-White (WPW) syndrome is said to be present. When the bypass tract manifests only retrograde conduction, it is termed a *concealed bypass tract* (Fig. 230-7*B*). In these cases, the QRS complex during sinus rhythm is normal. In the absence of the WPW syndrome, reentry through the AV node or through a concealed bypass tract makes up more than 90% of all PSVTs.

AV NODAL REENTRANT TACHYCARDIA

There is no age or disease predisposition for the development of AV nodal reentrant tachycardia, the most common cause of supraventricular tachycardia. It is, however, more commonly observed in women. It usually presents as a regular narrow QRS complex tachycardia at rates of 120 to 250 bpm.APCsthat initiate the arrhythmia are almost always associated with a prolonged PR interval. Retrograde P waves may be absent, buried in the QRS complex, or appear as distortions at the terminal parts of the QRS complex (Fig. 230-7*A*).

AVnodal reentrantPSVT(Fig. 230-8) can be reproducibly initiated and terminated by appropriately timed atrial premature stimuli. The onset of the tachycardia is almost always associated with prolongation of the PR interval due to marked AV nodal conduction delay (prolonged AH interval) following theAPC that is critical for the genesis of the arrhythmia. The sudden prolongation of the AH interval is consistent with the concept of dual AV nodal pathways: a *fast pathway*, which exhibits rapid conduction and a long refractory period, and a *slow pathway*, which has a short refractory period but conducts slowly. During sinus rhythm, only conduction over the fast pathway is manifest, resulting in a normal PR interval (Fig. 230-8). Atrial extrastimuli at a critical coupling interval are blocked in the fast pathway because of its longer refractory period and are conducted slowly through the slow pathway. If conduction down the slow pathway is slow enough to allow the previously refractory fast pathway time to recover excitability, a single atrial (echo) reentrant beat or sustained tachycardia ensues. A critical balance between conduction velocity and refractoriness within the node is required to sustain AV nodal reentry. Retrograde atrial and antegrade ventricular activation occur simultaneously, explaining why P waves may not be apparent on the surfaceECG.

Clinical Features AV nodal reentry may produce palpitations, syncope, and heart failure depending on the rate and duration of the arrhythmia and the presence and severity of any underlying heart disease. Hypotension and syncope may occur because of the sudden loss of the atrial contribution to ventricular filling; this can also lead to a marked increase in atrial pressure, acute pulmonary edema, and a reduction in ventricular filling. Simultaneous atrial and ventricular contraction produces cannon *a* waves with each heartbeat.

TREATMENT

In patients without hypotension, vagal maneuvers, particularly carotid sinus massage, can terminate the arrhythmia in 80% of cases. If hypotension is present, raising the blood pressure by the cautious use of intravenous phenylephrine in 0.1-mg increments may terminate the arrhythmia alone or in combination with carotid sinus pressure. If these maneuvers are unsuccessful, verapamil (2.5 to 10 mg intravenously) or adenosine (6 to 12 mg intravenously) is the agent of choice. We prefer to use adenosine because of its extremely short half-life, lessening the consequences of any side effects. Beta blockers may also be used to slow or terminate the tachycardia but are agents of second choice. Digitalis glycosides have a slower onset of action and should *not* be used for acute therapy. When these drugs fail to terminate the tachycardia, or when the tachycardia is recurrent, atrial or ventricular pacing via a temporary pacemaker inserted pervenously may be used to terminate the arrhythmia. However, if severe ischemia and/or hypotension is caused by the tachycardia, dc cardioversion should be considered.

AVnodal reentry can usually be prevented by the use of drugs that act primarily on the antegrade slow pathway (such as digitalis, beta blockers, or calcium channel antagonists) or on the fast pathway (class IA or IC;Table 230-4;Fig. 230-CD1). We favor initial therapy with beta blockers, calcium channel antagonists, or digoxin because the risk-benefit ratio associated with treatment with these agents is more favorable than that

of IA or IC agents. Drugs most likely to avert recurrences prevent induction of the arrhythmias by programmed stimulation. This technique utilizes temporary pacemaker catheters connected to a physiologic stimulator capable of variable rate pacing and stimulation with one or more precisely timed premature impulses. In symptomatic patients who require chronic therapy, radiofrequency catheter modification of the AV node (Fig. 230-CD2) should be considered. This technique can cure AV nodal reentry in >90% of cases and has been proven to be safe, although a 1 to 2% risk of AV block requiring a permanent pacemaker exists.

AV REENTRANT TACHYCARDIA

PSVTdue to AV reentry incorporates a concealed AV bypass tract as part of the tachycardia circuit. Thus the impulse passes antegradely from the atria through the AV node and His-Purkinje system to the ventricles and then retrogradely through the (concealed) bypass tract back to the atrium. Patients with this disorder manifest the same type of PSVT as do patients with theWPWsyndrome (see below), but the bypass tract cannot conduct in an antegrade direction during sinus rhythm or other atrial tachyarrhythmias.

AVreentrant tachycardia can be initiated and terminated by eitherAPCs orVPCs. Initiation ofPSVT by a VPC is virtually diagnostic of AV reentry. Alternation of the QRS complexes occurs in approximately one-third of such tachycardias. Since atrial activation must follow ventricular activation during AV reentry, the P wave usually occurs after the QRS complex (Fig. 230-7*B*).

Atrial activation mapping is of major value in evaluating the origin of these tachycardias. Most concealed bypass tracts are left-sided. Thus, duringPSVT or during ventricular pacing, the earliest activation sequence is recorded in the left atrium, usually via a catheter in the coronary sinus. This eccentric atrial activation is quite distinct from the normal retrograde activation sequence in which the earliest activation of the atria is in the area of theAVjunction. The ability of a ventricular stimulus to conduct to the atrium at a time when the bundle of His is refractory and the termination of the tachycardia by a ventricular stimulus that does not reach the atrium are diagnostic of retrograde conduction over a concealed bypass tract.

TREATMENT

This is similar to the treatment forAV nodal reentry tachycardia. Although pharmacologic agents may be used, patients who require chronic therapy should be considered candidates for radiofrequency catheter ablation of the bypass tract. This requires detailed electrophysiologic study to exclude other arrhythmias that may be responsible for patients' symptoms and to determine the location of the bypass tract(s). The efficacy of this procedure exceeds 90%, with minimal risks. In the remaining small number of patients failing catheter ablation, surgical ablation or pharmacologic therapy can be used.

SINUS NODE REENTRY AND OTHER ATRIAL TACHYCARDIAS

Reentry in the region of the sinus node or within the atria is invariably initiated byAPCs.

These arrhythmias are less common thanAV nodal or AV reentry and are more often associated with underlying cardiac disease. During sinus node reentry, the P-wave morphology is identical to that occurring in sinus rhythm, but the PR interval is prolonged. This is in contrast to sinus tachycardia, in which the PR interval tends to shorten. With intraatrial reentry, the P-wave configuration differs from that during sinus rhythm, and the PR interval is prolonged (Fig. 230-7*C*).

TREATMENT

Sinus node and atrial reentrant arrhythmias are managed like other reentrantPSVTs, except that catheter ablation is less successful because multiple foci may be present.

NONREENTRANT ATRIAL TACHYCARDIAS

These may be a manifestation of digitalis intoxication or may be associated with severe pulmonary or cardiac disease, with hypokalemia, or with the administration of theophylline or adrenergic drugs. Multifocal atrial tachycardia (MAT) (Fig. 230-9) is particularly common following theophylline administration. By definition, MAT requires three or more consecutive P waves of different morphologies at rates greater than 100 beats per minute. MAT usually has an irregular ventricular rate because of varyingAVconduction. There is a high incidence of atrial fibrillation (50 to 70%) in patients with MAT. Treatment should be directed at the underlying disorder. The digitalis-induced arrhythmias are caused by triggered activity. In such atrial tachycardias with AV block secondary to digitalis intoxication, the atrial rate rarely exceeds 180 bpm, and typically 2:1 block is present. Atrial arrhythmias precipitated by digitalis can usually be treated by withdrawal of the drug.

Automatic atrial tachycardias not caused by digitalis are difficult to terminate, and in such cases the main goal of therapy should be to control the ventricular response, either by drugs that affect theAV node, such as digitalis, beta blockers, or calcium channel antagonists, or by ablation techniques. Catheter ablation and surgery have been employed to eradicate the arrhythmia's focus or create heart block for rate control.

PREEXCITATION (WPW) SYNDROME

The most frequently encountered type of ventricular preexcitation is that associated withAVbypass tracts (Fig. 230-CD3). These connections are composed of strands of atrial-like muscle which may occur almost anywhere around the AV rings. The term *Wolff-Parkinson-White syndrome* is applied to patients with both preexcitation on theECG and paroxysmal tachycardias. AV bypass tracts can be associated with certain congenital abnormalities, the most important of which is Ebstein's anomaly.

AVbypass tracts that conduct in an antegrade direction produce a typicalECGpattern of a short PR interval (<0.12 s), a slurred upstroke of the QRS complex (delta wave), and a wide QRS complex. This pattern results from a fusion of activation of the ventricles over both the bypass tract and the AV nodal His-Purkinje system (Fig. 230-10). The relative contribution of activation over each system determines the amount of preexcitation.

DuringPSVT inWPW, the impulse is usually conducted antegradely over the normalAVsystem and retrogradely through the bypass tract. The characteristics are identical to those described on p. 1299. Rarely (approximately 5%), tachycardias occurring in patients with WPW will exhibit a reverse pattern with antegrade conduction through the bypass tract and retrograde conduction through the normal AV system. This produces a tachycardia with a wide QRS complex in which the ventricles are totally activated by the bypass tract. Atrial flutter andAF also occur commonly in patients with WPW syndrome. Since the bypass tract does not have the same decremental conducting properties as the AV node, the ventricular responses during atrial flutter or fibrillation may be unusually rapid and may cause ventricular fibrillation (VF).

The goals of electrophysiologic evaluation in patients suspected of having theWPWsyndrome are (1) to confirm the diagnosis, (2) to localize the bypass tract and determine how many bypass tracts are present, (3) to demonstrate the role of the bypass tract in the genesis of the arrhythmias, (4) to determine the potential for the development of possibly life-threatening rates during atrial flutter or fibrillation, and (5) to evaluate therapeutic options.

TREATMENT

Pharmacologic therapy is aimed at altering the electrophysiologic properties (i.e., refractoriness or conduction velocity) of one or more components of the reentrant circuit. This is most often accomplished by agents such as beta blockers or calcium channel blockers that slow conduction and increase refractoriness of theAV node or by agents such as quinidine or flecainide that slow conduction and increase refractoriness primarily in the bypass tract. Some drugs may affect multiple sites (Fig. 230-11).

Acute management of episodes ofPSVT in patients withWPWsyndrome is similar to that of PSVT in patients with concealed bypass tracts.

In patients with theWPWsyndrome andAF, dc cardioversion should be carried out if there is a life-threatening, rapid ventricular response. In non-life-threatening situations, lidocaine (3 to 5 mg/kg) or procainamide (15 mg/kg) administered intravenously over 15 to 20 min will usually slow the ventricular response. More recently, ibutilide has become available as an alternative therapy for preexcitation tachycardia. Caution should be employed when using digitalis or intravenous verapamil in patients with the WPW syndrome and AF, since these drugs can shorten the refractory period of the accessory pathway and can increase the ventricular rate, thereby placing the patient at increased risk forVF. Chronic oral therapy with verapamil is not associated with this risk. In addition to these drugs, beta-blocking agents are of no utility in controlling the ventricular response during AF when conduction proceeds over the bypass tract. Although atrial or ventricular pacing can almost always terminatePSVT in patients with the WPW syndrome, they can induce AF. As such, chronic pacemaker therapy is to be discouraged.

While surgical ablation of bypass tracts offers a permanent cure of supraventricular tachycardia (SVT) and mostAFs associated with SVT, the advent of radiofrequency catheter ablation has virtually eliminated the need for surgery. Catheter ablation of bypass tracts is possible in >90% of patients and is the treatment of choice in patients

with symptomatic arrhythmias. It is safer, more cost-effective, and just as successful as surgery. Nevertheless, surgical ablation may be required in the occasional patient in whom catheter ablation fails.

NONPAROXYSMAL JUNCTIONAL TACHYCARDIA

This rhythm usually results from conditions that produce enhanced automaticity or triggered activity in theAVjunction and is most commonly due to digitalis intoxication, inferior wall myocardial infarction, myocarditis, endogenous or exogenous catecholamine excess, acute rheumatic fever, or valve surgery.

The onset of nonparoxysmal junctional tachycardia is usually gradual, with a "warm-up" period prior to stabilization of the rate, which can range from 70 to 150 bpm, faster rates usually being associated with digitalis intoxication. Nonparoxysmal junctional tachycardia is recognized by a QRS complex identical to that of sinus rhythm. The rate can be influenced by autonomic tone and can be increased by catecholamines, vagolytic agents, or exercise and slowed somewhat by carotid sinus pressure. When this rhythm is due to digitalis intoxication, it usually is associated withAV block and/or dissociation. Soon after cardiac surgery, retrograde conduction is more likely to be present because of the heightened sympathetic state.

TREATMENT

This is directed toward elimination of the underlying etiologic factors. Since digitalis is the most common cause of this rhythm, discontinuation of this drug is indicated. If the rhythm is associated with other serious manifestations of digitalis intoxication, such as ventricular or atrial irritability, active intervention with lidocaine or a beta blocker may be useful, and in some instances, use of digitalis antibodies (Fab fragments) should be considered. Cardioversion of this rhythm should not be attempted, particularly in the setting of digitalis intoxication. WhenAVconduction is intact, atrial pacing can capture and override the junctional focus and provide the AV synchrony necessary to maximize cardiac output. Nonparoxysmal junctional tachycardia is usually not a chronic, recurrent problem, and attention to the acute precipitating events can often resolve the tachycardia.

VENTRICULAR TACHYCARDIA

Sustained ventricular tachycardia is defined asVT that persists for more than 30 s or requires termination because of hemodynamic collapse. VT generally accompanies some form of structural heart disease, most commonly chronic ischemic heart disease associated with a prior myocardial infarction. Sustained VT may also be associated with nonischemic cardiomyopathies, metabolic disorders, drug toxicity, or prolonged QT syndrome, and it occurs occasionally in the absence of heart disease or other predisposing factors. Nonsustained VT (three beats to 30 s) is also associated with cardiac disease but occurs in its absence more often than the sustained arrhythmia. While nonsustained VT usually does not produce symptoms, sustained VT is almost always symptomatic and is often associated with marked hemodynamic compromise and/or the development of myocardial ischemia. A fixed anatomic substrate, not acute ischemia, is responsible for most recurrent episodes of sustained uniform VT. Acute

ischemia appears to have little role in the genesis of sustained uniform VT associated with chronic infarction but may play a role in the degeneration of stable VT intoVF or initiation of polymorphic VT. Most episodes of VF begin with VT.

TheECGdiagnosis ofVT is suggested by a wide-complex QRS tachycardia at a rate exceeding 100 bpm. The QRS configuration during any episode of VT may be uniform (monomorphic), or it may vary from beat to beat (polymorphic). *Bidirectional tachycardia* refers to VT that shows an alternation in QRS amplitude and axis. Typically this appears as a QRS with a right bundle branch block pattern with alternating superior (leftward) and inferior axes (rightward). While the rhythm is usually quite regular, slight irregularity may exist. Atrial activity may be dissociated from ventricular activity, or the atria may be depolarized retrogradely. The onset of the tachycardia is generally abrupt, but in nonparoxysmal tachycardias it can be gradual. Paroxysmal VT is usually initiated by aVPC.

It is important to distinguishSVT with aberration of intraventricular conduction fromVTbecause the clinical implications and management of these two arrhythmias are totally different. The most important clinical predictor of VT is the presence of structural heart disease. The observation of intermittent cannon *a* waves and varying first heart sounds suggestsAVdissociation and is diagnostic of VT. In a majority of cases, the diagnosis can and should be made by close examination of the 12-leadECG. Pharmacologic maneuvers, such as administration of intravenous verapamil or adenosine, can be hazardous and should be avoided. It is always useful to have a 12-lead ECG recorded during sinus rhythm for comparison with that during tachycardia. When the tracing obtained during sinus rhythm demonstrates the same morphologic features as those during the tachycardia, the diagnosis ofPSVTwith aberration is favored. An infarction pattern on the sinus rhythm tracing suggests the potential presence of the anatomic substrate necessary for VT. Characteristics of the 12-lead ECG during the tachycardia that suggest a ventricular origin for the arrhythmia are (1) a QRS complex>0.14 s in the absence of antiarrhythmic therapy, (2) AV dissociation (with or without fusion or captured beats) or variable retrograde conduction (Fig. 230-12), (3) a superior QRS axis in the presence of a right bundle branch block pattern, (4) concordance of the QRS pattern in all precordial leads (i.e., all positive or all negative deflections), and (5) other QRS patterns (morphology) with prolonged duration that are inconsistent with typical right or left bundle branch block patterns. (SeeTable 230-5 for a detailed synopsis of ECG criteria that favor the diagnosis of VT over SVT for wide complex tachycardia.) A wide, complex, bizarre tachycardia that is very irregular suggestsAF with conduction over an AV bypass tract. Similarly, a QRS complex in excess of 0.20 s is uncommon during VT in the absence of drug therapy and is more common with preexcitation. Intravenous verapamil will stop most recalcitrant SVTs involving the AV junction, but it is rarely effective for VT. Because of this property, verapamil has been utilized to attempt to differentiate SVT with aberrant conduction from VT. However, this is extremely hazardous, since intravenous verapamil can precipitate cardiac arrest in patients with VT.

It has been possible to replicate sustained uniformVT in more than 95% of patients with this arrhythmia using programmed electrical stimulation. In most patients the tachycardia is initiated with ventricular premature stimuli. A sustained monomorphic VT with a morphology identical to that of the spontaneous arrhythmia is the rule. The

clinical significance of polymorphic VT initiated by programmed stimulation is not clear, since more aggressive stimulation (i.e., the use of three or four extrastimuli) can induce polymorphic VT and evenVF in some normal subjects and in patients who have never had a clinical arrhythmia.

Sustained uniformVT can be terminated by programmed stimulation or rapid pacing in at least 75% of patients; the remainder require cardioversion. The ability to reproducibly initiate and terminate a sustained, uniform VT permits assessment of pharmacologic and electrical therapy of these arrhythmias.

The reproducible termination ofVT by programmed stimulation permits evaluation of the effectiveness of antitachycardia pacemakers for long-term therapy of paroxysmal episodes of arrhythmia. Unfortunately, rapid pacing, the most effective form of therapy, can accelerate the tachycardia and/or produceVF. Therefore, antitachycardia pacing is a viable form of therapy only when the pacing device includes backup defibrillation capabilities.

Clinical Features Symptoms resulting fromVTdepend on the ventricular rate, duration of the tachycardia, and presence and extent of underlying cardiac disease. When the tachycardia is rapid and associated with severe myocardial dysfunction and cerebrovascular disease, hypotension and syncope are common. However, the presence of hemodynamic stability does not preclude a diagnosis of VT. The rate, loss of the atrial contribution to ventricular filling, and abnormal sequence of ventricular activation are important factors producing a decreased cardiac output during VT.

The *prognosis* ofVTdepends on the underlying disease state. If sustained VT develops within the first 6 weeks following acute myocardial infarction, the prognosis is poor, with a 75% mortality rate at 1 year. Patients with nonsustained VT following myocardial infarction have a threefold greater risk of death than a comparable group of patients without this arrhythmia. However, a cause-and-effect relationship between the nonsustained tachycardia and subsequent sudden death has not been established. Patients without heart disease who have uniform VT have a good prognosis and an extremely low risk of sudden death.

TREATMENT

The risk-benefit ratio of treating each specific type ofVTshould be considered before beginning therapy. This is important because antiarrhythmic agents can produce or exacerbate the very arrhythmias that they are given to prevent. In general, patients with VT but without organic heart disease have a benign course; such patients with asymptomatic, nonsustained VT need not be treated because their prognosis will not be affected. An exception is the patient with congenital long QT syndrome. Such patients have recurrent polymorphic VT and a high mortality from sudden death if untreated. Patients with sustained VT in the absence of heart disease usually require therapy because the arrhythmia causes symptoms. These tachycardias may respond to beta blockers; verapamil; class IA, IC, or III agents (Fig. 230-CD4); or amiodarone. In patients with VT and organic heart disease, if marked hemodynamic compromise is present or if there is evidence of ischemia, congestive heart failure, or central nervous system hypoperfusion, the rhythm should be promptly terminated by dc cardioversion

(see below). If the patient with organic heart disease tolerates the VT well, pharmacologic therapy may be tried. Procainamide is probably the most effective agent for acute therapy. It may or may not terminate the tachycardia but almost always slows the rate. In stable patients in whom these drugs do not terminate the arrhythmia, a pacing catheter can be inserted pervenously into the right ventricular apex, and the tachycardia can be terminated by overdrive pacing.

Programmed stimulation is probably the most effective way to select the appropriate antiarrhythmic agent to prevent recurrent, sustainedVT. After demonstrating that the tachycardia can be initiated reproducibly in the absence of antiarrhythmic agents, drugs can be studied serially, and the drug that prevents initiation of the tachycardia can be selected; long-term (>2 years) successful prevention of the arrhythmia can then be expected in 80% of patients if a complete stimulation protocol is used following drug administration. Failure to perform a complete protocol will lead to recurrences, which are often blamed on the lack of utility of programmed stimulation as a method of evaluating drug efficacy. Drug levels demonstrated to be successful in the laboratory need to be maintained chronically. Unfortunately, prevention of inducible VT is expected in only 50% of cases. Use of Holter monitor for guided therapy, although advocated by some, is of less value.

Antitachycardia pacing has been used as a means to terminate tachycardias that have been reproducibly terminated by pacing in the electrophysiology laboratory. Automatic antitachycardia pacing devices are not used alone because pacing duringVT may accelerate tachycardia, converting a stable arrhythmia into an unstable one and resulting in severe hemodynamic compromise. However, devices combining antitachycardia pacing with anICD (see below) afford a "backup" means of terminating unstable arrhythmias.

The advent of endocardial catheter and intraoperative mapping led to the development of surgical techniques for the management ofVT. Activation mapping permits localization of the site of origin of the arrhythmia. In centers in which expertise in mapping is available, operation has been successfully employed to cure tachycardias in the majority of patients in whom it has been undertaken. Even though most patients with VT and ischemic heart disease have markedly impaired left ventricular function and multivessel coronary artery disease, the operative mortality rate has ranged between 8 and 15%. Following operation, >90% of survivors are controlled either off (two-thirds of patients) or on (one-third) antiarrhythmic agents that were previously ineffective in controlling these rhythms. With the development of radiofrequency ablation and refinement of mapping criteria to locate critical sites of the VT circuit, precisely, catheter ablation can be performed as a curative procedure in selected patients. In experienced centers cure of VT in these *selected* patients approaches 75%.

Specific Types of VT *Torsade de pointes* (Fig. 230-13) refers toVTcharacterized by polymorphic QRS complexes that change in amplitude and cycle length, giving the appearance of oscillations around the baseline. This rhythm is, by definition, associated with QT prolongation. The latter may result from electrolyte disturbances (particularly hypokalemia and hypomagnesemia), use of a variety of antiarrhythmic drugs (especially quinidine), phenothiazines and tricyclic antidepressants, liquid protein diets, intracranial events, and bradyarrhythmias, particularly third-degree AV block. It also may occur as a

congenital anomaly that most often presents with torsade de pointes (syncope or sudden death) at a young age.

The electrocardiographic hallmark is polymorphicVTpreceded by marked QT prolongation, often in excess of 0.60 s. These patients often have multiple episodes of nonsustained polymorphic VT associated with recurrent syncope, but they also may developVF and sudden cardiac death.

Therapy should be directed at removing the precipitating factors, i.e., correcting metabolic abnormalities and removing drugs that have induced the prolonged QT interval. In the setting of drug-induced torsade de pointes, atrial or ventricular overdrive pacing and the administration of magnesium have also been useful in terminating and preventing the arrhythmia. For patients with the congenital prolonged QT interval syndrome, b-adrenergic blocking agents have been the mainstay of therapy; agents that shorten the QT interval may also be useful (e.g., phenytoin). Cervicothoracic sympathectomy has been proposed as a form of therapy for congenital prolonged QT syndrome, but it is not often effective as the sole therapy. Pacing in combination with beta blockers and sympathectomy has been used by some investigators when beta blockers fail, but it is not uniformly successful and results in a Horner's syndrome. More recently,ICDswith dual chambered pacing capability and beta blockers have become the treatment of choice for patients with recurrent episodes despite beta blockers.

Polymorphic tachycardias associated with normal QT intervals in patients with ischemic heart disease that are initiated by "R-on-T"VPCs are probably caused by reentry, and their treatment is totally different. This is not true torsade de pointes. In such cases, class I or III agents may be the most effective form of therapy and should be administered in full antiarrhythmic doses. However, these arrhythmias may also result from acute, severe ischemia and will only respond to abolition of the ischemia, usually by revascularization.

Accelerated idioventricular rhythm, also termed *slow VT*, with a rate that ranges from 60 to 120 bpm, usually occurs in acute myocardial infarction, often during reperfusion. It may also be seen following cardiac operations; in patients with cardiomyopathy, rheumatic fever, or digitalis intoxication; and in patients with no evidence of heart disease. The rhythm is usually transient and rarely causes significant hemodynamic compromise or symptoms.

Treatment is rarely necessary and should usually be considered only if symptoms arise due to impaired hemodynamics, most commonly due toAVdissociation. In most cases, atropine can accelerate the sinus rate to overdrive the ventricular rhythm.

VENTRICULAR FLUTTER AND VENTRICULAR FIBRILLATION (Fig. 230-14; See alsoChap. 39)

These arrhythmias occur most often in patients with ischemic heart disease. They also occur following administration of antiarrhythmic drugs, particularly those that induce prolonged QT intervals and torsade de pointes (see above), in patients with severe hypoxia or ischemia, and in those withWPW who developAF with an extremely rapid ventricular response (p. 1299). Electrical accidents frequently cause cardiac arrest due

to the development ofVF. The onset of these arrhythmias is rapidly followed by loss of consciousness and, if untreated, death. Episodes of cardiac arrest recorded during Holter monitoring reveal that approximately three-fourths of the sudden deaths are due toVT or VF.

In patients with nonischemicVF, the onset usually begins with a short run of rapidVT, which is initiated by a relatively late coupledVPC. In patients with acute myocardial infarction or ischemia, however, VF is usually precipitated by a single early ventricular complex beat falling on the T wave (the vulnerable period), which produces a rapid VT that degenerates into VF (Fig. 230-14).

The clinical setting in whichVFoccurs is important. Most patients who have primary VF within the first 48 h of the onset of acute infarction have a good long-term prognosis, with a very low rate of recurrence or sudden cardiac death. Their short-term mortality may, however, be slightly increased. In contrast, patients who experience VF unassociated with the development of acute myocardial infarction have a recurrence rate of 20 to 30% in the year following the event (Chap. 39).

Ventricular flutter usually appears as a sine wave with a rate between 150 and 300 bpm. These oscillations make it impossible to assign a specific morphology to the arrhythmia and in some cases to distinguish it from rapidVT.VF is recognized by grossly irregular undulations of varying amplitudes, contours, and rates (Fig. 230-14). Electrophysiologic studies have demonstrated that regardless of the apparent gross irregularity on the surfaceECG, VF usually starts out with a rapid repetitive sequence of VT that ultimately breaks down into multiple wavelets of reentry.

Electrophysiologic studies have been useful in patients who have been resuscitated from cardiac arrest. In approximately 70% of patients with prior infarction, programmed stimulation can reproducibly initiate a sustainedVT. Ablation may be possible in some of these patients, particularly if the VT can be slowed so that it can be mapped. Several recent secondary prevention trials have demonstrated superior survival (3 years) in patients treated withICDsversus amiodarone (Table 230-6). However, in patients with ejection fractions >35% or<20%, survival was comparable. Further subgroup analysis is necessary to identify those patients most likely to be benefited by ICDs.

GENETIC CONSIDERATIONS

Many advances have been made in the identification of genes responsible for syndromes associated with ventricular tachycardias and sudden cardiac death. Four specific examples include the congenital long QT syndrome (LQTS), hypertrophic obstructive cardiomyopathy (Chap. 238), arrhythmogenic right ventricular dysplasia, and the Brugada syndrome. The latter is a recently described disorder characterized by the electrocardiographic profile of a pseudo bundle branch block pattern with ST elevation and terminal T-wave inversion in leads V_1-V_3(Fig. 230-15). The clinical presentation isVF in patients with structurally normal hearts. A mutation in the cardiac sodium channel, SCN 5A, is believed to be responsible. While the same gene is responsible for the LQTS, the mutation is different in the two syndromes.

TREATMENT

Pharmacologic Antiarrhythmic Therapy Prior to initiation of pharmacologic antiarrhythmic therapy, potential aggravating factors such as transient metabolic abnormalities, congestive heart failure, or acute ischemia must be corrected; in some cases this may suffice to control arrhythmias. In addition, the potential role of drugs as a cause or exacerbating factor in the development of the arrhythmia must be considered. It must be recognized that we do not have a good understanding of the effects of antiarrhythmic agents on the spontaneous onset of tachyarrhythmias. In some cases, they may facilitate the onset.

Antiarrhythmic drugs are used in three principal situations: (1) to terminate an acute arrhythmia; (2) to prevent recurrence of an arrhythmia; and (3) to prevent a life-threatening arrhythmia for which the patient is perceived to be at risk but which has never occurred.

Most currently available antiarrhythmic agents (Table 230-4) have a relatively low toxic/therapeutic ratio; all can exert proarrhythmic effects (Table 230-7), and therefore they may exacerbate underlying arrhythmias. Serum levels can be determined for most currently available antiarrhythmic agents. Standards for therapeutic and toxic levels can serve only as a rough guide for selecting the appropriate dose in any individual patient. In the final analysis, the therapeutic level in a given patient is the concentration that achieves the desired antiarrhythmic effect, and the toxic level for each patient is the concentration at which undesirable side effects occur. Since many adverse effects are directly related to drug concentrations, the lowest serum level that achieves an effective antiarrhythmic response should be chosen.

In order to determine the therapeutic level for a patient, one must have a standard to judge drug efficacy. For a patient with an incessant arrhythmia, antiarrhythmic drugs may be administered empirically until the arrhythmia is suppressed. If a reproducible precipitating factor such as exercise can be identified, serial drug testing during such a provocative maneuver may be performed. Unfortunately, most arrhythmias are sporadic and occur unpredictably without identifiable precipitating factors. In these cases, if one waits to observe spontaneous recurrences on each antiarrhythmic drug, assessment of drug efficacy may require months. This type of assessment of efficacy may be adequate for arrhythmias that are not life-threatening. However, this mode of assessment is inadequate for arrhythmias that compromise hemodynamic stability, result in syncope, or cause cardiac arrest. In such cases, two methods for determination of arrhythmic drug efficacy have been utilized. The first, which consists of continuousECGmonitoring in the control state and then in the presence of antiarrhythmic drugs, has been used in order to determine the effect that each drug has on spontaneous atrial or ventricular ectopy. This method presupposes that the mechanism responsible for sustained arrhythmias is the same as that causing isolated premature depolarizations (which may or may not be true) and that therefore eradication of isolated ectopy will correlate with prevention of sustained arrhythmias. This method has a number of limitations. First, patients frequently show marked degrees of spontaneous variation in frequency of ectopy, which may mimic antiarrhythmic drug effects. Second, 25 to 30% of patients with sustained ventricular arrhythmias such asVT orVFdemonstrate only rare spontaneous ectopy. Finally, many patients demonstrate a dissociation between the effects of antiarrhythmic agents on spontaneous ectopy and the effects of the same

agent on sustained arrhythmias.

An alternative method to assess drug efficacy is programmed stimulation. Numerous studies have demonstrated that most clinically occurring supraventricular and ventricular tachyarrhythmias may be reproducibly initiated and terminated safely using this technique. Studies are performed initially in a baseline state in the absence of antiarrhythmic drugs. If the patient's clinical arrhythmia can be reproducibly initiated, then the ability of individual antiarrhythmic drugs to prevent reinduction of the arrhythmia can be assessed either after the drug is administered intravenously or after several days of oral loading in order to achieve a steady-state serum concentration. Use of this method assumes that (1) the induced and spontaneous arrhythmias are identical, and (2) prevention of induction of arrhythmias will correlate with prevention of recurrent spontaneous tachycardias on the same drug regimen. This technique has been validated in patients with a variety of reentrantPSVTs,VT, andVF. The technique is safe when carefully performed, the potential complications being those of any intravascular catheterization. Appropriate interpretation of the results of programmed stimulation is critically dependent on correlating the patient's spontaneous arrhythmias with those induced in the laboratory, with regard to rate and morphology, in order to be certain that the arrhythmia induced in the laboratory represents the same arrhythmia that occurred spontaneously and caused symptoms.

Classification of Antiarrhythmic Drugs A number of classifications of antiarrhythmic drugs have been proposed; the most frequently used is a modification of one proposed by Vaughan-Williams (Table 230-2). This classification is based in part on the ability of antiarrhythmic drugs to modify the cardiac cellular (1) excitatory currents (Na^+ or Ca^{2+}), (2) action potential duration, and (3) automaticity (phase 4 depolarization). These effects of the drugs on isolated cardiac cells are thought to account for some of the antiarrhythmic properties of the drugs. Thus depression of excitatory currents by class I and class IV antiarrhythmics results in slowing of conduction velocity and may interrupt arrhythmias by blocking conduction in areas of marginal excitability, where conduction velocity is already slow. Class III antiarrhythmics allegedly exert their action by increasing refractoriness through prolongation of the action potential duration. However, this classification has a number of limitations. The electrophysiologic effects of these drugs in vivo may differ from their effects on isolated cells. Also, the effects of heart rate and fiber geometry are not considered. Not all drugs (e.g., adenosine) fit into the classifications. Finally, some drugs (e.g., amiodarone) exhibit properties consistent with multiple classes. The uses, actions, and toxic actions of currently available antiarrhythmic drugs are summarized in Tables 230-4 and230-7.

Electrical Therapy of Tachyarrhythmias

Pacemakers Cardiac pacing can be used to terminate and in selected cases prevent recurrent supraventricular and ventricular arrhythmias. Because many tachyarrhythmias appear to be due to a reentrant mechanism with the impulse traveling in a circuit, a properly timed paced impulse can penetrate and prematurely depolarize part of the circuit, rendering it refractory to the next circulating wavefront and thereby interrupting the circus movement. Pacing therapy for arrhythmias is generally reserved for patients whose arrhythmias are refractory to drug therapy and who remain hemodynamically stable during the tachycardia. All forms of pacing therapy require repeated

demonstration of their effectiveness and reliability in terminating the arrhythmias during electrophysiologic testing prior to implantation of the pacing device.

The type of pacing device and modality selected for arrhythmia termination depends on (1) the rate of the tachycardia (rates >160 bpm are rarely terminated by a single premature stimulus), (2) the type of arrhythmia (atrial flutter andVT are rarely terminated by single extrastimuli), and (3) concomitant drug therapy.

Because many tachycardias cannot be terminated by single premature stimuli, pacemakers have been developed that allow for multiple extrastimuli (burst pacing) to be introduced. In the current era, antitachycardia pacing is almost exclusively for ventricular arrhythmias because of the success of radiofrequency ablative therapy for supraventricular arrhythmias.

Cardiac pacing has also been used to prevent ventricular tachyarrhythmias. PolymorphicVTassociated with a long QT interval and bradycardia (torsade de pointes, p. 1304) is most likely to respond. Pacing the atrium and/or ventricle at rates between 90 and 120 bpm appears to increase the homogeneity of electrical recovery and markedly reduces the propensity for a recurrence of arrhythmias.

Pacemakers may be self-contained or energized by an external radiofrequency source. The self-contained pacemaker may function automatically [i.e., it incorporates an arrhythmia recognition program (circuit)], or it may be activated by an external magnet. The major advantage of a fully automatic system is that there is no need for the patient to recognize the arrhythmia in order for termination to occur. The advantages of the externally activated system (rarely used today) include (1) the decreased risk of unnecessary treatment because of faulty sensing, and (2) the opportunity to initiate monitoring at the time of attempted termination of arrhythmia. This type of monitoring is frequently helpful if pacing techniques are employed to terminateVT, given the risk of acceleration of the arrhythmia by pacing.

The limitations of pacing therapy are primarily related to (1) the changes in the characteristics of the arrhythmia over time such that programmed pacing parameters no longer terminate the tachycardia, (2) the risk of acceleration of the tachycardia with the development ofAF when stimulating the atrium and the development of rapidVT andVF when stimulating the ventricles, and (3) inappropriate recognition of supraventricular tachyarrhythmias as ventricular tachycardias, leading to delivery of therapy unnecessarily, which can initiate VT or VF. Future pacing generators that can perform cardioversion and defibrillation will increase the applicability of pacing therapy for the treatment of arrhythmias (see below).

Cardioversion and Defibrillation Electrical cardioversion and defibrillation remain the most reliable methods for terminating arrhythmias. By depolarizing all or at least a large portion of excitable myocardium in a near homogeneous fashion, the electrical shock can interrupt reentrant arrhythmias. External cardioversion is routinely performed by placing two paddles 12 cm in diameter in firm contact with the chest wall, with one paddle usually located to the right of the sternum at the level of the second rib and the other in the left anterior axillary line in the fifth intercostal space. If the patient is conscious, a short-acting barbiturate to act as an anesthetic or an amnesic drug such as

diazepam or medazolam should be administered to prevent patient discomfort. A person skilled in maintaining an airway should be present.

Energy is delivered synchronously with the QRS complex for all arrhythmias except ventricular flutter andVF, since asynchronous shocks can produce VF. The amount of energy used will vary with the type of tachycardia being treated. With the exception ofAF,SVTs can frequently be terminated with energy levels in the range of 25 to 50 W× s, while AF usually requires³100 W × s for termination. For terminatingVT, energy levels ³100 W× s should probably be employed. While energies as low as 25 W × s may be used successfully, they also have a higher incidence of producing VF or AF. At least 200 W× s of energy should be used for initial attempts at terminating VF. If the initial shock fails, all repeated attempts at defibrillation should be with the maximum energy that the defibrillator is capable of delivering (320 to 400 W ×s).

Indications for cardioversion depend on the clinical setting and the patient's general condition. Any tachycardia (except sinus tachycardia) that produces hypotension, myocardial ischemia, or heart failure warrants consideration of prompt termination using external cardioversion. Arrhythmias that fail to terminate with pharmacologic therapy may also be terminated by electrical cardioversion. Transient bradycardias and supraventricular and ventricular irritability following cardioversion are common and usually do not warrant antiarrhythmic intervention.

Implanted Cardioverter/Defibrillator (Fig. 230-CD5) ICDdevices have been developed that will promptly recognize and terminate life-threatening ventricular arrhythmias. These devices can deliver<1 to 40 W × s, the amount of which can be programmed. Current devices have antitachycardia pacing capabilities such thatVT can be sensed and terminated without resorting to a painful shock. In such devices, high-energy shocks are reserved for hypotensive VT, acceleration of VT, or failure to terminate VT after a programmed duration (Fig. 230-16). ICDs now can be implanted transvenously, and some are small enough to be implanted in a manner similar to pacemakers. Clinical trials testing the function of these devices in patients with drug-refractory ventricular arrhythmias have demonstrated survival from sudden death at 1 year ranging between 92 and 100%. Currently, ICDs should be considered for patients with VT that is not hemodynamically tolerated. As mentioned earlier, recent randomized trials suggest that ICDs confer improved mortality over amiodarone in patients with hemodynamically untolerated VT and a cardiac arrest not due to reversible causes (Table 230-6). Finally, they are indicated for patients with depressed left ventricular function, prior myocardial infarction, nonsustained and sustained VT at electrophysiologic study (Table 230-8). Guidelines for their use are given inTable 230-9.

The most frequent problem with theICD has been its inappropriate discharge in the absence of sustained ventricular arrhythmias. Additional potential problems include an increase in defibrillation threshold and decrease in tachycardia rates below the rate cut-off of the device in response to many antiarrhythmic drugs. Permanently implanted ventricular pacemakers may interfere with the device's ability to senseVF. This can be avoided by using committed bipolar pacing systems that are better able to sense local ventricular activity. Diagnostic features of newer, all-in-one devices are able to identify the probable cause of an ICD discharge (e.g.,AF,SVT, fractured lead) and to adjust pharmacologic therapy or reprogram the device to avoid such inappropriate shocks.

These newer devices have the capability to take a "second look" prior to shock delivery and thus may abort delivery for self-terminating arrhythmias. In addition, the range of candidates suitable for implantation will be expanded because the newer devices have the capability of shock therapy for patients whose arrhythmias do not cause loss of consciousness.

Newer generations ofICDs are smaller and frequently allow placement of a second lead in the right atria. This lead senses atrial activity and provides enhanced discrimination of atrial from ventricular electrical activity. This enhanced discrimination ofSVT fromVTprevents inappropriate shocks for SVT that may be misinterpreted as VT and allows the device to switch from a dual-chamber to a single-chamber device should an SVT-likeAFdevelop. These dual-chamber devices also allowAVsequential pacing. Finally, ICDs are now available that have defibrillation coils in the right atrium as well as right ventricle. These devices are suited for patients with infrequent but highly symptomatic atrial fibrillation. Patients with these atrial defibrillators can activate the device themselves and terminate their atrial fibrillation without going to the hospital.

Ablative Therapy for Arrhythmias Catheter-based mapping techniques have provided a nonoperative approach to the identification and cure of a variety of arrhythmias. In fact, catheter ablation techniques are now the procedures of choice for symptomatic patients with (1) concealed or manifest (WPW) bypass tracts, (2)AV nodal reentrantSVT, (3) typical atrial flutter, and (4) poorly controlled ventricular responses to atrial arrhythmias, most commonlyAF. Successful ablation of bypass tracts and modifications of the AV node by radiofrequency energy are extremely successful and cost-effective and are the procedure of choice for patients with recurrent episodes. The creation of AV block with implantation of a pacemaker is the method of choice in managing patients with AF and poorly controlled ventricular response. IdiopathicVTs (Fig. 230-17) and some VTs that are associated with coronary artery disease are also amenable to ablation, but the result is less successful than for ablation of SVTs.

Surgical therapy is now relegated to cases of sustainedVTassociated with coronary artery disease when operative intervention is needed for coronary bypass surgery and/or aneurysmectomy or VT associated with specific structural abnormalities (e.g., idiopathic left ventricle aneurysm, s/p surgery for tetralogy of Fallot). It also may be undertaken for the unusual instances of failed catheter ablation forSVTs associated with bypass tracts.

(Bibliography omitted in Palm version)

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SECTION 3 -DISORDERS OF THE HEART

231. NORMAL AND ABNORMAL MYOCARDIAL FUNCTION - *Eugene Braunwald*

CELLULAR BASIS OF CARDIAC CONTRACTION

THE CARDIAC ULTRASTRUCTURE

About three-fourths of the ventricular *myocardium* is composed of individual striated muscle cells (myocytes), normally 17 to 25 um in diameter and 60 to 140 um in length (Fig. 231-1*A*). Each fiber contains multiple, rodlike cross-banded strands (myofibrils) that run the length of the fiber and are, in turn, composed of serially repeating structures, the sarcomeres. The cytoplasm between the myofibrils contains other cell constituents (Fig. 231-1*B*), such as the single centrally located nucleus, numerous mitochondria, and intracellular membrane system, the sarcoplasmic reticulum.

The *sarcomere*, the structural and functional unit of contraction, is delimited by two adjacent dark lines, the Z lines (Fig. 231-1*C*). The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 um. Within the confines of the sarcomere are alternating light and dark bands, giving the myocardial fibers their striated appearance under the light microscope. At the center of the sarcomere is a dark band of constant length (1.5 um), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, is made up of two sets of interdigitating myofilaments (Fig. 232-1*D*). Thicker filaments, composed principally of the protein myosin, traverse the A band. They are about 10 nm (100 A) in diameter, with tapered ends, and measure 1.5 to 1.6 um in length. Thinner filaments, composed primarily of actin, course from the Z line through the I band into the A band. They are approximately 5 nm (50 A) in diameter and 1.0 um in length. Thus there is overlapping of thick and thin filaments only within the A band, while the I band contains only thin filaments (Fig. 232-1*C*). On electron-microscopic examination, bridges may be seen to extend between the thick and thin filaments within the A band.

THE CONTRACTILE PROCESS

The sliding model for muscle rests on the fundamental observation that the thick and thin filaments are constant in overall length during both contraction and relaxation. With activation, the actin filaments are propelled further into the A band. In the process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The *myosin* molecule is a complex, asymmetric fibrous protein with a molecular weight of about 500,000; it has a rodlike portion that is about 150 nm (1500 A) in length with a globular portion at its end (Fig. 231-1*D*). This globular portion of the myosin is the site of ATPase activity and also forms the bridges between the myosin and actin.In forming the thick myofilament, which is composed of ~300 longitudinally stacked myosin molecules, the rodlike segments of the myosin molecules are laid down in an orderly, polarized manner, leaving the globular portions projecting outward so that they can interact with actin to generate force and shortening (Fig. 231-2). *Actin* has a molecular weight of

about 47,000. The thin filament is composed of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin, which serves as a "backbone" to the thin filament. A group of these regulatory proteins, troponins C, I, and T, are spaced at regular intervals on this filament (Fig. 231-3). In contrast to myosin, actin has no intrinsic enzymatic activity, but it has the ability to combine reversibly with myosin in the presence of ATP and Ca^{2+}. The latter activates the myosin ATPase, which in turn breaks down ATP, the energy source for contraction. In relaxed muscle this interaction is inhibited by tropomyosin. *Titin* (Fig. 231-1*D*) is a large, flexible, myofibrillar protein that connects myosin to the Z line. Its stretching is believed to contribute to the elasticity of the heart.

During activation of the myocyte, Ca^{2+}becomes attached to troponin C, which results in a conformational change in the regulatory protein tropomyosin, which in turn exposes the actin cross-bridge interaction sites. Repetitive interaction between myosin heads and actin filaments is termed *cross-bridge cycling*, which results in sliding of the actin along the myosin filaments, ultimately causing muscle shortening and/or the development of tension. The splitting of ATP, which is synthesized in the mitochondria, then dissociates the myosin cross-bridge from the actin. In the presence of ATP (Fig. 231-2), linkages between actin and myosin filaments are made and broken cyclically as long as sufficient Ca^{2+} is present; these linkages cease when $[Ca^{2+}]$ falls below a critical level, and the troponin-tropomyosin complex once more prevents interactions between the myosin cross-bridges and the actin filaments. Intracytoplasmic Ca^{2+} is a principal mediator of the inotropic state of the heart; the fundamental action of most positive inotropic drugs, including the digitalis glycosides,b-adrenergic agonists, and phosphodiesterase inhibitors, is to raise the $[Ca^{2+}]$ in the vicinity of the myofilaments. Cyclic AMP enhances the phosphorylation of troponin I, a protein that accelerates cardiac relaxation.

The *sarcoplasmic reticulum* (SR) (Fig. 231-1*B*) is a complex network of anastomosing intracellular channels that invests the myofibrils. It is less profuse in cardiac than in skeletal muscle. Its longitudinally disposed membrane-lined tubules are closely applied to the surfaces of individual sarcomeres but have no direct continuity with the outside of the cell. However, closely related to the SR, both structurally and functionally, are the transverse tubules, or T system, formed by tubelike invaginations of the sarcolemma that extend into the myocardial fiber along the Z lines, i.e., the ends of the sarcomeres.

CARDIAC ACTIVATION

At rest, the cardiac cell is polarized, i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of -80 to-100 mV (Chap. 229). The sarcolemma, which in the resting state is largely impermeable to Na^+, has a Na^+- and K^+-stimulating pump energized by ATP that extrudes Na^+ from the cell; the pump plays a critical role in establishing this resting potential. Thus, on the inside of the cell $[K^+]$ is relatively high and $[Na^+]$ is far lower, while in the extracellular milieu $[Na^+]$ is high and $[K^+]$ is low. At the same time, in the resting state, the extracellular $[Ca^{2+}]$ greatly exceeds the free intracellular $[Ca^{2+}]$.

During the plateau of the action potential (phase 2) there is a slow inward current through L-type Ca^{2+}channels in the sarcolemma (Fig. 231-4). The absolute quantity of

Ca^{2+}that crosses the surface membrane is relatively small and itself appears to be incapable of bringing about full activation of the contractile apparatus. The depolarizing current not only extends across the surface of the cell but penetrates deeply into the cell by way of the ramifying T system; this Ca^{2+}current triggers the release of much larger quantities of $Ca^{2+}$from theSR, a process termed *Ca^{2+}-induced Ca^{2+}release*.

The Ca^{2+}released from theSR then diffuses toward the sarcomere and, as already described, combines with troponin C. By repressing this inhibitor of contraction, Ca^{2+}activates the myofilaments to shorten. During repolarization the activity of the Ca^{2+}pump in the SR reaccumulates Ca^{2+}against a concentration gradient, and the Ca^{2+} is stored by its attachment to a protein *calsequestrin*. This is an energy-requiring process that lowers the [Ca^{2+}] in the vicinity of the myofibrils to a level that inhibits the actin-myosin interaction responsible for contraction and in this manner leads to relaxation. Also, there is an exchange of Ca^{2+} for Na^{+} at the sarcolemma, reducing the cytoplasmic [Ca^{2+}]. Thus, the combination of the cell membrane, transverse tubules, and SR, with their ability to transmit the action potential, to release, and then to reaccumulate Ca^{2+}, appears to play a fundamental role in the rhythmic contraction and relaxation of heart muscle.

The ATP formed from substrate oxidation is the principal source of energy for almost all of the mechanical work of contraction performed by the myocardial cell. The high-energy phosphate stores in ATP are in equilibrium with those in the form of creatine phosphate. The activity of myosin ATPase determines the rate of forming and breaking of the actin-myosin cross-bridges and ultimately the velocity of muscle contraction.

THE ROLE OF MUSCLE LENGTH

In all striated muscle, including cardiac muscle, the force of contraction depends on initial muscle length. The sarcomere length associated with the most forceful contraction is approximately 2.2 um. At this length the two sets of myofilaments of the sarcomere are configured so as to provide the greatest area for their interaction. The length of the sarcomere also regulates the extent of activation of the contractile system, i.e., its sensitivity to Ca^{2+}. According to this concept, termed *length-dependent activation*, at the optimal sarcomere length of 2.2 um, the myofilament sensitivity to Ca^{2+} is maximal.

The relation between the initial length of the muscle fibers and the developed force is of prime importance for the function of heart muscle. This forms the basis of the Frank-Starling relation (Starling's law of the heart), which states that, within limits, the force of ventricular contraction is a function of the end-diastolic length of the cardiac muscle, which in turn is closely related to the ventricular end-diastolic volume.

MYOCARDIAL MECHANICS

THE FORCE-VELOCITY CURVE

The mechanical activity of striated muscle, skeletal and cardiac, may be expressed externally in two ways: by shortening and by the development of tension. In both forms of striated muscle the velocity of shortening is inversely related to the tension

development, an expression of the so-called force-velocity relation (Fig. 231-5). Expressed simply, the greater the load the muscle is called upon to lift, the lower the velocity (and extent) of shortening, and vice versa. Skeletal muscle fibers have a single, essentially fixed, force-velocity curve; i.e., at any given muscle length, the inverse relation between force and velocity is fixed. The contractile activity of skeletal muscle is controlled by varying the frequency of nerve impulses stimulating the muscle, and thereby the number of contractions of each fiber per unit of time, as well as by the number of muscle fibers, i.e., motor units, that contact, while the contractile properties of each individual fiber remain constant. Although the muscle's resting length also influences the characteristics of contraction, this variable remains essentially fixed in vivo because of the muscles' skeletal attachments. In contrast to skeletal muscle, the number of myocardial cells and within them the myofibrils and sarcomeres that become activated during each contraction is constant. However, the contractile activity of the myocardium is readily altered under physiologic conditions by changes in resting fiber length and by changes in the inotropic state, i.e., the contractility, both of which shift the myocardial force-velocity curve. Many neurohumoral influences affect contractility, but the most important influence is the adrenergic nervous system operating via its neurotransmitter, norepinephrine.

VENTRICULAR EJECTION AND FILLING

Analysis of the heart as a pump has classically centered on the relation between the end-diastolic volume of the ventricle (which is related to the length of the muscle fibers) and its stroke volume (the Frank-Starling relation). The end-diastolic or "filling" pressure of the ventricle is sometimes used as a surrogate for the end-diastolic volume. In the heart-lung preparation the stroke volume varies directly with the diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between the ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular function curve) provides a useful definition of the level of *myocardial contractility* (also termed the contractile, or inotropic, state of the ventricle). An increase in ventricular contractility is accompanied by a shift of the ventricular function curve upward and to the left [greater stroke work at any level of ventricular end-diastolic pressure (or volume), or lower end-diastolic pressure at any level of stroke work], while depression of contractility is characterized by a shift downward and to the right (Fig. 231-6).

During the adrenergic stimulation of the myocardium that accompanies exercise, relatively little change in ventricular end-diastolic volume occurs, while cardiac output, aortic flow velocity, stroke work, and the rate of ventricular pressure development are all augmented, reflecting an increase in myocardial contractility.

The important influence of the adrenergic neurotransmitter, norepinephrine (Chap. 72), on the mechanical properties of the myocardium has long been recognized. Direct stimulation of the cardiac adrenergic nerves augments ventricular function as a consequence of the release of norepinephrine from adrenergic nerve endings in the heart. Norepinephrine activates myocardial b receptors and through a series of G (guanine nucleotide binding) protein mediated changes activates the enzyme adenylate cyclase, which leads to the formation of cyclic AMP from ATP (Fig. 231-7). The latter, in

turn, activates protein kinase, which causes a more rapid, forceful contraction by phosphorylating the Ca^{2+}channel in the myocardial sarcolemma, thereby enhancing the influx of Ca^{2+}into the myocyte. Ca^{2+}acts on the contractile apparatus, as described on p. 1311. Cyclic AMP also phosphorylates theSRprotein phospholamban, which increases the uptake of Ca^{2+} by the SR, thereby enhancing the rate of relaxation. Adrenergic activation is evidenced by tachycardia, a reduction in cardiac dimensions, and increased rates of ejection and filling.

ASSESSMENT OF CARDIAC FUNCTION

Several techniques are available for defining impaired cardiac function in patients. With the patient at rest, and at a normal or elevated ventricular end-diastolic pressure, the cardiac output and stroke volume may be depressed in the presence of heart failure, but not uncommonly these variables are within normal limits. A more sensitive index is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value = 67 ± 8%), which may be estimated by radiocontrast or radionuclide angiography or echocardiography, and it is frequently depressed in systolic heart failure even when the stroke volume itself is normal. Alternatively, the detection of abnormally elevated ventricular end-diastolic volumes (normal value = 70± 20 mL/m^2) in the presence of a normal stroke volume signifies impairment of left ventricular systolic function. A limitation of cardiac output, ejection fraction, and ventricular volume in the assessment of cardiac function is that these variables are influenced strongly by ventricular loading conditions. Thus, a depressed ejection fraction and lowered cardiac output may be observed in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure.

The end-systolic left ventricular pressure-volume relationship is a particularly useful index of ventricular performance since it is independent of both preload and afterload (Fig. 231-8). At any level of myocardial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines, end-systolic volume (at any level of end-systolic pressure) rises. Noninvasive techniques, particularly echocardiography and radionuclide angiography (Chap. 227), are of great value in the clinical assessment of myocardial function. They provide measurements of end-systolic volume (or end-systolic dimension) that can be related to systolic arterial pressure. In addition, they provide convenient measurements of ejection fraction and systolic shortening rate and allow measurement of ventricular filling (see below).

Exercise A useful technique for evaluating ventricular performance involves the measurement of the circulatory changes occurring during exercise. Thus, left ventricular performance may be estimated accurately by measuring the left ventricular end-diastolic pressure, cardiac output, and total-body O_2consumption at rest and during exercise. In persons with normal cardiac function, the cardiac output rises by more than 500 mL/min for each 100-mL increase in O_2consumption per minute. The left ventricular end-diastolic pressure at rest is less than 12 mmHg and changes little during exercise, while cardiac output, and to a lesser extent stroke volume, rise, the latter especially when exercise is carried out in the upright position. The failing left ventricle, on the other hand, is characterized by an elevation of end-diastolic pressure during exercise to above 12 mmHg, accompanied by either no change or a fall in stroke volume and a

subnormal increase in cardiac output related to the increase in minute O_2consumption. The overall performance of the cardiopulmonary system in delivering oxygen to the metabolizing tissue can also be estimated by measuring the maximal O_2consumption achieved during escalating treadmill exercise ($_{max}O_2$). Normal values exceed 20 mL/min per kilogram, while values under 10 mL/min per kilogram represent severe impairment of function, usually seen in patients with severe heart failure and a poor prognosis.

The potential value of stressing the left ventricle in assessing its performance is emphasized by the fact that the normal range of left ventricular end-diastolic pressure, cardiac index, and ventricular stroke work in the resting state are wide, with values that frequently overlap those seen in patients with ventricular dysfunction.

DIASTOLIC FUNCTION (Fig. 231-9)

This important variable is best assessed by continuously measuring the flow velocity across the mitral valve using Doppler echocardiography. Normally, the velocity of inflow is more rapid in early diastole than during atrial systole; with impaired relaxation the rate of early diastolic filling declines, while the rate of presystolic filling rises. With severe impairment of filling the pattern is "pseudo-normalized" and early ventricular filling becomes more rapid as left atrial pressure upstream to the stiff left ventricle rises.

CONTROL OF CARDIAC PERFORMANCE AND OUTPUT

The extent of shortening of heart muscle and, therefore, the stroke volume of the intact ventricle are determined by three influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the inotropic state of the muscle, i.e., the position of its force-velocity-length relation and its end-diastolic-shortening-relation; and (3) the tension that the muscle is called upon to develop during contraction, i.e., the afterload. Within wide limits, heart rate determines the cardiac output at any stroke volume as long as the other three influences remain constant. Ventricular filling is influenced by the extent and speed of myocardial relaxation, which in turn is determined by the rate of uptake of Ca^{2+} by the SR; the latter may be reduced by ischemia. Filling may be also impeded by the stiffness of the ventricular wall, which may be increased by ventricular hypertrophy and conditions that infiltrate the ventricle, such as amyloid, or by an extrinsic constraint (e.g., pericardial compression).

VENTRICULAR END-DIASTOLIC VOLUME (PRELOAD)

At any level of inotropic state and afterload, the performance of the myocardium is influenced profoundly by ventricular end-diastolic fiber length and therefore by diastolic ventricular volume, i.e., by operation of the Frank-Starling mechanism (Fig. 231-6). The following are the major determinants of ventricular preload in the intact organism:

Total Blood Volume When blood volume is depleted, as in hemorrhage or dehydration, venous return to the heart declines (Chap. 38) and ventricular end-diastolic volume (preload) falls, as does ventricular performance, as reflected in stroke volume and ventricular work.

Distribution of Blood Volume The ventricular end-diastolic volume is influenced by the

distribution of blood volume between the intra- and extrathoracic compartments. This distribution in turn is influenced by the following:

1. *Body position*. Gravitational forces pool blood in dependent portions of the body; upright posture augments extrathoracic at the expense of intrathoracic blood volume and reduces ventricular work.

2. *Intrathoracic pressure*. Normally, mean intrathoracic pressure is negative, which increases thoracic blood volume and ventricular end-diastolic volume and enhances the return of blood to the heart, particularly during inspiration, when this pressure becomes more negative. Elevation of intrathoracic pressure, as occurs during the Valsalva maneuver or prolonged bouts of coughing or with positive-pressure ventilation, has the opposite effect. It impedes venous return, diminishes intrathoracic blood volume, and reduces stroke volume and ventricular work.

3. *Intrapericardial pressure*. When this pressure is elevated, as in pericardial tamponade (Chap. 239), there is interference with cardiac filling, and the resultant reduction in ventricular diastolic volume reduces stroke volume and ventricular work.

4. *Venous tone*. The venous system is not a simple system of passive conduits between the systemic capillary bed and the right atrium. Instead, the smooth muscle in the walls of the venules and veins responds to a variety of neural and humoral stimuli. Venoconstriction occurs during muscular exercise, deep respiration, fright, or marked hypovolemic shock, reducing extrathoracic and augmenting intrathoracic and intraventricular blood volumes and ventricular performance.

5. *The pumping action of skeletal muscle*. During muscular exercise the contracting skeletal muscles squeeze blood out of the venous bed and, with the aid of the venous valves, displace it centrally, thereby increasing intrathoracic blood volume, ventricular end-diastolic volume, and ventricular work.

Atrial Contraction Vigorous, appropriately timed atrial contraction augments ventricular filling and end-diastolic volume. The atrial contribution to ventricular filling, the so-called atrial kick, is of particular importance in patients with concentric ventricular hypertrophy. In such patients, the loss of atrial systole (as occurs with the development of atrial fibrillation) reduces ventricular end-diastolic pressure and volume, ultimately lowering myocardial performance. The atrial contribution to ventricular filling may also be reduced by atrioventricular dissociation, prolongation or abbreviation of the P-R interval, and depression of atrial contractility.

INOTROPIC STATE (MYOCARDIAL CONTRACTILITY)

A number of factors determine the level of ventricular performance at any given ventricular end-diastolic volume, i.e., the position of the ventricular function curve (Fig. 231-6) as well as the position of the left ventricular pressure-volume plane (Fig. 231-8). These influences may be considered to operate by modifying myocardial force-velocity relations. In the final analysis, most of these influences act by altering the [Ca^{2+}] in the vicinity of the myofilaments, which in turn trigger cross-bridge cycling (p. 1293).

Adrenergic Nerve Activity (See also Chap. 72) The quantity of norepinephrine released by adrenergic nerve endings in the heart is determined by the adrenergic nerve impulse traffic; alterations in the frequency of these nerve impulses modify the quantity of norepinephrine released and acting on theb-adrenergic receptors in the myocardium. This mechanism is the most important one that acutely modifies myocardial contractility under physiologic conditions.

Circulating Catecholamines (See also Chap. 72) When it is stimulated by adrenergic nerve impulse, the adrenal medulla releases catecholamines, which, when they reach the heart, augment both heart rate and myocardial contractility.

The Force-Frequency Relation The position of the myocardial force-velocity curve is also influenced by the rate and rhythm of cardiac contraction; e.g., ventricular extrasystoles result in postextrasystolic potentiation, presumably by increasing the quantity of Ca^{2+}that enters the cardiac cell. The contractility of the normal (but not of the failing) heart is augmented by an increase in frequency of contraction.

Exogenously Administered Inotropic Agents Isoproterenol, dopamine, dobutamine, and other sympathomimetic agents, cardiac glycosides, Ca^{2+}, amrinone, milrinone, and other phosphodiesterase inhibitors all improve the myocardial force-velocity relation and therefore may be used to stimulate ventricular performance.

Physiologic Depressants Included among these are severe myocardial hypoxia, ischemia, and acidosis. Acting either singly or in combination, these influences depress the myocardial force-velocity curve and left ventricular work at any given ventricular end-diastolic volume.

Pharmacologic Depressants These include many antiarrhythmic drugs such as procainamide and disopyramide; calcium antagonists such as verapamil; beta blockers; and large doses of barbiturates, alcohol, and general anesthetics as well as many other drugs.

Loss of Myocytes When a sufficiently large portion of ventricular myocardium becomes nonfunctional or necrotic, as occurs transiently during ischemia (Chap. 244) and permanently in myocardial infarction (Chap. 243), total ventricular performance at any given level of end-diastolic volume becomes depressed. Programmed cell death (apoptosis) can also cause loss of myocytes and, when sufficiently widespread, can impair ventricular function and cause heart failure.

Intrinsic Myocardial Depression Although the fundamental mechanisms responsible for depression of myocardial contractility in most cases of chronic congestive heart failure secondary to prolonged ventricular overload or cardiomyopathy remain to be elucidated (p. 1316), it is now apparent that in this condition the inotropic state of individual surviving myocytes is depressed, and as a consequence the ventricular performance at any ventricular preload and afterload is lowered.

VENTRICULAR AFTERLOAD

The stroke volume is ultimately a function of the extent of ventricular fiber shortening. In

the intact heart, as in isolated cardiac muscle, the velocity and extent of shortening of ventricular muscle fibers at any level of preload and myocardial contractility are inversely related to the afterload, i.e., the load that opposes shortening. In the intact heart the afterload may be defined as the tension or stress developed in the ventricular wall during ejection. Therefore, the afterload is determined by the aortic pressure as well as the volume and thickness of the ventricular cavity. Laplace's law indicates that the tension of the myocardial fiber is a function of the product of the intracavitary ventricular pressure and ventricular radius divided by the wall thickness. Therefore, at any given level of aortic pressure, the afterload faced by a dilated left ventricle of normal thickness is higher than that encountered by a normal-sized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload of a thick-walled ventricle is lower than of a thin-walled chamber. The aortic pressure, in turn, is determined by the peripheral vascular resistance, the physical characteristics of the arterial tree, and the volume of blood it contains at the onset of ejection.

The critical role played by the ventricular afterload in cardiovascular regulation is shown in Fig. 231-10. As already noted, increases in both preload and contractility increase myocardial fiber shortening, while increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size are the determinants of stroke volume. Arterial pressure, in turn, is related to the product of cardiac output and systemic vascular resistance, while afterload is a function of left ventricular volume, wall thickness, and arterial pressure. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume. This in turn tends to limit the increase in pressure.

When myocardial contractility becomes impaired and the ventricle dilates, afterload rises and becomes increasingly important in determining cardiac output. Increases in afterload may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further while myocardial oxygen requirements are increased. This can cause a vicious cycle. Treatment with vasodilators has the opposite effect; by reducing afterload, cardiac output rises (Chap. 232).

Under normal circumstances, the various influences acting on cardiac performance enumerated above interact in a complex fashion to maintain cardiac output at a level appropriate to the requirements of the metabolizing tissues, and interference with any one of these mechanisms may not influence the cardiac output. For example, a moderate reduction of blood volume *or* the loss of the atrial contribution to ventricular contraction can ordinarily be sustained without a reduction in the cardiac output at rest. Other factors, such as increases in the frequency of adrenergic nerve impulses to the heart and in heart rate, will, in a normal individual, serve as compensatory mechanisms, augment contractility, and sustain cardiac output.

EXERCISE

The hemodynamic changes that occur normally during exercise in the upright position are complex (Fig. 231-6). Hyperventilation, the pumping action of the exercising muscles, and the venoconstriction during exercise all augment venous return and hence ventricular filling and preload. Simultaneously, the increase in the adrenergic nerve

impulse traffic to the myocardium, the increased concentration of circulating catecholamines, and the tachycardia that occur during exercise combine to augment the contractile state of the myocardium (Fig. 231-6, curves 1 and 2) and lead to an elevation of stroke work and stroke volume, without change or even a reduction of end-diastolic pressure and volume (Fig. 231-6, points A and B). Vasodilatation occurs in the exercising muscles, thus tending to limit the increase in arterial pressure that would otherwise occur as cardiac output rises to levels as high as five times basal during maximal exercise. This vasodilatation ultimately allows the achievement of a greatly elevated cardiac output during exercise, at an arterial pressure only moderately higher than in the resting state.

THE FAILING HEART

Although heart failure may be readily described as a clinical syndrome, characterized by well-known symptoms and physical signs (Chap. 232), a precise physiologic or biochemical definition is far more difficult. However, from the clinical point of view, heart failure may be considered to be the condition in which *an abnormality of cardiac function is responsible for the inability of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or allows it to do so only from an abnormally elevated ventricular diastolic volume*. Abnormalities during systole and/or diastole may be present in heart failure (Fig. 231-9). In so-called *systolic heart failure* (p. 1320), an impairment of myocardial contractility causes weakened systolic contraction, which leads, ultimately, to a reduction in stroke volume and cardiac output, inadequate ventricular emptying, cardiac dilatation, and often elevation of ventricular diastolic pressure. Idiopathic dilated cardiomyopathy (Chap. 238) is the prototype of systolic heart failure. In *diastolic heart failure* (p. 1320), the principal abnormality is impaired relaxation and filling of the ventricle, which leads to an elevation of ventricular diastolic pressure at any given diastolic volume (Fig. 231-9). Failure of relaxation can be functional and transient, as during ischemia, which reduced the ATP required for theSR pump to lower cytoplasmic Ca^{2+}. Chronically impaired ventricular filling can be caused by a stiffened, thickened ventricle. Typical conditions in which diastolic failure occurs are restrictive cardiomyopathy secondary to infiltrative conditions, such as amyloidosis or hemochromatosis, as well as hypertrophic cardiomyopathy (Chap. 238). The concentric hypertrophy associated with chronic hypertension can also impair ventricular filling but rarely causes overt heart failure. In many patients with cardiac hypertrophy and dilatation, systolic and diastolic failure coexist; the left ventricle both empties and fills abnormally. There may be cardiac dilatation, but the ventricle's pressure-volume relation is shifted, raising the ventricular diastolic pressure at any given volume.

Although a defect in myocardial contraction is characteristic of systolic heart failure, many conditions may cause such a defect. These include a primary abnormality in the heart muscle, as occurs in cardiomyopathy, or an abnormality secondary to a chronic excessive work load as in hypertension or valvular heart disease. In ischemic heart disease, systolic heart failure results from a loss in the quantity of normally contracting cells (secondary to myocardial necrosis and apoptosis) and/or from transient loss of function in reversibly ischemic (hibernating) myocardium (Chap. 244).

Heart failure should be distinguished from conditions that resemble it, such as (1) states of circulatory insufficiency in which myocardial function is not primarily impaired, such as

cardiac tamponade or hemorrhagic shock; (2) conditions in which there is circulatory congestion because of abnormal salt and water retention but in which there is no serious disturbance of the heart's function, such as acute glomerulonephritis; and (3) conditions in which a normal myocardium is suddenly presented with a load that exceeds its capacity, such as accelerated hypertension or rupture of a valve cusp secondary to infective endocarditis.

ADAPTIVE MECHANISMS

A number of mechanisms aid the heart faced with an increased hemodynamic burden (such as pressure or volume overload) or that has sustained loss of myocardium or contractility. These mechanisms include the following:

1. The *Frank-Starling mechanism* operating through an increase in preload (p. 1314). As outlined above, an increase in the end-diastolic volume of the ventricle is associated with stretching of the sarcomeres, which increases the interaction between actin and myosin filaments and their sensitivity to Ca^{2+}. Ventricular dilatation may become maladaptive when it becomes excessive, as may occur in severe aortic or mitral regurgitation; this increases wall stress through the operation of LaPlace's law and reduces shortening.

2. *Increased afterload*, as occurs in aortic stenosis and hypertension, also augments wall tension, leading to concentric hypertrophy, which in turn restores elevated ventricular wall stress to normal (Figs. 231-CD1 and231-CD2). However, ventricular hypertrophy impairs ventricular filling, and if the hypertrophy is insufficient to restore wall stress to normal, the ventricle dilates and this increases wall stress further, leading to a vicious circle.

3. *Redistribution of a subnormal cardiac output* away from the skin, skeletal muscle, and kidneys with maintenance of blood flow to the brain and the heart.

4. *Neurohumoral adjustments*, which tend to maintain arterial pressure and are discussed inChap. 72. Like the other adaptive mechanisms, when neurohumoral adjustments are severe and chronic they impair cardiac function (see below).

BIOCHEMICAL ABNORMALITIES IN HEART FAILURE

There is no unifying theory providing a biochemical basis for heart failure. However, a number of abnormalities have been described.

Reduction in Cardiac Efficiency The common forms of low-output systolic heart failure, secondary to coronary atherosclerosis, hypertension, cardiomyopathy, and certain valvular and congenital lesions, are characterized by an absolute or a relative reduction in the external work delivered by the heart, while myocardial oxygen consumption remains normal or nearly so. Therefore, the external efficiency, i.e., the ratio of external work performed to energy consumed, is often depressed.

Alterations in Energy Metabolism When heart failure occurs in the presence of acute or chronic ischemia, it can be attributed to reduced myocardial energy supplies. Severe

ventricular hypertrophy and/or dilatation of any etiology can also cause relative ischemia, especially in the subendocardium, and this can impair both ventricular contraction and filling. In some forms of experimental and clinical heart failure without ischemia, myocardial energy stores in the form of creatine phosphate are decreased, as is the activity of the enzyme creatin kinase required for the shuttling of high-energy phosphate between creatine phosphate and adenosine diphosphate, suggesting that reductions in myocardial energy reserves may play a role.

Alterations in Regulatory Proteins Changes in the cardiac regulatory proteins frequently occur in chronic heart failure. These include a reduction of myosin ATPase activity, which may be caused by an alteration in the expression of troponin T and/or of myosin light chain kinase 2, alterations that could be responsible for lowering the rate of interaction between myosin and actin myofilaments, leading to systolic heart failure.

Abnormalities of Excitation-Contraction Coupling Substantial evidence supports the view that in many forms of heart failure the delivery of Ca^{2+} to the contractile sites is reduced, thereby impairing cardiac performance (Table 231-1). However, the molecular basis of this abnormality -- indeed of the subcellular structures involved, i.e., the sarcolemma, T tubules, and/orSR -- has yet to be defined. There is, however, evidence for a reduction in the activity of the Ca^{2+}release channel in the SR and of messenger RNAs of the proteins regulating Ca^{2+}movements. These include the sarcolemmal Ca^{2+}channels, the Ca^{2+}release channels, and the Ca^{2+}uptake pump, which play critical roles in the movement of Ca^{2+}between the SR and the cytoplasm. Impaired expression of the genes encoding these proteins can impair both myocardial contraction and relaxation and thereby contribute to the development of heart failure.

NEUROHUMORAL AND CYTOKINE ADJUSTMENTS

A reduction in cardiac performance evokes a series of neurohumoral adjustments, which, at different times, may be adaptive and maladaptive. Although they are useful because they maintain arterial perfusion pressure in the face of a sudden reduction of cardiac output, these neurohumoral adjustments increase the hemodynamic burden and oxygen requirements of the failing ventricle (Fig. 231-11).

The Adrenergic Nervous System In patients with heart failure the levels of circulating norepinephrine may be markedly elevated, reflecting the increased activity of the adrenergic nervous system; indeed the prognosis in patients with heart failure varies inversely with the concentration of plasma norepinephrine. This increased activity of the adrenergic neurons supports ventricular contractility in *acute* heart failure. Heart failure is intensified when large doses of b-adrenergic blocking agents are administered acutely, providing evidence for the protective action of adrenergic nervous activation. However, the *chronic* adrenergic stimulation that occurs in heart failure may increase afterload by raising vascular resistance, cause cardiac arrhythmias, and may damage myocytes further, perhaps by causing Ca^{2+}overload.

The density of adrenergic receptors, their coupling to G proteins, and the concentration of cardiac norepinephrine stores are all reduced in chronic, severe heart failure. These changes are accompanied by a reduction in the activity of adenylate cyclase, which may lower the intracellular concentration of cyclic AMP. The latter in turn reduces the

activation of protein kinase, the phosphorylation of Ca^{2+}channels, transarcolemmal Ca^{2+}entry, as well as the phosphorylation of phospholamban, a protein in the SR, which reduces the reuptake of Ca^{2+} by the latter (Fig. 231-7). Changes in the G proteins, which couple the b receptor to the catalytic adenylate cyclase (which is responsible for the production of cyclic AMP), may also occur in heart failure, with increased activity of the inhibitory subunit.

The Renin-Angiotensin-Aldosterone System When cardiac output declines, the renin-angiotensin-aldosterone system (Chap. 331;Fig. 231-CD3) is activated. Concentrations of both circulating angiotensin II and aldosterone are increased, the former contributing to excess vasoconstriction and the latter to the retention of salt and water and perhaps to cardiac fibrosis. The local (tissue) renin-angiotensin system is also activated in heart failure. Patients with heart failure are usually improved by blocking this system with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists (Chap. 232).

Endothelin The concentration of circulatory endothelin, a polypeptide that is a very powerful vasoconstrictor, is increased in heart failure. A number of studies have shown that blockade of endothelin receptors improves left ventricular function in patients and experimental animals with heart failure.

Tumor Necrosis Factora The overexpression of a number of cytokines also appears to play a prominent role in the pathogenesis of heart failure. It has now been well established that patients exhibit elevated levels of tumor necrosis factor (TNF) a, both in the circulation and in cardiac muscle; the pathophysiologic significance of this finding is just unfolding. Transgenic mice with overexpressed cardiac TNF-a have systolic dysfunction, myocarditis, ventricular dilatation, heart failure, and shortened survival. The infusion of TNF-a impairs ventricular function, and this can be reversed with a TNF-aantagonist.

Vasodilator Peptides A number of vasodilator peptides are released by the dilated heart. Best known are the natriuretic peptides atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). When stretch receptors in the atria (ANP and BNP) and ventricles (BNP) are activated, these hormones (or their prohormones) are released and act on specific natriuretic peptide receptors, which increase the concentrations of cyclic GMP in the kidney, adrenal glomerulose, vascular smooth muscle, and platelets. Urine volume and sodium excretion are augmented, vascular resistance is reduced, and the release of renin and the secretion of aldosterone are reduced. These effects, while beneficial, are not sufficiently powerful to oppose the sodium-retaining and vasoconstrictor influences of the other neurohumoral systems activated in heart failure. Elevated circulating concentrations of ANP and particularly BNP correlate with a poor prognosis in heart failure. Drugs that augment the concentrations of these compounds are under development.

Figure 231-11 illustrates current concepts of neurohumoral-cytokine activation in heart failure. The activation of the adrenergic nervous system and the renin-angiotensin-aldosterone system and the enhanced elaboration of endothelin and arginine vasopressin appear to be adaptive in *acute*, severe heart failure. However, they all appear to exert a maladaptive response in chronic heart failure. Inflammatory

cytokines and oxidative stress are emerging as potent noxious stimuli as well. Together they result in a vicious circle, causing myocyte hypertrophy, remodeling, and cell death, the latter often due to myocardial apoptosis, all resulting in further impairment of cardiac function and myocardial injury. Effective agents that interfere with the adverse effects of these stimuli on cardiac function, such as endothelin receptor blockers andTNF-aantagonists, are becoming available, and these neurohumoral and cytokine blockers appear capable of interrupting the vicious circle.

HEART FAILURE -- A DISTURBANCE OF THE MYOCARDIAL PUMP

In the final analysis, in systolic heart failure the basic problem is depression of the myocardial force-velocity relationship and of the length-active tension curve, reflecting reductions in the contractile state of the myocardium (Fig. 231-6, curves 1 to 3,Fig. 231-8, right). In diastolic failure there is upward displacement of the diastolic pressure-volume relation (Fig. 231-9). In many instances, cardiac output and external ventricular performance at rest are within normal limits but are maintained at these levels only by an increased end-diastolic fiber length and an elevated ventricular end-diastolic volume, i.e., through the operation of the Frank-Starling mechanism (Fig. 231-6, points A to D). The elevation of left ventricular preload is associated with increases in the pulmonary capillary pressure, contributing to the dyspnea experienced by patients with heart failure, while elevation of right ventricular preload raises systemic venous pressure and contributes to the development of edema. The improvement of contractility that normally accompanies augmented adrenergic activity during exercise is attenuated or even prevented by norepinephrine depletion and downregulation of myocardial b receptors, which occur in severe heart failure (Fig. 231-6, curves 3 and 3¢).

The factors that augment ventricular filling during exercise in the normal individual push the failing myocardium along its flattened length-active tension curve, and although the left ventricle may perform somewhat better at this higher diastolic volume, this occurs only as a consequence of an inordinate elevation of ventricular end-diastolic volume and pressure and, therefore, of the pulmonary capillary pressure. The latter intensifies dyspnea and therefore plays an important role in limiting the intensity of exercise that the patient can perform. Left ventricular failure becomes fatal when the myocardial length-active tension curve is depressed (Fig. 231-6, curve 4) to the point at which cardiac performance fails to satisfy the requirements of the peripheral tissues even at rest, and/or the left ventricular end-diastolic and pulmonary capillary pressures are elevated to levels that result in pulmonary edema (Fig. 231-6, point E).

(Bibliography omitted in Palm version)

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232. HEART FAILURE - *Eugene Braunwald*

Heart failure (HF) is the pathophysiologic state in which an abnormality of *cardiac* function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the me tabolizing tissues *and/or* allows it to do so only from an abnormally elevated diastolic volume. HF is frequently, but not always, caused by a defect in myocardial contraction, and then the term *myocardial failure* is appropriate. The latter may result from a primary abnormality in heart muscle, as occurs in the cardiomyopathies, in viral myocarditis (Chap. 238), and with excessive programmed cell death (apoptosis). HF also results commonly from coronary atherosclerosis, which interferes with cardiac contraction by causing myocardial infarction and ischemia. HF may also occur in valvular and/or congenital heart disease in which the heart muscle is damaged by the long-standing excessive hemodynamic burden imposed by the valvular abnormality or cardiac malformation.

In other patients withHF, however, a similar clinical syndrome is present but without any detectable abnormality of *myocardial* function. In some of these patients the normal heart is suddenly presented with a mechanical load that exceeds its capacity, such as an acute hypertensive crisis, rupture of an aortic valve cusp, or massive pulmonary embolism. HF in the presence of normal myocardial function also occurs in chronic conditions in which there is impaired filling of the ventricles due to a mechanical abnormality such as tricuspid and/or mitral stenosis, constrictive pericarditis without myocardial involvement, endocardial fibrosis, and some forms of hypertrophic cardiomyopathy. In many patients with HF, particularly those with valvular or congenital heart disease, there is a combination of impaired myocardial function and hemodynamic overload.

Heart failure should be distinguished from (1) conditions in which there is circulatory congestion secondary to abnormal salt and water retention but in which there is no disturbance of cardiac function per se, as occurs in renal failure; and (2) noncardiac causes of inadequate cardiac output, such as hypovolemic shock (Chap. 38).

The ventricles respond to a chronically increased hemodynamic burden with the development of hypertrophy (Fig. 232-1). When the ventricle is called on to deliver an elevated cardiac output for prolonged periods, as in valvular regurgitation, it develops *eccentric hypertrophy*, i.e., cavity dilatation, with an increase in muscle mass so that the ratio between wall thickness and ventricular cavity size remains relatively constant early in the process. With chronic pressure overload, as in valvular aortic stenosis or untreated hypertension, *concentric ventricular hypertrophy* develops; in this condition the ratio between wall thickness and ventricular cavity size increases. In both eccentric and concentric hypertrophy, a stable hyperfunctioning state may exist for many years, but myocardial function may ultimately deteriorate, leading toHF. Often at this time, the ventricle dilates and the ratio between wall thickness and cavity size declines, leading to increased stress on each unit of myocardium, further dilatation, and a vicious circle.

Heart failure represents a major public health problem in industrialized nations. It appears to be the only common cardiovascular condition that is increasing in prevalence and incidence. In the United States,HF is responsible for almost 1 million hospital admissions and 40,000 deaths annually. Since HF is more common in the elderly, its

prevalence is likely to continue to increase as the population ages.

CAUSES OF HEART FAILURE

In evaluating patients withHF, it is important to identify not only the *underlying* but also the *precipitating cause*. The cardiac abnormality produced by a congenital or acquired lesion such as valvular aortic stenosis may exist for many years and cause no clinical disability. Frequently, however, clinical manifestations of HF are precipitated for the first time in the course of some acute disturbance that places an additional load on a myocardium that is chronically excessively burdened (see below). Such a heart may be compensated but have little additional reserve, and the additional load imposed by a precipitating cause results in further deterioration of cardiac function. Identification of such precipitating causes is of critical importance because their prompt alleviation may be lifesaving. In the absence of underlying heart disease, these acute disturbances do not by themselves lead to HF.

PRECIPITATING CAUSES

1. *Infection*. Patients with pulmonary vascular congestion due to left ventricular failure are more susceptible to pulmonary infection than are normal persons; any infection may precipitateHF. The resulting fever, tachycardia, and hypoxemia and the increased metabolic demands may place a further burden on an overloaded, but compensated, myocardium of a patient with chronic heart disease.

2. *Anemia*. In the presence of anemia, the oxygen needs of the metabolizing tissues can be met only by an increase in the cardiac output (Chap. 61). Although such an increase in cardiac output can be sustained by a normal heart, a diseased, overloaded, but otherwise compensated heart may be unable to augment sufficiently the volume of blood that it delivers to the periphery. In this manner, the combination of anemia and previously compensated heart disease can precipitateHF and lead to inadequate delivery of oxygen to the periphery.

3. *Thyrotoxicosis and pregnancy*. Similar to anemia and fever, thyrotoxicosis and pregnancy are also high cardiac output states. The development or intensification ofHF in a patient with previously compensated heart disease may actually be one of the first clinical manifestations of hyperthyroidism (Chap. 330). Similarly, HF not infrequently occurs for the first time during pregnancy in women with rheumatic valvular disease, in whom cardiac compensation may return following delivery (Chap. 7).

4. *Arrhythmias*. In patients with compensated heart disease, arrhythmias are among the most frequent precipitating causes ofHF. They exert a deleterious effect for a variety of reasons: (a) Tachyarrhythmias reduce the time period available for ventricular filling and in patients with ischemic heart disease they may also cause ischemic myocardial dysfunction. (b) The dissociation between atrial and ventricular contractions characteristic of many brady- and tachyarrhythmias results in the loss of the atrial booster pump mechanism, thereby raising atrial pressures. (c) Cardiac performance may become further impaired because of the loss of normally synchronized ventricular contraction in any arrhythmia associated with abnormal intraventricular conduction. (d) Marked bradycardia associated with complete atrioventricular block or other severe

bradyarrhythmias reduces cardiac output unless stroke volume rises reciprocally; this compensatory response cannot occur with serious myocardial dysfunction, even in the absence of HF (Chaps. 229 and230).

5. *Rheumatic, viral, and other forms of myocarditis*. Acute rheumatic fever and a variety of other inflammatory or infectious processes affecting the myocardium may precipitateHF in patients with or without preexisting heart disease (Chaps. 235 and238).

6. *Infective endocarditis*. The additional valvular damage, anemia, fever, and myocarditis that often occur as a consequence of infective endocarditis may, singly or in concert, frequently precipitateHF(Chap. 126).

7. *Physical, dietary, fluid, environmental, and emotional excesses*. The sudden augmentation of sodium intake as with a large meal, the inappropriate discontinuation of pharmaceuticals to treatHF, blood transfusions, physical overexertion, excessive environmental heat or humidity, and emotional crises all may precipitate HF in patients with heart disease who were previously compensated.

8. *Systemic hypertension*. Rapid elevation of arterial pressure, as may occur in some instances of hypertension of renal origin or upon discontinuation of antihypertensive medication in patients with essential hypertension, may result in cardiac decompensation (Chap. 246).

9. *Myocardial infarction*. In patients with chronic but compensated ischemic heart disease, a fresh infarct, sometimes otherwise silent clinically, may further impair ventricular function and precipitateHF(Chap. 243).

10. *Pulmonary embolism.* Physically inactive patients with low cardiac output are at increased risk of developing thrombi in the veins of the lower extremities or the pelvis. Pulmonary emboli may result in further elevation of pulmonary arterial pressure, which in turn may produce or intensify ventricular failure. In the presence of pulmonary vascular congestion, such emboli also may cause pulmonary infarction (Chap. 261).

A systematic search for these precipitating causes should be made in every patient with the new development or recent intensification ofHF. If properly recognized, the precipitating cause of HF usually can be treated more effectively than the underlying cause. Therefore, the prognosis in patients with HF in whom a precipitating cause can be identified, treated, and eliminated is more favorable than in patients in whom the underlying disease process has progressed to the point of producing HF without a precipitating cause.

FORMS OF HEART FAILURE

HFmay be described as *systolic* or *diastolic*, *high-output* or *low-output*, *acute* or *chronic*, *right-sided* or *left-sided*, and *forward* or *backward*. These descriptors are often useful in a clinical setting, particularly early in the patient's course, but late in the course of chronic HF the differences between them often become blurred.

SYSTOLIC VERSUS DIASTOLIC FAILURE

The distinction between these two forms ofHF, described in Fig. 231-9, relates to whether the principal abnormality is the inability of the ventricle to contract normally and expel sufficient blood (systolic failure) or to relax and/or fill normally (diastolic failure). The major clinical manifestations of systolic failure relate to an inadequate cardiac output with weakness, fatigue, reduced exercise tolerance, and other symptoms of hypoperfusion, while in diastolic HF the manifestations relate principally to the elevation of filling pressures. Many patients, particularly those who have both ventricular hypertrophy *and* dilatation, exhibit abnormalities both of contraction and relaxation coexist.

DiastolicHF may be caused by increased resistance to ventricular inflow and reduced ventricular diastolic capacity (constrictive pericarditis and restrictive, hypertensive, and hypertrophic cardiomyopathy), impaired ventricular relaxation (acute myocardial ischemia), and myocardial fibrosis and infiltration (restrictive cardiomyopathy).

HIGH-OUTPUT VERSUS LOW-OUTPUT HEART FAILURE

It is useful to classify patients withHF into those with a low cardiac output, i.e., *low-output HF*, and those with an elevated cardiac output, i.e., *high-output HF*. The former occurs secondary to ischemic heart disease, hypertension, dilated cardiomyopathy, and valvular and pericardial disease, while the latter is seen in patients with HF and hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease. In clinical practice, however, low-output and high-output HF cannot always be readily distinguished. The normal range of cardiac output is wide [2.2 to 3.5 (L/min)/m_2]; in many patients with so-called low-output HF, the cardiac output may actually be just within the normal range at rest (although lower than it had been previously), but it fails to rise normally during exertion. On the other hand, in patients with so-called high-output HF, the output may not exceed the upper limits of normal (although it would have been elevated had it been measured before HF supervened); rather, it may have fallen to within normal limits. Regardless of the *absolute* level of the cardiac output, however, cardiac failure may be said to be present when the characteristic clinical manifestations described below are accompanied by a depression of the curve relating ventricular end-diastolic volume to cardiac performance (seeFig. 231-6).

An integral physiologic component of *systolic*HF is the delivery of an inadequate quantity of oxygen required by the metabolizing tissues. In the absence of peripheral shunting of blood, this is reflected in an abnormal widening of the normal arterial-mixed venous oxygen difference (35 to 50 mL/L in the basal state). In mild cases, such an abnormality may not be present at rest but becomes evident only during exertion or other hypermetabolic states. In patients with high cardiac output states, such as those associated with arteriovenous fistula or thyrotoxicosis, the arterial-mixed venous oxygen difference is normal or low. The mixed venous oxygen saturation is raised by the admixture of blood that has been diverted away from the metabolizing tissues, and it may be presumed that even in these patients the delivery of oxygen to the latter is reduced despite the normal or even elevated mixed venous oxygen saturation. When HF occurs in such patients, the arterial-mixed venous oxygen difference, regardless of the absolute value, still exceeds the level that existed prior to the development of HF.

Therefore, the cardiac output, though normal or even elevated, is lower than before HF supervened.

In most forms of high-outputHF, the heart is called on to pump abnormally large quantities of blood in order to deliver the oxygen required by the metabolizing tissues. The hemodynamic burden placed on the myocardium by the increased flow load resembles that produced by chronic aortic regurgitation. In addition, thyrotoxicosis and beriberi may also impair myocardial metabolism directly, while very severe anemia may interfere with myocardial function by producing myocardial anoxia, especially in the subendocardium and in the presence of underlying obstructive coronary artery disease.

ACUTE VERSUS CHRONIC HEART FAILURE

The prototype of *acute HF* is the sudden development of a large myocardial infarction or rupture of a cardiac valve in a patient who previously was entirely well. *Chronic HF* is typically observed in patients with dilated cardiomyopathy or multivalvular heart disease that develops or progresses slowly. AcuteHF is usually predominantly systolic, and the sudden reduction in cardiac output often results in systemic hypotension without peripheral edema. In contrast, in chronic HF, arterial pressure is ordinarily well maintained until very late in the course, but there is often accumulation of edema.

RIGHT-SIDED VERSUS LEFT-SIDED HEART FAILURE

Many of the clinical manifestations of HFresult from the accumulation of excess fluid behind either one or both ventricles (Chaps. 32 and37). This fluid usually localizes upstream to (behind) the ventricle that is initially affected. For example, patients in whom the left ventricle is hemodynamically overloaded (e.g., aortic stenosis) or weakened (e.g., postmyocardial infarction) develop dyspnea and orthopnea as a result of pulmonary congestion, a condition referred to as *left-sided HF*. In contrast, when the underlying abnormality affects the right ventricle primarily (e.g., congenital valvular pulmonic stenosis or pulmonary hypertension secondary to pulmonary thromboembolism), symptoms resulting from pulmonary congestion are uncommon, and edema, congestive hepatomegaly, and systemic venous distention, i.e., clinical manifestations of *right-sided HF*, are more prominent. When HF has existed for months or years, such localization of excess fluid behind the failing ventricle may no longer exist. For example, patients with long-standing aortic valve disease or systemic hypertension may develop ankle edema, congestive hepatomegaly, and systemic venous distention late in the course of their disease, even though the abnormal hemodynamic burden initially was placed on the left ventricle. This occurs in part because of the secondary pulmonary hypertension and resultant right-sided HF but also because of the retention of salt and water characteristic of HF (Chap. 37). The muscle bundles composing both ventricles are continuous, and both ventricles share a common wall, the interventricular septum. Also, biochemical changes that occur in HF and that may be involved in the impairment of myocardial function (Chap. 231), such as norepinephrine depletion and alterations in the activity of myosin ATPase, occur in the myocardium of *both* ventricles, regardless of the specific chamber on which the abnormal hemodynamic burden is placed initially.

BACKWARD VERSUS FORWARD HEART FAILURE

For many years a controversy has revolved around the question of the mechanism of the clinical manifestations resulting fromHF. The concept of *backward HF* contends that in HF, one or the other ventricle fails to discharge its contents or fails to fill normally. As a consequence, the pressures in the atrium and venous system behind the failing ventricle rise, and retention of sodium and water occurs as a consequence of the elevation of systemic venous and capillary pressures and the resultant transudation of fluid into the interstitial space (Chap. 37). In contrast, the proponents of the *forward HF* hypothesis maintain that the clinical manifestations of HF result directly from an inadequate discharge of blood into the arterial system. According to this concept, salt and water retention is a consequence of diminished renal perfusion and excessive proximal tubular sodium reabsorption and of excessive distal tubular reabsorption through activation of the renin-angiotensin-aldosterone (RAA) system.

A rigid distinction between *backward* and *forward*HF (like a rigid distinction between right and left HF) is artificial, since both mechanisms appear to operate to varying extents in most patients with HF. However, the rate of onset of HF often influences the clinical manifestations. For example, when a large portion of the left ventricle is suddenly destroyed, as in myocardial infarction, although stroke volume and blood pressure are suddenly reduced (both manifestations of forward failure), the patient may succumb to acute pulmonary edema, a manifestation of backward failure. If the patient survives the acute insult, clinical manifestations resulting from a chronically depressed cardiac output, including the abnormal retention of fluid within the systemic vascular bed, may develop. Similarly, in the case of massive pulmonary embolism, the right ventricle may dilate and the systemic venous pressure may rise to high levels (backward failure), or the patient may develop shock secondary to low cardiac output (forward failure), but this low-output state may have to be maintained for some days before sodium and water retention sufficient to produce peripheral edema occurs.

REDISTRIBUTION OF CARDIAC OUTPUT

InHF, systemic blood flow is redistributed so that the delivery of oxygen to vital organs, such as the brain and myocardium, is maintained at normal or near-normal levels, while flow to less critical areas, such as the cutaneous and muscular beds and the viscera, is reduced. This redistribution serves as an important compensatory mechanism when cardiac output is reduced. It is most marked when a patient with HF exercises, but as HF advances, redistribution occurs even in the basal state. Vasoconstriction mediated by the adrenergic nervous system is largely responsible for redistribution, which in turn may be responsible for many of the clinical manifestations of HF, such as fluid accumulation (reduction of renal blood flow), low-grade fever (reduction of cutaneous flow), and fatigue (reduction of muscle flow).

SALT AND WATER RETENTION (See also Chap. 37)

When the volume of blood pumped by the left ventricle into the systemic vascular bed is reduced, a complex sequence of adjustments occurs that ultimately results in the abnormal accumulation of fluid. On the one hand, many of the troubling clinical manifestations ofHF are secondary to this excessive retention of fluid; on the other, this abnormal fluid accumulation and the expansion of blood volume that accompanies it

also constitute an important compensatory mechanism that tends to maintain cardiac output and therefore perfusion of the vital organs. Except in the terminal stages of HF, the ventricle operates on an ascending, albeit depressed and flattened, function curve (Fig. 231-6, p. 1313), and the augmented ventricular end-diastolic volume and pressure characteristic of HF must be regarded as helping to maintain the reduced cardiac output, despite causing pulmonary and/or systemic venous congestion.

CongestiveHF is also characterized by a complex series of neurohumoral adjustments. The activation of the adrenergic nervous system is discussed on p. 1315; there is also activation of theRAAsystem and increased release of antidiuretic hormone and endothelin. These influences elevate systemic vascular resistance and enhance sodium and water retention and potassium excretion. These actions are, to a minor extent, opposed by the release of atrial and brain natriuretic peptide, which also occurs in congestive HF. Patients with severe HF may exhibit a reduced capacity to excrete a water load, which may result in dilutional hyponatremia. In the presence of HF, effective filling of the systemic arterial bed is reduced, a condition that initiates the renal and hormonal changes mentioned above (Fig. 37-2).

The elevation of systemic venous pressure and the alterations of renal and adrenal function characteristic ofHF vary in their relative importance in the production of edema in different patients. The RAAaxis is activated most intensely by acute HF, and its activity tends to decline as HF becomes chronic. In patients with tricuspid valve disease or constrictive pericarditis, the elevated venous pressure and the transudation of fluid from systemic capillaries appear to play the dominant role in edema formation. On the other hand, severe edema may be present in patients with ischemic or hypertensive heart disease, in whom systemic venous pressure is within normal limits or is only minimally elevated. In such patients, the retention of salt and water is probably due primarily to a redistribution of cardiac output and a concomitant reduction in renal perfusion, as well as activation of the RAA axis. Regardless of the mechanisms involved in fluid retention, untreated patients with chronic congestive HF have elevations of total blood volume, interstitial fluid volume, and body sodium. These abnormalities diminish after clinical compensation has been achieved by effective treatment, especially with diuretics.

CLINICAL MANIFESTATIONS OF HEART FAILURE

DYSPNEA

Respiratory distress that occurs as the result of increased effort in breathing is the most common symptom ofHF(Chap. 32). In early HF, dyspnea is observed only during activity, when it may simply represent an aggravation of the breathlessness that occurs normally under these circumstances. As HF advances, however, dyspnea appears with progressively less strenuous activity and ultimately is present even when the patient is at rest. The principal difference between exertional dyspnea in normal persons and in patients with HF is the degree of activity necessary to induce this symptom. Cardiac dyspnea is observed most frequently in patients with elevations of pulmonary venous and capillary pressures. Such patients usually have engorged pulmonary vessels and interstitial pulmonary edema, which may be evident on radiologic examination. This interstitial pulmonary edema reduces the compliance of the lungs and thereby increases

the work of the respiratory muscles required to inflate the lungs. The activation of receptors in the lungs results in the rapid, shallow breathing characteristic of cardiac dyspnea. The oxygen cost of breathing is increased by the excessive work of the respiratory muscles. This is coupled with the diminished delivery of oxygen to these muscles, which occurs as a consequence of the reduced cardiac output and which may contribute to fatigue of the respiratory muscles and the sensation of shortness of breath.

Orthopnea Dyspnea in the recumbent position is usually a later manifestation ofHF than exertional dyspnea. Orthopnea occurs because of the redistribution of fluid from the abdomen and lower extremities into the chest during recumbency causing an increase in the pulmonary capillary hydrostatic pressure, as well as elevation of the diaphragm accompanying supine posture. Patients with orthopnea must elevate their heads on several pillows at night and frequently awaken short of breath or coughing (the so-called nocturnal cough) if their heads slip off the pillows. The sensation of breathlessness is usually relieved by sitting upright, since this position reduces venous return and pulmonary capillary pressure, and many patients report that they find relief from sitting in front of an open window. In advanced HF, orthopnea may become so severe that patients cannot lie down at all and must spend the entire night in a sitting position. On the other hand, in other patients with long-standing, severe left ventricular failure, symptoms of pulmonary congestion may actually diminish with time as the function of the right ventricle becomes impaired.

Paroxysmal (Nocturnal) Dyspnea This term refers to attacks of severe shortness of breath and coughing that generally occur at night, usually awaken the patient from sleep, and may be quite frightening. Though simple orthopnea may be relieved by sitting upright at the side of the bed with legs dependent, in the patient with paroxysmal nocturnal dyspnea, coughing and wheezing often persist even in this position. Paradoxical nocturnal dyspnea may be caused in part by the depression of the respiratory center during sleep, which may reduce ventilation sufficiently to lower arterial oxygen tension, particularly in patients with interstitial lung edema and reduced pulmonary compliance. Also, ventricular function may be further impaired at night because of reduced adrenergic stimulation of myocardial function. *Cardiac asthma* is closely related to paroxysmal nocturnal dyspnea and nocturnal cough and is characterized by wheezing secondary to bronchospasm -- most prominent at night. *Acute pulmonary edema* (Chap. 32) is a severe form of cardiac asthma due to marked elevation of pulmonary capillary pressure leading to alveolar edema, associated with extreme shortness of breath, rales over the lung fields, and the transudation and expectoration of blood-tinged fluid. If not treated promptly, acute pulmonary edema may be fatal.

CHEYNE-STOKES RESPIRATION

Also known as *periodic respiration* or *cyclic respiration*, Cheyne-Stokes respiration is characterized by diminished sensitivity of the respiratory center to arterial P_{CO_2}. There is an apneic phase, during which the arterial P_{O_2}falls and the arterial P_{CO_2}rises. These changes in the arterial blood stimulate the depressed respiratory center, resulting in hyperventilation and hypocapnia, followed in turn by recurrence of apnea. Cheyne-Stokes respiration occurs most often in patients with cerebral atherosclerosis and other cerebral lesions, but the prolongation of the circulation time from the lung to

the brain that occurs inHF, particularly in patients with hypertension and coronary artery disease and associated cerebral vascular disease, also appears to precipitate this form of breathing.

FATIGUE AND WEAKNESS

These nonspecific but common symptoms ofHF are related to the reduction of perfusion of skeletal muscle. Exercise capacity is reduced by the limited ability of the failing heart to increase its output and deliver oxygen to the exercising muscle.

ABDOMINAL SYMPTOMS

Anorexia and nausea associated with abdominal pain and fullness are frequent complaints and may be related to the congested liver and portal venous system.

CEREBRAL SYMPTOMS

In severeHF, particularly in elderly patients with accompanying cerebral arteriosclerosis, reduced cerebral perfusion, and arterial hypoxemia, there may be alterations in the mental state characterized by confusion, difficulty in concentration, impairment of memory, headache, insomnia, and anxiety. *Nocturia* is common in HF and may contribute to insomnia.

PHYSICAL FINDINGS (SeeChap. 225)

In moderateHF, the patient is in no distress at rest except that he or she may be uncomfortable when lying flat for more than a few minutes. In more severe HF, the pulse pressure may be diminished, reflecting a reduction in stroke volume, and the diastolic arterial pressure may be elevated as a consequence of generalized vasoconstriction. In acute HF, severe hypotension may be present. There may be cyanosis of the lips and nail beds (Chap. 36) and sinus tachycardia, and the patient may insist on sitting upright. *Systemic venous pressure* is often abnormally elevated in HF, and this may be reflected in distention of the jugular veins. In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated during and immediately after exertion as well as with sustained pressure on the abdomen (positive abdominojugular reflux).

Third and fourth heart sounds are often audible but are not specific forHF, and *pulsus alternans*, i.e., a regular rhythm in which there is alternation of strong and weak cardiac contractions and therefore alternation in the strength of the peripheral pulses, may be present. Pulsus alternans, a sign of severe HF, may be detected by sphygmomanometry and in more severe instances by palpation; it frequently follows an extrasystole and is observed most commonly in patients with cardiomyopathy or hypertensive or ischemic heart disease.

Pulmonary Rales Moist, inspiratory, crepitant rales and dullness to percussion over the lung bases are common in patients withHF and elevated pulmonary venous and capillary pressures. In patients with pulmonary edema, rales may be heard widely over both lung fields; they are frequently coarse and sibilant and may be accompanied by

expiratory wheezing. Rales may, however, be caused by many conditions other than left ventricular failure. Some patients with long-standing HF have no rales because of increased lymphatic drainage of alveolar fluid.

Cardiac Edema (See Chap. 37) This is usually symmetric and dependent, occurring in the legs, particularly in the pretibial region and ankles in ambulatory patients, in whom it is most prominent in the evening. Cardiac edema occurs in the sacral region of patients who are bed-ridden. Pitting edema of the arms and face occurs rarely and then only late in the course of HF.

Hydrothorax and Ascites Pleural effusion in congestiveHFresults from the elevation of pleural capillary pressure and transudation of fluid into the pleural cavities. Since the pleural veins drain into *both* the systemic and pulmonary veins, hydrothorax occurs most commonly with marked elevation of pressure in both venous systems but also may be seen with marked elevation of pressure in either venous bed. It is more frequent in the right pleural cavity than in the left. *Ascites* also occurs as a consequence of transudation and results from increased pressure in the hepatic veins and the veins draining the peritoneum (Chap. 46). Marked ascites occurs most frequently in patients with tricuspid valve disease and constrictive pericarditis.

Congestive Hepatomegaly An enlarged, tender, pulsating liver also accompanies systemic venous hypertension and is observed not only in the same conditions in which ascites occurs but also in milder forms ofHF from any cause. With prolonged, severe hepatomegaly, as in patients with tricuspid valve disease or chronic constrictive pericarditis, enlargement of the spleen, i.e., congestive splenomegaly, may also occur.

Jaundice This is a late finding in HFand is associated with elevations of both the direct- and indirect-reacting bilirubin; it results from impairment of hepatic function secondary to hepatic congestion and the hepatocellular hypoxia associated with central lobular atrophy. Hepatic enzymes are frequently elevated. If hepatic congestion occurs acutely, the jaundice may be severe and the enzymes strikingly elevated.

Cardiac Cachexia With severe chronicHF there may be serious weight loss and cachexia because of (1) elevation of circulating concentrations of tumor necrosis factor; (2) elevation of the metabolic rate, which results in part from the extra work performed by the respiratory muscles, the increased oxygen needs of the hypertrophied heart, and/or the discomfort associated with severe HF; (3) anorexia, nausea, and vomiting due to central causes, to digitalis intoxication, or to congestive hepatomegaly and abdominal fullness; (4) impairment of intestinal absorption due to congestion of the intestinal veins; and (5) rarely, due to protein-losing enteropathy in patients with particularly severe failure of the right side of the heart.

Other Manifestations With reduction of blood flow, the extremities may be cold, pale, and diaphoretic. Urine flow is depressed, and the urine contains albumin and has a high specific gravity and a low concentration of sodium. In addition, prerenal azotemia may be present. In patients with long-standing severeHF, impotence and depression are common.

ROENTGENOGRAPHIC AND ECHOCARDIOGRAPHIC FINDINGS

In addition to the enlargement of the particular chambers characteristic of the lesion responsible forHF, distention of pulmonary veins and redistribution to the apices is common in patients with HF and elevated pulmonary vascular pressures. Also, pleural effusions may be evident and associated with interlobar effusions.

DIFFERENTIAL DIAGNOSIS (FIG. 232-CD1)

The diagnosis of congestiveHF may be established by observing some combination of the clinical manifestations of HF described above, together with the findings characteristic of one of the etiologic forms of heart disease.Table 232-1 shows the Framingham criteria, which are useful in the diagnosis of HF. Since chronic HF is often associated with cardiac enlargement, the diagnosis should be questioned, but is by no means excluded, when all chambers are normal in size. Two-dimensional echocardiography (Chap. 227) is particularly useful in assessing the dimensions of each cardiac chamber. HF is sometimes difficult to distinguish from pulmonary disease, and the differential diagnosis is discussed inChap. 32. Pulmonary embolism also presents many of the manifestations of HF, but hemoptysis, pleuritic chest pain, a right ventricular lift, and the characteristic mismatch between ventilation and perfusion on lung scan should point to this diagnosis (Chap. 261).

Ankle edema may be due to varicose veins, cyclic edema, or gravitational effects (Chap. 37), but in these patients there is no jugular venous hypertension at rest or with pressure over the abdomen. Edema secondary to renal disease can usually be recognized by appropriate renal function tests and urinalysis and is rarely associated with elevation of venous pressure. Enlargement of the liver and ascites occur in patients with hepatic cirrhosis and also may be distinguished fromHF by normal jugular venous pressure and absence of a positive abdominojugular reflux.

TREATMENT

(SeePractice Guidelines) The treatment ofHF may be divided into four components: (1) removal of the precipitating cause, (2) correction of the underlying cause, (3) prevention of deterioration of cardiac function, and (4) control of the congestive HF state. The first two components are discussed in other chapters together with each specific disease entity or complication. Examples of removal of precipitating causes are the treatment of pneumococcal pneumonia or the restoration of sinus rhythm in a patient with atrial fibrillation. In many instances, surgical treatment will correct or at least alleviate the underlying cause of HF. The third component of the treatment of HF, i.e., the prevention of deterioration of cardiac function, involves the administration of angiotensin-converting enzyme (ACE) inhibitors andb-adrenergic blockers as well as reduction of cardiac work load. Control of the congestive heart failure state requires reduction of the excessive retention of salt and water as well as enhancement of myocardial contractility. The vigor with which each of these measures is pursued in any individual patient should depend on the severity of HF and the tempo of the disease. Following effective treatment, recurrence of the clinical manifestations of HF can often be prevented by continuing those measures that were originally effective.

While a simple rule for the treatment of all patients withHFcannot be formulated

because of its varied etiologies, hemodynamic features, clinical manifestations, and severity of HF, insofar as the treatment of chronic congestive failure is concerned, the administration of anACEinhibitor retards the development of HF and should be begun early in patients with left ventricular systolic dysfunction (ejection fraction< 0.40), even if they are asymptomatic. Then, as symptoms develop, simple measures such as moderate restriction of activity and sodium intake and oral diuretics should be tried.b-adrenergic receptor blockers and digitalis glycosides are given for patients with systolic HF. If these measures are insufficient, the next step is more rigorous restriction of salt intake and higher doses and multiple diuretics. If HF persists, hospitalization with rigid salt restriction, bed rest, intravenous vasodilators, and positive inotropic agents are tried. Assisted circulation and cardiac transplantation (Chap. 233) are considered for patients with severe, intractable HF and a poor prognosis.

Prevention of Deterioration of Myocardial Infarction Chronic activation of theRAA axis and of the sympathetic nervous systems inHFresult in a maladaptive response and cause further deterioration of cardiac function and/or potentially fatal arrhythmias (Chap. 231). Drugs that block these two systems have been found to be useful in the management of HF (Tables 232-2 and232-3).

Angiotensin-Converting Enzyme Inhibitors In many patients withHF, the left ventricular afterload is increased as a consequence of the several neural and humoral influences that act to constrict the peripheral vascular bed. In addition to the vasoconstriction, the ventricular end-diastolic and -systolic volumes rise in systolic HF. As a consequence of the operation of Laplace's law, which relates myocardial wall tension to the product of intraventricular pressure and radius (both of which may become elevated in HF), the aortic impedance, i.e., the force that opposes left ventricular ejection, or the ventricular afterload, rises, which reduces stroke volume (Fig. 231-10, p. 1316). In many patients with systolic HF, a modest reduction of systemic vascular resistance and afterload elevates the stroke volume and reduces the elevated ventricular filling pressure of the failing ventricle.

The pharmacologic reduction of impedance to left ventricular ejection with anACEinhibitor represents an important component of the management ofHF. This approach may be particularly helpful in (but is by no means limited to) patients with systolic HF due to myocardial infarction (Chap. 243), and in patients with valvular regurgitation (Chap. 236). ACE inhibition should not be used in hypotensive patients. In patients with both acute and chronic systolic HF who are treated with ACE inhibitors, cardiac output rises, the pulmonary wedge pressure falls, the signs and symptoms of HF are relieved, and a new steady state is achieved in which cardiac output is higher and afterload lower with no or only mild reduction of arterial pressure. The administration of ACE inhibitors has been shown to prevent or retard the development of HF in patients with left ventricular dysfunction without HF, to reduce symptoms, enhance exercise performance, and to reduce long-term mortality when they are begun in such patients shortly after acute myocardial infarction. These beneficial effects are related only in part to the salutary hemodynamic effects, i.e., the reduction of preload and afterload. Their major effect appears to be on inhibition of local (tissue) renin-angiotensin systems.

Lisinopril in doses of 20 mg qd or enalapril 10 mg bid have been shown to be useful in

the management of heart failure.

Angiotensin Receptor Blockers In patients who cannot tolerateACEinhibitors (because of cough, angioneurotic edema, leukopenia), an angiotensin II receptor blocker (type AT1) antagonist (e.g., losartan 50 mg qid) may be used instead.

Aldosterone Antagonist The activation of theRAA axis in HFincreases not only circulating and tissue angiotensin II but also aldosterone. The latter, in addition to causing sodium retention and worsening edema (Chaps. 331 and37), causes sympathetic activation, myocardial, vascular, and perivascular fibrosis and reduces arterial compliance. In one large multicenter trial in patients with advanced heart failure and reduced ejection fraction (RALES), spironolactone, 25 mg/d reduced total mortality, as well as sudden death and death from pump failure (Table 232-3). Since spironolactone is also a useful diuretic (see below), its widespread use in systolic heart failure should be considered.

b-Adrenoceptor Blockers While the abrupt administration of large doses ofb-adrenergic receptor blockers can intensifyHF, the administration of gradually escalating doses of metoprolol, carvedilol, and bisoprolol have been reported to improve the symptoms of HF, and to reduce all-cause death, cardiovascular death, sudden death, and pump failure death (Table 232-3). In patients with moderately severe HF (classes II and III), the administration of 12.5 mg metoprolol CR/XL qd, increasing over 4 weeks to a target dose of 200 mg qid, has been shown to be beneficial. b-Adrenoceptor blockers are not indicated in HF patients who are unstable, in New York Heart Association Class IV, in HF patients shortly after acute myocardial infarction, or in those with HF and normal ejection fraction, i.e., with diastolic HF.

Reduction of Cardiac Work Load This consists of reducing physical activity, instituting emotional rest, and reducing afterload (see above). Modest restriction of physical activity in mild cases and rest in bed or in a chair in severe failure are useful. In acute, severe failure, meals should be small in quantity, but more frequent, and every effort should be made to diminish the patient's anxiety; sometimes drugs such as diazepam (2 to 5 mg tid) for several days are useful. Physical and emotional rest tends to lower arterial pressure and reduce the load on the myocardium by diminishing the requirements for cardiac output.

Reduced physical exertion should be continued for several days after the patient's condition has stabilized. The hazards of phlebothrombosis and pulmonary embolism which occur with bed rest may be reduced with anticoagulants, leg exercises, and elastic stockings. *Absolute* bed rest is rarely required or advisable, and the patient should ordinarily be encouraged to sit in a chair. Heavy sedation should be avoided. In ambulatory patients with chronic, moderately severeHF, additional periods of rest on weekends frequently allow continuation of gainful employment. Following recovery from HF, the patient's activities should be assessed, and often, professional, community, and/or family responsibilities should be curtailed. Intermittent rest during the day (e.g., a scheduled 1-h nap or rest following lunch) and the avoidance of strenuous exertion are often helpful. Regular, nonexhausting exercise such as walking or riding a stationary-bicycle ergometer as tolerated should be employed once the patient has become compensated. Weight reduction by restriction of caloric intake in obese patients

with HF also diminishes cardiac work load and is an essential component of the therapeutic program.

Control of Excessive Fluid Many of the clinical manifestations ofHFresult from expansion of the extracellular fluid volume. A negative sodium balance can be achieved by reducing the dietary intake and increasing the urinary excretion of this ion with the aid of diuretics. Rarely, in severe HF, mechanical removal of extracellular fluid by means of thoracentesis and paracentesis may be necessary.

Diet In patients with mild HF, symptomatic improvement may result simply from reducing the sodium intake, particularly if accompanied by periods of physical rest. The normal diet contains approximately 6 to 10 g sodium chloride; this intake can be reduced by half simply by excluding salt-rich foods and salt added at the table. Reduction of the ordinary dietary intake to approximately one-fourth of normal may be achieved if, in addition, all salt is omitted from cooking. In patients with severe HF who have fluid accumulation despite diuretic therapy (see below), the dietary intake of sodium chloride should be reduced to between 500 and 1000 mg, and in order to achieve this, milk, cheese, bread, cereals, canned vegetables and soups, some salted cuts of meat, and some fresh vegetables (including spinach, celery, and beets) must be eliminated. A variety of fresh fruit, green vegetables, specially processed breads and milk, and salt substitutes are permissible. Late in the course of HF, dilutional hyponatremia may develop in patients who are unable to excrete a water load, sometimes because of excessive secretion of antidiuretic hormone. In such cases, water intake as well as sodium intake must be restricted.

Calories should be restricted in obese patients withHF. In patients with severe HF and cardiac cachexia, on the other hand, an attempt must be made to maintain nutritional intake and to avoid caloric and vitamin deficiencies; nutritional supplements may be in order.

Diuretics Diuretics should be given to relieve fluid accumulation and thus reduce or prevent edema and jugular venous distention. A variety of diuretic agents are available (Table 246-6, p. 1422), and almost all are effective in patients with mildHF. However, in the more severe forms of HF, the selection of diuretics is more difficult, and abnormalities in serum electrolytes must be taken into account. Overtreatment must be avoided, since the resultant hypovolemia may reduce cardiac output, interfere with renal function, and produce profound weakness and lethargy.

THIAZIDE DIURETICS These agents are used widely and are useful by themselves in patients with mildHF and in combination with other diuretics in those with severe HF. In patients with chronic mild or moderate HF, the continued administration of a thiazide diuretic abolishes or diminishes the need for rigid dietary sodium restriction, although salty foods and table salt still should be avoided. Thiazide diuretics reduce the reabsorption of sodium and chloride in the first half of the distal convoluted tubule and a portion of the cortical ascending limb of the loop of Henle, and water follows the unreabsorbed salt. Thiazides fail to increase free water clearance and in some instances reduce it. This may result in the excretion of a hypertonic urine and may contribute to dilutional hyponatremia. As a consequence of increased delivery of sodium to the distal nephron, sodium-potassium ion exchange is enhanced, and kaliuresis

results. In contrast to the loop diuretics, which enhance calcium excretion, the thiazides have the opposite effect.

Thiazide diuretics are effective and useful in the treatment ofHF as long as the glomerular filtration rate exceeds approximately 50% of normal. Chlorothiazide is administered in doses of up to 500 mg every 6 h. Many derivatives of this compound are available but differ principally in dosage and duration of action. Chlorthalidone (25 to 50 mg/d) is especially useful since it may be administered once daily.

Potassium depletion and metabolic alkalosis (the latter due to increased H^+secretion as a substitute for the depleted intracellular stores of potassium) are the chief adverse metabolic effects following prolonged administration of the thiazides, of metolazone, and of the loop diuretics. Hypokalemia may seriously enhance the dangers of digitalis intoxication (see below), and induce fatigue and lethargy; these may be prevented by oral supplementation with potassium chloride or preferably by the addition of a potassium-retaining diuretic, such as a spironolactone or triamterene. Other side effects of thiazides include reduction of the excretion of uric acid, which may lead to hyperuricemia, and impaired glucose tolerance, which rarely may precipitate hyperosmolar coma in poorly regulated diabetic patients. Skin rashes, thrombocytopenia, and granulocytopenia have also been reported.

METOLAZONE This quinethazone derivative has a site of action and potency similar to those of the thiazides but has been reported to be effective in the presence of moderate renal failure. The usual dose is 5 to 10 mg/d. Metolazone may be added to thiazide and loop diuretics in severeHF.

FUROSEMIDE, BUMETANIDE, ETHACRYNIC ACID, PIRETANIDE, AND TORSEMIDE These "loop" diuretics are similar physiologically but differ chemically from one another. These drugs reversibly inhibit the reabsorption of sodium, potassium, and chloride in the thick ascending limb of Henle's loop, apparently by blocking a cotransport system in the luminal membrane. They may induce renal cortical vasodilatation and can produce rates of urine formation that may be as high as one-fourth of the glomerular filtration rate. Metabolic alkalosis may be caused by a large increase in the urinary excretion of chloride, hydrogen, and potassium ions. Hypokalemia, hyperuricemia, and hyperglycemia are observed occasionally, as with thiazide diuretics. The reabsorption of free water is decreased. All five of these drugs are readily absorbed orally, are excreted in the bile and urine, and are usually effective both intravenously and by mouth. Weakness, nausea, and dizziness may complicate the administration of all loop diuretics; ethacrynic acid has been associated with transient or even permanent deafness as well as with skin rash and granulocytopenia.

These powerful diuretics are useful in all forms ofHF, particularly in patients with otherwise refractory HF and pulmonary edema. They have been shown to be effective in patients with hypoalbuminemia, hyponatremia, hypochloremia, hypokalemia, and with reductions in the glomerular filtration rate and to produce a diuresis in patients in whom thiazide diuretics and aldosterone antagonists, alone and in combination, are ineffective. In patients with refractory HF, the action of loop diuretics may be potentiated by intravenous administration and by the addition of other diuretics, i.e., thiazides, metozalone, osmotic diuretics, and the potassium-sparing diuretics -- spironolactone,

triamterene, and amiloride.

ALDOSTERONE ANTAGONISTS These agents act on the cortical collecting ducts, are relatively weak, and therefore are rarely indicated as sole agents. However, their potassium-sparing properties make them particularly useful in conjunction with the more potent kaliuretic agents, i.e., the loop diuretics, thiazides, and metozalone. The potassium-sparing agents fall into two classes.

The spironolactones resemble aldosterone structurally and act by competitive inhibition of aldosterone, thereby blocking the exchange between sodium and both potassium and hydrogen in the distal tubules and collecting ducts. These agents produce a sodium diuresis, and in contrast to the thiazides, ethacrynic acid, and furosemide, they result in potassium retention. Although secondary hyperaldosteronism exists in some patients with congestiveHF, the spironolactones are effective even in patients in whom the serum aldosterone concentration is within normal limits.

Spironolactone may be administered in doses of 25 mg daily to 50 mg three to four times daily by mouth. The maximal effect of this regimen is not observed for approximately 4 days. Spironolactones are most effective when administered in combination with loop and/or thiazide diuretics. The opposing action of these drugs on urine and serum potassium makes possible a sodium diuresis without either hyper- or hypokalemia when spironolactone and one of these other agents are administered in combination. Also, since spironolactone, triamterene, and amiloride act on the distal tubule, they are particularly effective when used in combination with one of these other diuretics that act more proximally. Spironolactone, triamterene, and amiloride should not be administered alone to patients with hyperkalemia, renal failure, or hyponatremia. Reported complications of Aldactone A include nausea, epigastric distress, mental confusion, drowsiness, gynecomastia, and erythematous eruptions.

As mentioned above, a lower dose of spironolactone (25 mg/d), which exerts little if any diuretic effect, has been shown to prolong life in patients with advancedHF(Table 232-3).

Triamterene and *amiloride* exert renal effects similar to those of the spironolactones; i.e., they block sodium reabsorption and secondarily inhibit potassium secretion in the distal tubules. However, their action does not depend on the presence of aldosterone. The effective dose of triamterene is 100 mg once or twice daily, and that of amiloride is 5 mg daily. Side effects include nausea, vomiting, diarrhea, headache, granulocytopenia, eosinophilia, and skin rash. Both triamterene and the chemically unrelated diuretic amiloride resemble Aldactone A in that their diuretic potency is not great, but they are effective in preventing the hypokalemia characteristic of loop diuretics and thiazides. A number of diuretic preparations contain a combination of a thiazide and either triamterene or amiloride in a single capsule. They may be useful in patients who develop hypokalemia with a thiazide but should not be used in patients with impaired renal function and/or hyperkalemia.

When *choosing a diuretic*, orally administered loop diuretics or thiazides are the agents of choice in the treatment of chronic cardiac edema of mild to moderate degree in patients without hyperglycemia, hyperuricemia, or hypokalemia. Spironolactones,

triamterene, and amiloride are not potent diuretics when used alone, but they potentiate the thiazide and loop diuretics. Loop diuretics, given alone or with spironolactone or triamterene, are the agents of choice in patients with severe HF refractory to other diuretics. In very severe HF, the combination of a loop diuretic, a thiazide, and a potassium-sparing diuretic is required.

Vasodilators Direct vasodilators may be useful in patients with severe, acuteHF who demonstrate systemic vasoconstriction despiteACEinhibitor therapy. The ideal vasodilator for the treatment of *acute* HF should have a rapid onset and brief duration of action when administered by intravenous infusion; sodium nitroprusside (0.1 to 3.0 ug/kg per minute) qualifies as such a drug, but its use requires careful monitoring of the arterial pressure and, if possible, of the pulmonary artery wedge pressure. The combination of hydralazine (up to 300 mg qd orally) and isosorbide diuretics (up to 160 mg qd orally) may be useful for chronic oral administration.

Enhancement of Myocardial Contractility

Digitalis The improvement of myocardial contractility by means of cardiac glycosides is useful in the control ofHF. *Digoxin*, which has a half-life of 1.6 days, is filtered in the glomeruli and secreted by the renal tubules. Significant reductions of the glomerular filtration rate reduce the elimination of digoxin and, therefore, may prolong digoxin's effect, allowing it to accumulate to toxic levels. In patients with normal renal function, a plateau concentration in the blood and tissue is reached after 5 days of daily maintenance treatment without a loading dose (seeFig. 70-2).

MECHANISM OF ACTION The most important effect of digitalis on cardiac muscle is to shift its force-velocity relation upward (Fig. 231-5, p. 1313). Cardiac glycosides inhibit the monovalent cation transport enzyme-coupled Na^+,K^+-ATPase and increase intracellular sodium content; this, in turn, increases intracellular Ca^{2+}through a Na^+-Ca^{2+}exchange carrier mechanism. The increased myocardial uptake of Ca^{2+}augments Ca^{2+}released to the myofilaments during excitation and, therefore, invokes a positive inotropic response.

Cardiac glycosides also produce alterations in the electrical properties of both the contractile cells and the specialized automatic cells, leading to increased automaticity and ectopic impulse activity. They also prolong the effective *refractory period* of the atrioventricular node and thereby slow ventricular rate in atrial flutter and fibrillation.

USE IN HEART FAILURE Digitalis is particularly effective in patients with systolicHFcomplicated by atrial flutter and fibrillation and a rapid ventricular rate, who benefit from both slowing of the ventricular rate and the positive inotropic effect. Although digitalis does not improve survival in patients with systolic HF and sinus rhythm, it reduces the need for hospitalization. By stimulating myocardial contractility moderately, digitalis improves ventricular emptying; i.e., it increases cardiac output, augments the ejection fraction, promotes diuresis, and reduces the elevated diastolic pressure and volume and the end-systolic volume of the failing ventricle. This action reduces symptoms resulting from pulmonary vascular congestion and elevated systemic venous pressure. Digitalis is of little or no value in patients with HF, sinus rhythm, and the following conditions: hypertrophic cardiomyopathy, myocarditis, mitral stenosis,

chronic constrictive pericarditis, and any form of diastolic HF.

The maintenance dose of digoxin is 0.25 mg qd for most adults; in the elderly and others with mild impairment of renal function, it is 0.125 mg qd. Loading doses, four times the maintenance dose, may be administered in acute systolic failure.

DIGITALIS INTOXICATION This is a serious and potentially fatal complication. Advanced age, acute myocardial infarction or ischemia, hypoxemia, magnesium depletion, renal insufficiency, hypercalcemia, electrical cardioversion, and hypothyroidism all may reduce tolerance to digitalis. The most common precipitating cause of digitalis intoxication, however, is depletion of potassium stores, which often occurs in patients withHF as a result of diuretic therapy and secondary hyperaldosteronism.

Anorexia, nausea, and vomiting are among the earliest signs of digitalis intoxication. The most frequent disturbances of cardiac rhythm are ventricular premature beats, bigeminy, ventricular tachycardia, and, rarely, ventricular fibrillation. Atrioventricular block of varying degrees of severity may occur. Nonparoxysmal atrial tachycardia with variable atrioventricular block is characteristic of digitalis intoxication. Chronic digitalis intoxication may be insidious in onset and characterized by exacerbations ofHF, weight loss, cachexia, neuralgias, gynecomastia, yellow vision, and delirium.

The administration of quinidine, verapamil, amiodarone, and propafenone to patients receiving digoxin raises the serum concentration of the latter by reducing both the renal and nonrenal elimination of digoxin and by reducing its volume of distribution. These drugs increase the propensity to digitalis intoxication, and the dose of digitalis should be reduced by half in patients receiving these drugs.

TREATMENT OF DIGITALIS INTOXICATION When tachyarrhythmias result from digitalis intoxication, withdrawal of the drug and treatment withb-adrenoceptor blocker or lidocaine are indicated. If hypokalemia is present, potassium should be administered cautiously and by the oral route. Fab fragments of purified, intact digitalis antibodies are a potentially lifesaving approach to the treatment of severe intoxication.

Sympathomimetic Amines (See also Chap. 72) Two sympathomimetic amines that act largely on b-adrenergic receptors -- dopamine and dobutamine -- improve myocardial contractility (Table 72-1) and are effective in the management ofHF; they must be administered by constant intravenous infusion for up to 1 week and are useful in patients with intractable, severe HF, particularly those with a reversible component, such as exists in patients who have undergone cardiac surgery, in patients with acute myocardial infarction and shock or pulmonary edema, and in patients with refractory HF as a "bridge" to transplantation. While these sympathomimetic amines improve the hemodynamics and symptoms in these conditions, it is not clear that they improve survival. Their administration should be accompanied by careful and continuous monitoring of the electrocardiogram, arterial pressure, and, if possible, pulmonary artery wedge pressure.

Dopamine is a naturally occurring immediate precursor of norepinephrine and has a combination of actions that makes it particularly useful in the treatment of a variety of

hypotensive states ofHF. At very low doses, i.e., 1 to 2 (ug/kg)/min, it dilates renal and mesenteric blood vessels through stimulation of specific dopaminergic receptors, thereby augmenting renal and mesenteric blood flow and sodium excretion. In the range of 2 to 10 (ug/kg)/min, dopamine stimulates myocardial$b_1$receptors but induces relatively little tachycardia, while at higher doses it also stimulates a-adrenergic receptors and elevates arterial pressure.

Dobutamine is a synthetic catecholamine that acts onb_1,b_2, anda receptors. It exerts a potent inotropic action, has only a modest cardioaccelerating effect, and lowers peripheral vascular resistance, but since it simultaneously raises cardiac output, it may not lower systemic arterial pressure in patients with severeHF. Dobutamine, given in continuous infusions of 2.5 to 10 (ug/kg)/min, is useful in the treatment of acute HF without hypotension.

A major problem with sympathomimetics is the loss of responsiveness, apparently due to "downregulation" of adrenergic receptors, which becomes evident within 8 h of continuous administration. This problem may be managed by intermittent therapy.

Phosphodiesterase Inhibitors These bipyridines, amrinone and milrinone, are noncatecholamine, nonglycoside agents that exert both positive inotropic and vasodilator actions by inhibiting a specific phosphodiesterase. They are suitable for intravenous use only; by simultaneously stimulating cardiac contractility and dilating the systemic vascular bed they reverse the major hemodynamic abnormalities associated with intractableHF. Amrinone and milrinone may be administered for the same conditions in which sympathomimetics are useful and may be employed together with dopamine or dobutamine.

Other Measures

Anticoagulants Patients with severeHF are at increased risk of pulmonary emboli secondary to venous thrombosis and of systemic emboli secondary to intracardiac thrombi and should be treated with warfarin. Patients with HF and atrial fibrillation, previous venous thrombosis, and pulmonary or systemic emboli are at especially high risk and should receive heparin followed by warfarin.

Diastolic Heart Failure The major goal in the treatment of this condition is to eliminate or reduce the causes of diastolic dysfunction, such as ventricular hypertrophy, fibrosis, or ischemia. The second is to reduce pulmonary and/or systemic venous congestion, a major consequence of diastolic dysfunction.

Management of Arrhythmias (See also Chap. 230) Premature ventricular contractions and episodes of asymptomatic ventricular tachycardia are common in advancedHF. Sudden death, presumably due to ventricular fibrillation, is responsible for about one-half of all deaths in this condition. (The remainder are due to failure of the cardiac pump.) The management of arrhythmias should commence with correction of electrolyte and acid-base disturbances (Chaps. 49 and50), especially diuretic-induced hypokalemia, as well as digitalis intoxication (see above). Treatment with class I antiarrhythmics such as quinidine, procainamide, or flecainide (Chap. 230) is fraught with danger because these drugs are proarrhythmic in patients with HF. Amiodarone, a

class III antiarrhythmic, on the other hand, is well tolerated and is the drug of choice for patients with heart failure and atrial fibrillation. Patients who have been resuscitated from sudden death, those with syncope or presyncope due to ventricular arrhythmias, and those with asymptomatic ventricular tachyarrhythmias in whom ventricular tachycardia can be induced during electrophysiologic testing should be considered for the implantable automatic defibrillator. This may prevent recurrence of the arrhythmia and sudden death; back-up pacing may prevent sudden death due to bradyarrhythmias.

Refractory Heart Failure When the response to ordinary treatment is inadequate,HF is considered to be refractory. Before assuming that this condition simply reflects advanced, terminal, myocardial depression, careful consideration must be given to several possibilities: (1) an underlying and overlooked cause of the heart disease that may be amenable to specific surgical or medical therapy, such as infective endocarditis, hypertension, thyrotoxicosis, or silent aortic or mitral stenosis; (2) one or a combination of the precipitating causes of HF, such as pulmonary or urinary tract infection, recurrent pulmonary emboli, arterial hypoxemia, anemia, or arrhythmia; and (3) complications of overly vigorous therapy, such as digitalis intoxication, hypovolemia, or electrolyte imbalance. Recognition and proper treatment of the aforementioned complications are likely to restore responsiveness to therapy.

Hyponatremia is a manifestation of advanced refractoryHF. It may be a complication of overaggressive diuresis leading to reduced glomerular filtration rate and decreased delivery of NaCl to the diluting sites in the distal tubule. Hyponatremia may also result from nonosmotic stimuli for the continued secretion of antidiuretic hormone. Therapy involves improvement of the cardiovascular status, if possible (sometimes requiring the administration of a sympathomimetic amine), as well as temporary cessation of diuretic therapy and restriction of oral water intake. Hypertonic saline is very rarely indicated because total-body sodium is usually elevated, not depressed, in HF.

The combination of the intravenously administered vasodilator sodium nitroprusside, a phosphodiesterase inhibitor (amrinone or milrinone), together with a sympathomimetic amine (dopamine or dobutamine) often results in additive effects, raising cardiac output and lowering filling pressure.

In hospitalized patients with refractoryHF, therapy guided by hemodynamic measurements provided by a balloon flotation (Swan-Ganz) catheter may be helpful. The goal of manipulating diuretics, vasodilators, and inotropic agents is to achieve a pulmonary capillary wedge pressure of 15 to 18 mmHg, a right atrial pressure of 5 to 8 mmHg, a cardiac index > 2.2 (L/min)/m^2, and a systemic vascular resistance of 800 to 1200 dyne×s/cm^5. Once these values are achieved, an attempt should be made to convert the patient from intravenous to oral vasodilator therapy.

Assisted Circulation/Cardiac Transplantation When patients withHFbecome unresponsive to a combination of all the aforementioned therapeutic measures, are in New York Heart Association class IV, and are deemed unlikely to survive 1 year, they should be considered for temporary assisted circulation and/or cardiac transplantation (seeChap. 233).

Treatment of Acute Pulmonary Edema Pulmonary edema secondary to left ventricular

failure or mitral stenosis is described in Chap. 32. It is life-threatening and must be considered a medical emergency. As is the case for the more chronic forms of HF, in the treatment of pulmonary edema, attention must be directed to identifying and removing any precipitating causes of decompensation, such as an arrhythmia or infection. However, because of the acute nature of the problem, a number of additional nonspecific measures are necessary. If it does not delay treatment unduly, recording pulmonary vascular pressures through a Swan-Ganz catheter and intraarterial pressure directly is advisable. The first six measures listed below are ordinarily applied simultaneously or nearly so.

1. Morphine is administered intravenously repetitively, as needed, in doses from 2 to 5 mg. This drug reduces anxiety, reduces adrenergic vasoconstrictor stimuli to the arteriolar and venous beds, and thereby helps to break a vicious cycle. Naloxone should be available in case respiratory depression occurs.

2. Because the alveolar edema interferes with O_2 diffusion resulting in arterial hypoxemia, 100% O_2 should be administered, preferably under positive pressure. The latter increases intraalveolar pressure, reduces transudation of fluid from the alveolar capillaries, and impedes venous return to the thorax, reducing pulmonary capillary pressure.

3. The patient should be maintained in the sitting position, with the legs dangling along the side of the bed, if possible, which tends to reduce venous return.

4. Intravenous loop diuretics, such as furosemide or ethacrynic acid (40 to 100 mg) or bumetanide (1 mg), will, by rapidly establishing a diuresis, reduce circulating blood volume and thereby hasten the relief of pulmonary edema. In addition, when given intravenously, furosemide also exerts a venodilator action, reduces venous return, and thereby improves pulmonary edema even before the diuresis commences.

5. Afterload reduction is achieved with intravenous sodium nitroprusside at 20 to 30 ug/min in patients whose systolic arterial pressures exceed 100 mmHg.

6. Inotropic support should be provided by dopamine or dobutamine as described on p. 1327. Patients with systolic HF who are not receiving digitalis should receive 0.75 to 1.0 mg digoxin intravenously over 15 min.

7. Sometimes, aminophylline (theophylline ethylenediamine), 240 to 480 mg intravenously, is effective in diminishing bronchoconstriction, increasing renal blood flow and sodium excretion, and augmenting myocardial contractility.

8. If the above-mentioned measures are not sufficient, rotating tourniquets should be applied to the extremities.

After these emergency measures have been instituted and the precipitating factors treated, the diagnosis of the underlying cardiac disorder responsible for the pulmonary edema must be established, if it is not already known. After stabilization of the patient's condition, a long-range strategy for prevention of future episodes of pulmonary edema must be established, and this may require surgical treatment.

PROGNOSIS

The prognosis in patients withHFdepends primarily on the nature of the underlying heart disease and on the presence or absence of a precipitating factor that can be treated. When one of the latter can be identified and removed, the outlook for immediate survival is far better than if HF occurs without any obvious precipitating cause. In the latter situation, survival usually ranges between 6 months and 4 years depending on the severity (Fig. 232-2). The long-term prognosis is more favorable when the underlying forms of heart disease, e.g., valvular heart disease, can be treated effectively. The prognosis can be estimated by observing the response to treatment. When clinical improvement occurs with only modest dietary sodium restriction and small doses of diuretics, the outlook is far better than if, in addition to these measures, intensive diuretic therapy and vasodilators are necessary. Other factors that have been shown to be associated with a poor prognosis include a severely depressed ejection fraction (<25%), a reduced maximal O_2uptake [<10 (mL/kg)/min], the inability to walk on the level and at a normal pace for more than 3 min, reduced (<133 mEq/L) serum sodium concentration, reduced (<3 mEq/L) serum potassium concentration, elevated circulating atrial and brain natriuretic peptide and norepinephrine concentrations, as well as frequent ventricular extrasystoles. A large fraction of patients with HF die suddenly, presumably of ventricular fibrillation. Unfortunately, there is no evidence that this complication can be prevented by the administration of antiarrhythmic agents. SeeGuideline.

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233. CARDIAC TRANSPLANTATION - *John S. Schroeder*

Orthotopic allograft cadaver cardiac transplantation as a treatment for end-stage cardiac disease achieved its thirty-third anniversary on December 7, 2000. On that day in 1967 Dr. Christiaan Barnard accomplished the first successful cardiac transplant in a human, quickly followed by Dr. Norman Shumway and Dr. Richard Lower at Stanford University. After an initial early wave of enthusiasm, the problems of immunosuppression slowed application of the procedure until the introduction of cyclosporine in 1980. A subsequent worldwide expansion of cardiac transplantation has resulted in approximately 2500 cardiac transplants per year, with further increases limited only by the donor supply. Current 1- and 5-year survival rates of 85 and 70% (Fig. 233-CD1) indicate that cardiac transplantation is the therapy of choice in patients with end-stage heart disease who are unlikely to survive the next 6 to 12 months.

INDICATIONS AND SELECTION OF CANDIDATES

The limited donor supply and relatively high cost of cardiac transplantation have restricted it to patients most likely to survive and resume a functional life after transplantation. It is estimated that only 2000 potential donors in the United States, for a pool of at least 20,000 candidates based on current guidelines, become available yearly. Attempts to increase donor awareness in both physicians and the public are being made. Optimal candidates for this procedure are those who would be expected to return to a functional life if their hearts were replaced (Table 233-1). This requires a mentally vigorous, medically compliant person who has not suffered extensive other end-stage organ damage from cardiac failure, does not have other systemic disease such as severe diabetes mellitus or collagen vascular disease, or is not positive for HIV. Long-standing pulmonary hypertension or recurrent pulmonary emboli and infarction may result in irreversible pulmonary hypertension leading to intraoperative death. Several heart transplant centers have initiated cardiac transplantation for newborns with left ventricular hypoplasia, but long-term survival experience is still very limited.

Timing of the recommendation to undergo cardiac transplantation can be difficult and requires assessment of the patient's current disability, stability of course, and likelihood of surviving the next 6 to 12 months. Generally, left ventricular ejection fractions under 15 to 20% and presence of serious ventricular arrhythmias indicate a 1-year survival rate of 50% or less. Estimating prognosis remains very challenging. A maximal oxygen uptake during exercise (maximal$_{O2}$) of<10 mL O_2 per kilogram per minute usually indicates poor likelihood of survival for 1 year and has been a criterion for transplant candidacy in some programs. Maximal$_{O2}$values between 10 and 14 mL O_2 per kilogram per minute are in a borderline range, with values>14 usually predicting good 1- to 2-year survival. The increasing acceptance of cardiac transplantation as a treatment modality for heart failure without a corresponding increase in donor availability has led to prolonged waiting times of as much as 2 years or more. This longer waiting time has led to more rigorous medical care of the patient awaiting transplant with meticulous monitoring of electrolytes, fluid status, and overall well-being. Aggressive therapy for congestive heart failure with high-dose angiotensin-converting enzyme inhibitors and beta blockers and meticulous monitoring of serum electrolytes and renal function have led to stabilization and many times some improvement in the functional status of patients awaiting a donor. This has led to as many as 30 to 40% of listed patients being

placed "on hold" based on their improved status. Whether these patients can maintain their improved state or will subsequently deteriorate remains to be seen. Recurrent hospitalizations may be required. Patients may become dopamine/dobutamine-dependent to maintain adequate cardiac output. This dependency on an inotropic agent plus the need for a balloon flotation catheter for hemodynamic monitoring moves the patient to the highest priority (1a) for a donor heart.

In addition to these pharmacologic bridges to transplantation, mechanical bridges are occasionally used where pharmacologic therapy is no longer effective. Three approaches are currently used. The first is intraaortic balloon pumping, which can increase cardiac output by 15 to 20%. The second is a left ventricular assist device (LVAD) (Fig. 233-CD2), which empties blood via a tube placed in the apex of the left ventricle and pumps it with an electrically driven "bellows-type" mechanism into the abdominal aorta. This approach is highly effective and has been used for several months with successful subsequent transplantation. Limitations include right ventricular failure and/or high pulmonary vascular resistance, since the LVAD does not "unload" the right ventricle. Blood clotting in the device remains a problem, in addition to the obvious problems of infection. Finally, total mechanical heart replacement is also applied in some transplant centers. This complete replacement circumvents the problem of right ventricular failure but is limited by the greater complexity of the device, which can lead to clotting and systemic emboli. Patients who underwent mechanical assistance *and* received a donor heart have 1-year survival statistics similar to those who went directly to transplantation.

Tissue cross-matching between donor and recipient has generally not been done because of difficulty in obtaining good matches and lack of correlation between match and outcome. Size, ABO matching, negative lymphocyte cross-match, and avoidance of a transplantation from a cytomegalovirus (CMV)-positive donor to a CMV-negative recipient are more important.

OPERATIVE PROCEDURE

The surgeon removes the diseased heart but leaves the posterior wall of the right atrium in place and the superior and inferior venae cavae intact. The posterior wall of the left atrium is also left in situ with pulmonary veins intact. The donor heart is then removed in toto with the posterior wall of the right and left atria incised, which allows suturing of left atrial donor rim to recipient rim and right atrial donor rim to recipient rim, with anastomosis of the aorta and pulmonary artery.

IMMUNOSUPPRESSION AND REJECTION

Controlling rejection while avoiding the adverse side effects of immunosuppressive agents is pivotal to successful transplantation. Rejection is characterized by perivascular infiltration of killer T lymphocytes, which migrate into the myocardium and cause cellular necrosis if not checked. Since early rejection can be silent, it is important to detect it before necrosis occurs. Immunologic monitoring of activated T lymphocytes in peripheral blood offers clues to the timing of a rejection process but has not been sufficiently reliable to dictate antirejection therapy. Therefore, repeated percutaneous transvenous right ventricular endomyocardial biopsies via the right internal jugular vein

are required for histologic determination of the state of immunosuppression and rejection.

One widely used scheme for grading the stages of rejection is as follows: cannot rule out rejection, mild early rejection, moderate rejection, and severe rejection. Serial biopsies are taken every 1 to 2 weeks early after transplantation, with gradually widening intervals depending on the patient's course and rejection history. Prolongation of isovolumic relaxation time measured by echocardiography may also provide early clues to rejection.

Immunosuppressive therapy regimens vary but usually include triple therapy with cyclosporine, azathioprine, and prednisone. The immunosuppressive agent tacrolimus, as either "rescue therapy" for graft rejection unresponsive to cyclosporine or as initial immunosuppressive therapy, is increasingly popular. Another immunosuppressive agent, mycophenolate mofetil, has been introduced initially as a substitute for azathioprine, and in one trial appeared to be superior in reducing transplant coronary atherosclerosis and mortality. Prophylactic courses of monoclonal antibody OKT3 or antithymocyte globulin may also be given early after transplantation. Careful monitoring of the adverse side effects of these agents is extremely important because they include nephrotoxicity, bone marrow suppression, and opportunistic infections. For discussion of immunosuppressive drugs, see Chap. 272.

EARLY COURSE AND COMPLICATIONS

It is rare for a cardiac transplant patient to have a completely uncomplicated postoperative course. In the immediate postoperative period, right-sided heart failure due to pulmonary vascular disease is most life-threatening. During the 2 to 3 weeks after transplantation, the patient is hospitalized with meticulous monitoring for evidence of rejection and infections, repeated percutaneous transvenous endomyocardial biopsies, and adjustment of immunosuppressive drugs. During the ensuing 4 to 6 weeks, infectious complications, including bacterial, viral, and protozoan infections, are common. A successful transplant program requires a highly aggressive and sophisticated approach to diagnosis and therapy of infections in the immunocompromised host.CMVinfection involving multiple organs is common and accelerates graft rejection as well. Prophylaxis with ganciclovir can dramatically reduce severe CMV infections and graft rejection, leading to less morbidity and improved survival. Depending on the degree of cardiac cachexia preoperatively, the patient is usually functional at 1 week and discharged from the hospital at 2 to 3 weeks if no major complication occurs.

The average first-year cost ranges from $100,000 to $150,000, depending on the need for repeated hospitalization and cardiac biopsies, and is occasionally much higher. Yearly costs for immunosuppressive agents range from $10,000 to $30,000, in addition to the expense of medical surveillance for rejection or complications.

PHYSIOLOGY AND FUNCTION

Since the allografted heart remains denervated, cardiac function differs from that of the innervated heart during both rest and exercise. The electrocardiogram of a recipient

shows two P waves; the P wave of the recipient's heart reflects the residual sinus node and posterior walls of the remaining native atria but is dissociated from the QRS, since the depolarization impulse does not cross the suture line. Although it does not control donor heart rate, the recipient's sinus node remains innervated and under the influence of the autonomic nervous system. The donor sinus node controls the rate of the transplanted heart. The donor heart's P wave has a regular PR interval, reflecting conduction to the ventricles. Since the controlling sinus node is denervated, it maintains a heart rate of 100 to 110 beats per minute, and rate increase depends on alterations in chronotropic agents perfusing the sinus node. Partial reinnervation may occur in some patients late after transplantation. This is manifested primarily by the occurrence of angina-like symptoms in patients who have developed accelerated graft atherosclerosis (see below).

Ventricular function in response to isometric and isotonic exercise has been studied extensively. The early response to exercise is more dependent on the Frank-Starling mechanism and change in ventricular volume and filling pressure. As exercise proceeds and catecholamines are released with their positive inotropic and chronotropic effects, cardiac output begins to rise. The cardiac transplant recipient can achieve approximately 70% of the maximal cardiac output expected for his or her age, easily sufficient for the stresses of everyday life.

LATE COURSE AND COMPLICATIONS

Although the rejection process partially subsides, lifelong administration of immunosuppressive drugs, albeit at lower doses, is still required and remains a hazard. Infectious complications and unsuspected rejection continue to occur, requiring ongoing surveillance and monitoring. Routine cardiac biopsies are performed at 3-month intervals to monitor for unsuspected early rejection. Acute rejection or infection predominates in the first year after transplantation. Chronic rejection (i.e., accelerated coronary vascular disease) becomes the most important cause of death after the first year. The process is a fibrointimal hyperplasia that can go undetected by coronary arteriography at first and then cause diffuse atherosclerotic changes. Risk factors for its development may include repeated rejection episodes and elevated lipid levels.CMVinfections have also been associated with higher frequency of this disease. Immunocytochemistry on endomyocardial biopsies in cardiac transplant recipients has shown a high incidence of arterial endothelial cell activation, as reflected by the presence of intercellular adhesion molecule 1 and histocompatibility antigen HLA-DR during the first 3 months after transplantation. The presence of these markers has been associated with a high risk of the subsequent development of graft coronary artery atherosclerosis, with death or the need for a second transplant. Thus, activation of the arterial/arteriolar endothelium predicts development of coronary artery disease in and the subsequent failure of the transplanted heart.

Angina is rare, and patients may present with sudden death or silent myocardial infarction. This diffuse accelerated vascular process affects both proximal and distal coronary vessels so that standard approaches, such as angioplasty or coronary artery bypass grafting, are not generally useful but occasionally are successful.

Uncontrolled trials with anticoagulation, aspirin, and improved immunosuppression with

cyclosporine have done little to lower this frequency; 40 to 50% of patients show arteriographic evidence of coronary vascular disease 5 years after transplantation. Retransplantation has been employed for some patients with severe graft atherosclerosis, but it is limited by the scarcity of donors and poorer survival expectations after the second transplant. Diltiazem has been reported to reduce the severity and occurrence of this accelerated vascular process when started at the time of transplantation. Calcium channel blockers are the agents of choice for cyclosporine-induced hypertension, a common complication in the posttransplant patient. Pravastatin and simvastatin have been reported not only to lower lipid levels but also to reduce graft vessel coronary artery disease and improve survival. Administration of one of these drugs is advisable for all heart transplant recipients. A comparative trial of azathioprine versus mycophenolate mofetil reported less graft disease and cardiovascular mortality in the latter group.

In addition to the well-known hazards of long-term glucocorticoid usage, the immunosuppressed patient is at increased risk for neoplasia. An unusual form of lymphoma can occur frequently in extranodal locations, which is linked to prior Epstein-Barr viral infection. This lymphoma can be polyclonal or monoclonal, is associated with excessive immunosuppression, and may respond to simply lowering doses of cyclosporine and administration of acyclovir rather than requiring more aggressive chemo- or radiotherapy. Many cases regress fully and do not recur.

HEART-LUNG TRANSPLANTATION

Patients with congenital heart disease with Eisenmenger's complex (Chap. 234) or primary pulmonary hypertension (Chap. 260) are now considered for heart-lung transplantation. The surgical technique is similar to that for heart transplantation, except that the pulmonary venous attachments to the left atrium are left intact, and a tracheal anastomosis is required. The postoperative period is more complex, since the lungs may be rejected separately from the heart, requiring repeated endobronchoscopic biopsies when rejection is suspected. The immunosuppressive regimen is similar to that for heart transplants, except that glucocorticoids are avoided in the first 1 to 2 weeks to allow healing of the tracheal anastamosis. Long-term survival has in the past been limited by obliterative bronchiolitis due to chronic unrecognized rejection; survival rates have been approximately 60% at 1 year and 50% at 2 years but appear to be improving. Heart-lung transplants have also been applied to primary pulmonary hypertension, but more recent experience with single-lung transplants for these patients has been satisfactory, thus utilizing scarce donors more effectively. Single-lung transplants are also being applied increasingly for patients with advanced emphysema. Double-lung transplants for patients with cystic fibrosis have also become the operation of choice for this group.**For further discussion, see Chap. 267.*

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234. CONGENITAL HEART DISEASE IN THE ADULT - *William F. Friedman, John S. Child*

Congenital heart disease complicates approximately 1% of all live births. It occurs in about 4% of offspring of women with congenital heart disease. Substantial numbers of affected infants reach adulthood because of successful medical and/or surgical management, or because the alteration caused in cardiovascular physiology is well tolerated.

ETIOLOGY AND PREVENTION

Congenital cardiovascular malformations are generally the result of aberrant embryonic development of a normal structure, or failure of such a structure to progress beyond an early stage of embryonic or fetal development. Malformations are due to complex multifactorial genetic and environmental causes. Recognized chromosomal aberrations and mutations of single genes account for<10% of all cardiac malformations (Table 234-1).

The presence of a cardiac malformation as one component of the multiple system involvement in Down's, Turner's, and the trisomy 13-15(D1) and 17-18 (E) syndromes may be anticipated in occasional pregnancies by detection of abnormal chromosomes in fetal cells obtained from amniotic fluid or chorionic villus biopsy. Identification in such cells of the enzyme disorders characteristic of Hurler's syndrome, homocystinuria, or type II glycogen storage disease may also allow one to predict cardiac disease.

PATHOPHYSIOLOGY

The anatomic and physiologic changes in the heart and circulation due to any specific congenital cardiocirculatory lesion are not static but rather progress from prenatal life to adulthood. Thus, malformations that are benign or escape detection in childhood may become clinically significant in the adult. For example, the functionally normal, congenitally bicuspid aortic valve may thicken and calcify with time, resulting in significant aortic stenosis; or the well-tolerated left-to-right shunt of an atrial septal defect may not result in cardiac decompensation, with or without pulmonary hypertension, until the fourth or fifth decade.

Pulmonary Hypertension This is a common companion of many congenital cardiac lesions, and the status of the pulmonary vascular bed is often the principal determinant of the clinical manifestations, the course, and the feasibility of surgical repair. Increases in pulmonary arterial pressure result from elevation of pulmonary blood flow and/or resistance, the latter due sometimes to an increase in vascular tone but usually the result of obstructive, obliterative structural changes within the pulmonary vascular bed. Because pulmonary vascular obstructive disease can be the determining factor in assessing the advisability of operation, it is important to quantitate and compare pulmonary to systemic flows and resistances in patients with severe pulmonary hypertension. The causes of pulmonary vascular obstructive disease are unknown, although increased pulmonary blood flow, increased pulmonary arterial blood pressure, elevated pulmonary venous pressure, erythrocytosis, systemic hypoxemia, acidosis, and the bronchial circulation have been implicated. The designation *Eisenmenger*

syndrome is applied to patients with a large communication between the two circulations at the aortopulmonary, ventricular, or atrial levels and bidirectional or predominantly right-to-left shunts because of high-resistance and obstructive pulmonary hypertension. No specific treatment has proved beneficial for obstructive pulmonary vascular disease, although both single lung transplantation with intracardiac defect repair, and total heart-lung transplantation show promise (Chaps. 233 and267).

Erythrocytosis The chronic hypoxemia in cyanotic congenital heart disease results in *erythrocytosis* due to increased erythropoietin production (Chap. 36). The commonly used term *polycythemia* is a misnomer because white cell counts are normal and platelet counts are normal to decreased. Cyanotic patients with erythrocytosis may have compensated or decompensated hematocrits. Compensated erythrocytosis with iron-replete equilibrium hematocrits rarely results in symptoms of hyperviscosity at hematocrits <65% and occasionally not even with hematocrits ³70%. Therapeutic phlebotomy is rarely required in compensated erythrocytosis. In contrast, patients with decompensated erythrocytosis fail to establish equilibrium with unstable, rising hematocrits and recurrent hyperviscosity symptoms. Therapeutic phlebotomy, a two-edged sword, allows temporary relief of symptoms but begets instability of the hematocrit and compounds the problem by iron depletion. Iron-deficiency symptoms are usually indistinguishable from those of hyperviscosity; progressive symptoms after recurrent phlebotomy are usually due to iron depletion with hypochromic microcytosis. Iron depletion results in a larger number of smaller (microcytic) hypochromic red cells that are less capable of carrying oxygen and less deformable in the microcirculation. Because these microcytes are less deformable in the microcirculation and there are more of them relative to the plasma volume, the viscosity is greater than for an equivalent hematocrit with fewer, larger, iron-replete, deformable cells. As such, iron-depleted erythrocytosis results in increasing symptoms due to decreased oxygen delivery to the tissues.

Hemostasis is abnormal in cyanotic congenital heart disease, due in part to the increased blood volume and engorged capillaries, abnormalities in platelet function and sensitivity to aspirin or nonsteroidal anti-inflammatory agents, and abnormalities of the extrinsic and intrinsic coagulation system. Oral contraceptives are contraindicated for cyanotic women because of the enhanced risk of vascular thrombosis.

The risk of stroke is greatest in children younger than 4 years with cyanotic heart disease and iron deficiency, often with dehydration as an aggravating cause. In contrast, adults with cyanotic congenital heart disease do not appear to be at increased risk for stroke, unless there are excessive injudicious phlebotomies, inappropriate use of aspirin or anticoagulants, or the presence of atrial arrhythmias or infective endocarditis.

Symptoms of hyperviscosity can be produced in any cyanotic patient with erythrocytosis if dehydration causes a reduction of plasma volume. Phlebotomy, when required for symptoms of hyperviscosity not due to dehydration or iron deficiency, is a simple outpatient removal of 500 mL of blood over 45 min with isovolumetric replacement with isotonic saline (5% dextrose if congestive heart failure exists). Acute phlebotomy without volume replacement is contraindicated. Iron repletion in decompensated iron-depleted erythrocytosis ameliorates iron-deficiency symptoms but must be done gradually to avoid a sudden excessive rise in hematocrit and resultant hyperviscosity.

Pregnancy The physiologic alterations during normal gestation (Chap. 7) can create symptoms and physical findings that may be attributed erroneously to heart disease. Dyspnea due to the hormonal influence of progesterone and elevation of the diaphragm in association with peripheral edema and fatigability may be attributed inappropriately to heart failure. The jugular venous pulsations normally become more apparent after the twentieth week. Elevation of the diaphragm can cause basal rales (which disappear with deep breathing). Both ventricles are more easily palpated due to the normal increase in ventricular volumes and elevation of the diaphragm. Third heart sounds, already relatively frequent in normal nongravid young women, increase in frequency and intensity with pregnancy because of increased heart rate and volume of flow across the mitral and tricuspid valves. Midsystolic murmurs across the pulmonary outflow tract and supraclavicular systolic murmurs are caused by increased cardiac output. Venous hums and mammary souffles are usual during pregnancy.

These normal circulatory changes may impinge upon the woman's cardiac reserve. The mother is most at risk if she has a cardiovascular lesion associated with pulmonary vascular disease and pulmonary hypertension (e.g., Eisenmenger's physiology or mitral stenosis) or left ventricular (LV) outflow tract obstruction (e.g., aortic stenosis) but also risks death with any malformation that may cause heart failure or a hemodynamically important arrhythmia (Table 234-2). The fetus is most at risk in the presence of maternal cyanosis, heart failure, or pulmonary hypertension. Women with aortic coarctation or Marfan's syndrome are at risk for aortic dissection. Patients with cyanotic heart disease, pulmonary hypertension, or Marfan's syndrome should not become pregnant; those with correctable lesions should be counseled about the risks of pregnancy with an uncorrected malformation versus repair and later pregnancy. The effect of pregnancy in postoperative patients depends on the outcome of the repair including the presence and severity of residua, sequelae, or complications. Contraception is an important topic with such patients. Tubal ligation should be considered in those in whom pregnancy is strictly contraindicated.

INFECTIVE ENDOCARDITIS (See also Chap. 126)

Routine antimicrobial prophylaxis is recommended for most patients with congenital heart disease whether operated on or not. Antibiotic prophylaxis is not uniformly effective. Nonetheless, it is recommended for all dental procedures, gastrointestinal and genitourinary surgery, and diagnostic procedures such as proctosigmoidoscopy and cystoscopy. The clinical and bacteriologic profile of infective endocarditis in patients with congenital heart disease has changed with the advent of intracardiac surgery and of prosthetic devices. Two major predisposing causes of infective endocarditis are a susceptible cardiovascular substrate and a source of bacteremia. Prophylaxis includes both chemotherapeutic (antimicrobial) and nonchemotherapeutic (hygienic) measures. Meticulous dental and skin care is required.

EXERCISE

Advice on athletics and exercise is governed by the nature of the exercise and by the type and severity of the congenital cardiovascular lesion. Patients with lesions characterized byLVoutflow tract obstruction, if more than mild to moderate, or

pulmonary vascular disease, risk syncope or even sudden death. In Fallot's tetralogy, isotonic exercise-induced decrease in systemic vascular resistance relative to the right ventricular (RV) outflow obstruction augments the right-to-left shunt, increases hypoxemia, and causes an increase in subjective breathlessness due to the response of the respiratory center to the changes in blood gases and pH.

INSURABILITY AND EMPLOYABILITY

Most patients with congenital heart disease must pay significantly more than standard life insurance rates, assuming their anomaly places them in a category that companies have determined is eligible for insurance. A paucity of actuarial survival data beyond adolescence for persons with most congenital cardiac lesions that have undergone operative repair has made it difficult to convince insurance companies to offer reasonable cost insurance even to individual patients whose long-term prognosis is quite good.

Employment is affected by the patient's physical capacity relative to the type of job sought. Job discrimination exists, often because the employer is reluctant to accept health insurance responsibilities. Eligibility for some occupations is governed by public safety regulations, e.g., airline pilots, bus drivers.

SPECIFIC CARDIAC DEFECTS

Table 234-3 provides a classification of cardiac anomalies that recognizes the general categories of clinical presentation, functional consequences, and site of origin of congenital defects.

Categorizing the defect(s) in an individual patient requires an answer to a number of basic questions. Is the patient acyanotic or cyanotic? Is pulmonary arterial blood flow increased or not? Does the malformation originate in the left or right side of the heart? Which is the dominant ventricle? Is pulmonary hypertension present or not? With the above information as a foundation, the use of more refined diagnostic techniques such as transthoracic (precordial) and transesophageal echocardiography and Doppler imaging, magnetic resonance imaging, and/or hemodynamic study and angiocardiography leads to a precise anatomic and functional assessment.

ACYANOTIC CONGENITAL HEART DISEASE WITH A LEFT-TO-RIGHT SHUNT

ATRIAL SEPTAL DEFECT

This common cardiac anomaly in adults occurs more frequently in females. The *sinus venosus* type occurs high in the atrial septum near the entry of the superior vena cava and is associated frequently with anomalous connection of pulmonary veins from the right lung to the junction of the superior vena cava and right atrium (RA). *Ostium primum* anomalies are a form of atrioventricular septal defect that lie immediately adjacent to the atrioventricular valves, either of which may be deformed and incompetent. Ostium primum defects occur commonly in patients with Down's syndrome, although the more complex atrioventricular septal defects with a common atrioventricular valve and a posterior defect of the basal portion of the interventricular septum are more

characteristic of this chromosomal defect. The most common atrial septal defect involves the fossa ovalis, is midseptal in location, and is of the *ostium secundum* type. This type of defect should not be confused with a *patent foramen ovale*. Anatomic obliteration of the foramen ovale ordinarily follows its functional closure soon after birth, but residual "probe patency" is a normal variant; atrial septal defect denotes a true deficiency of the atrial septum and implies functional and anatomic patency.

The magnitude of the left-to-right shunt through an atrial septal defect depends on the defect size, the diastolic properties of both ventricles, and the relative impedance in the pulmonary and systemic circulations. The left-to-right shunt causes diastolic overloading of the RVand increased pulmonary blood flow.

Patients with atrial septal defect are usually asymptomatic in early life, although there may be some physical underdevelopment and an increased tendency for respiratory infections; cardiorespiratory symptoms occur in many older patients. Beyond the fourth decade, a significant number of patients develop atrial arrhythmias, pulmonary arterial hypertension, bidirectional and then right-to-left shunting of blood, and cardiac failure. Patients exposed to the chronic environmental hypoxia of high altitude tend to develop pulmonary hypertension at younger ages. In some older patients, left-to-right shunting across the defect increases as progressive systemic hypertension and/or coronary artery disease result in reduced compliance of theLV.

Physical Examination Examination usually reveals a prominentRVcardiac impulse and palpable pulmonary artery pulsation. The first heart sound is normal or split, with accentuation of the tricuspid valve closure sound. Increased flow across the pulmonic valve is responsible for a midsystolic pulmonary ejection murmur. The second heart sound is widely split and is relatively fixed in relation to respiration. A middiastolic rumbling murmur, loudest at the fourth intercostal space and along the left sternal border, reflects increased flow across the tricuspid valve. In patients with ostium primum defects, an apical thrill and holosystolic murmur indicate associated mitral or tricuspid incompetence or a ventricular septal defect.

The physical findings are altered when an increase in the pulmonary vascular resistance results in diminution of the left-to-right shunt. Both the pulmonary and tricuspid murmurs decrease in intensity, the pulmonic component of the second heart sound and a systolic ejection sound are accentuated, the two components of the second heart sound may fuse, and a diastolic murmur of pulmonic regurgitation appears. Cyanosis and clubbing accompany the development of a right-to-left shunt.

In adults with an atrial septal defect and atrial fibrillation, the physical findings may be confused with the findings of mitral stenosis with pulmonary hypertension because the tricuspid flow murmur and widely split second heart sound may be mistakenly thought to represent the diastolic murmur of mitral stenosis and the mitral "opening snap," respectively.

Electrocardiogram In patients with an ostium secundum defect, the electrocardiogram (ECG) usually shows right axis deviation and an rSr¢ pattern in the right precordial leads representing delayed posterobasal activation of the ventricular septum and enlargement of theRVoutflow tract. An ectopic atrial pacemaker or first-degree heart

block occurs occasionally in patients with defects of the sinus venosus type. In patients with an ostium primum defect, the RV conduction defect is characteristically accompanied by left axis deviation and by superior orientation and counterclockwise rotation of the QRS loop in the frontal plane. Varying degrees of RV andRAhypertrophy may occur with each type of defect, depending on the height of the pulmonary artery pressure. *Chest roentgenograms* reveal enlargement of the RA and RV, dilatation of the pulmonary artery and its branches, and increased pulmonary vascular marking.

Echocardiogram This test shows pulmonary arterial andRVdilatation, and anterior systolic (paradoxical) or flat interventricular septal motion if a significant RV volume overload is present. The defect may be visualized directly from subcostal, right parasternal, or apical echocardiographic windows. In most institutions, two-dimensional echocardiography, supplemented by conventional or color Doppler flow examination, has supplanted cardiac catheterization as the confirmatory test for atrial septal defect. Transesophageal echocardiography is indicated if the transthoracic echocardiogram is ambiguous, which is often the case with sinus venosus defects. Cardiac catheterization is then performed if inconsistencies exist in the clinical data, if significant pulmonary hypertension or associated malformations are suspected, or if coronary artery disease is a possibility.

TREATMENT

Operative repair, ideally in children age 3 to 6 years, should be advised for all patients with uncomplicated atrial septal defects in whom there is significant left-to-right shunting, i.e., with pulmonary-to-systemic flow ratios exceeding ~2.0:1.0. Excellent results may be anticipated, at low risk, even in patients older than 40 years in the absence of pulmonary hypertension. The defect is closed, usually with a patch of pericardium or of prosthetic material, with the patient on cardiopulmonary bypass. In patients with ostium primum defects, cleft, deformed, and incompetent valves often require repair. Intraoperative transesophageal echocardiography is used to monitor the surgical results of mitral valve repair. Operation should not be carried out in patients with small defects and trivial left-to-right shunts, or in those with severe pulmonary vascular disease without a significant left-to-right shunt.

Patients with atrial septal defect of the sinus venosus or ostium secundum types rarely die before the fifth decade. During the fifth and sixth decades the incidence of progressive symptoms, often leading to severe disability, increases substantially. Medical management should include prompt treatment of respiratory tract infections, antiarrhythmic medications for atrial fibrillation or supraventricular tachycardia, and the usual measures for hypertension, coronary disease, or heart failure (Chap. 232), if these complications occur. The risk of infective endocarditis is quite low unless the defect is complicated by valvular regurgitation or has recently been repaired with a patch (Chap. 126).

VENTRICULAR SEPTAL DEFECT

Defects of the ventricular septum are common as isolated defects and as one component of a combination of anomalies. The opening is usually single and situated in the membranous portion of the septum. The functional disturbance is dependent

primarily on its size and on the status of the pulmonary vascular bed, rather than on the location of the defect. Only small or moderate-size defects are usually seen initially in adulthood as most patients with isolated large defects come to medical and, often, surgical attention very early in life.

A wide spectrum exists in the natural history of ventricular septal defect, ranging from spontaneous closure to congestive cardiac failure and death in early infancy. Within this spectrum is the possible development of pulmonary vascular obstruction,RVoutflow tract obstruction, aortic regurgitation, and infective endocarditis. Spontaneous closure is more common in patients born with a small ventricular septal defect and occurs in early childhood in most patients.

Patients with large ventricular septal defects and pulmonary hypertension are those at greatest risk for developing pulmonary vascular obstruction. Thus, large defects should be corrected surgically early in life when pulmonary vascular disease is still reversible or not yet developed. In patients with severe pulmonary vascular obstruction (Eisenmenger syndrome), symptoms in adult life consist of exertional dyspnea, chest pain, syncope, and hemoptysis. The right-to-left shunt leads to cyanosis, clubbing, and erythrocytosis. In all patients, the degree to which pulmonary vascular resistance is elevated before operation is a critical factor determining prognosis. If the pulmonary vascular resistance is one-third or less of the systemic value, progression of pulmonary vascular disease after operation is unusual. However, if a moderate to severe increase in pulmonary vascular resistance exists preoperatively, either no change or a progression of pulmonary vascular disease is common postoperatively.

RVoutflow tract obstruction develops in ~5 to 10% of patients who present in infancy with a moderate to large left-to-right shunt. With time, as subvalvular RV outflow tract obstruction progresses, the findings in these patients begin to resemble more closely those of the cyanotic tetralogy of Fallot.

In ~5% of patients, incompetence of the aortic valve results from insufficient cusp tissue or prolapse of the cusp through the interventricular defect; the aortic regurgitation then complicates and usually dominates the clinical course.

Two-dimensional *echocardiography* with conventional or color Doppler examination can usually define the number and location of defects in the ventricular septum and detect associated anomalies. Hemodynamic and angiographic study may be employed to assess the status of the pulmonary vascular bed and clarify details of the altered anatomy.

TREATMENT

Surgery is not recommended for patients with normal pulmonary arterial pressures with small shunts (pulmonary-to-systemic flow ratios of less than 1.5 to 2.0:1.0). Operative correction is indicated when there is a moderate to large left-to-right shunt with a pulmonary-to-systemic flow ratio>1.5:1.0 or 2.0:1.0, in the absence of prohibitively high levels of pulmonary vascular resistance.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a vessel leading from the bifurcation of the pulmonary artery to the aorta just distal to the left subclavian artery. Normally, the vascular channel is open in the fetus but closes immediately after birth. The flow across the ductus is determined by the pressure and resistance relationships between the systemic and pulmonary circulations and by the cross-sectional area and length of the ductus. In most adults with this anomaly, pulmonary pressures are normal and a gradient and shunt from aorta to pulmonary artery persist throughout the cardiac cycle, resulting in a characteristic thrill and a continuous "machinery" murmur with a late systolic accentuation at the upper left sternal edge. In adults who were born with a large left-to-right shunt through the ductus arteriosus, pulmonary vascular obstruction (Eisenmenger syndrome) with pulmonary hypertension, right-to-left shunting, and cyanosis have usually developed. Severe pulmonary vascular disease results in reversal of flow through the ductus, unoxygenated blood is shunted to the descending aorta, and the toes, but not the fingers, become cyanotic and clubbed, a finding termed *differential cyanosis*. The leading causes of death in adults with patent ductus are cardiac failure and infective endocarditis; occasionally severe pulmonary vascular obstruction may cause aneurysmal dilatation, calcification, and rupture of the ductus.

TREATMENT

In the absence of severe pulmonary vascular disease and predominant left-to-right shunting of blood, the patent ductus should be surgically ligated or divided. Transcatheter closure is experimental, using coils, buttons, plugs, and umbrellas. Thoracoscopic surgical approaches are considered experimental. Operation should be deferred for several months in patients treated successfully for infective endocarditis, because the ductus may remain somewhat edematous and friable.

AORTIC ROOT TO RIGHT HEART SHUNTS

The three most common causes of aortic root to right heart shunts are congenital aneurysm of an aortic sinus of Valsalva with fistula, coronary arteriovenous fistula, and anomalous origin of the left coronary artery from the pulmonary trunk. *Aneurysm of an aortic sinus of Valsalva* consists of a separation or lack of fusion between the media of the aorta and the annulus fibrosis of the aortic valve. Rupture usually occurs in the third or fourth decade of life; most often the aorticocardiac fistula is between the right coronary cusp and theRV, but occasionally, when the noncoronary cusp is involved, the fistula drains into theRA. Abrupt rupture causes chest pain, bounding pulses, a continuous murmur accentuated in diastole, and volume overload of the heart. Diagnosis is confirmed by two-dimensional and Doppler echocardiographic studies; cardiac catheterization quantitates the left-to-right shunt, and thoracic aortography visualizes the fistula. Medical management is directed at cardiac failure, arrhythmias, or endocarditis. At operation, the aneurysm is closed and amputated, and the aortic wall is reunited with the heart, either by direct suture or with a prosthesis.

Coronary arteriovenous fistula, an unusual anomaly, consists of a communication between a coronary artery and another cardiac chamber, usually the coronary sinus,RA, orRV. The shunt is usually of small magnitude, and myocardial blood flow is not usually compromised. Potential complications include infective endocarditis, thrombus formation

with occlusion or distal embolization, rupture of an aneurysmal fistula, and rarely, pulmonary hypertension and congestive failure. A loud, superficial, continuous murmur at the lower or midsternal border usually prompts a further evaluation of asymptomatic patients. Doppler echocardiography demonstrates the site of drainage; if the site of origin is proximal, it may be detectable by two-dimensional echocardiography. Retrograde thoracic aortography or coronary arteriography permits identification of the size and anatomic features of the fistulous tract, which may be closed by suture or transcatheter obliteration.

The third anomaly causing a shunt from the aortic root to the right heart is *anomalous origin of the left coronary artery from the pulmonary artery*. Myocardial infarction and fibrosis commonly lead to death within the first year, though up to 20% of patients survive to adolescence and beyond without surgical correction. The diagnosis is supported by theECGfindings of an anterolateral myocardial infarction. Operative management of adults consists of coronary artery bypass with an internal mammary artery graft or saphenous vein-coronary artery graft.

ACYANOTIC CONGENITAL HEART DISEASE WITHOUT A SHUNT

CONGENITAL AORTIC STENOSIS

Malformations that cause obstruction toLVoutflow include congenital valvular aortic stenosis, discrete subaortic stenosis, supravalvular aortic stenosis, and hypertrophic obstructive cardiomyopathy (Chap. 238).

Valvular Aortic Stenosis This malformation occurs three to four times more often in males than in females. The congenital bicuspid aortic valve, which is not necessarily stenotic, is one of the most common congenital malformations of the heart, although it may go undetected in early life. Because bicuspid valves may become stenotic with time or be the site of infective endocarditis, the lesion may be difficult to distinguish in adults from acquired rheumatic or degenerative calcific aortic stenosis.

The dynamics of blood flow associated with a congenitally deformed, rigid aortic valve commonly lead to thickening of the cusps and, in later life, to calcification. Hemodynamically significant obstruction causes concentric hypertrophy of theLV wall and dilatation of the ascending aorta.**The clinical manifestations and hemodynamic abnormalities are discussed in Chap. 236.*

TREATMENT

The medical management of congenital valvular aortic stenosis includes prophylaxis against infective endocarditis and, in patients with diminished cardiac reserve, the administration of digitalis and diuretics and sodium restriction while awaiting operation. If severe aortic stenosis is present, strenuous physical activity should be avoided even when the patient is asymptomatic, and participation in competitive sports should probably be restricted in patients with milder degrees of obstruction. Aortic valve replacement is indicated in adults with critical obstruction, i.e., with an aortic valve area<0.5 cm^2/m^2, with symptoms secondary toLVdysfunction or myocardial ischemia, or with hemodynamic evidence of LV dysfunction. In asymptomatic children or adolescents

or young adults with critical aortic stenosis without valvular calcification or these features, aortic balloon valvuloplasty is often useful (Chap. 245). If surgery is contraindicated in older patients because of a complicating medical problem such as malignancy or renal or hepatic failure, balloon valvuloplasty may provide short-term improvement. It may serve as a bridge to aortic valve replacement in patients with severe heart failure.

Subaortic Stenosis The most common form of subaortic stenosis is the *idiopathic hypertrophic* variety, also termed *hypertrophic cardiomyopathy*, which is present at birth in about one-third of the patients and is discussed inChap. 238. In contrast, both clinically and physiologically, the *discrete* form of subaortic stenosis resembles valvular aortic stenosis. The lesion usually consists of a membranous diaphragm or fibrous ring encircling the LV outflow tract just beneath the base of the aortic valve. Echocardiography demonstrates the subaortic obstruction; Doppler studies show turbulence proximal to the aortic valve and also detect and quantitate the pressure gradient and severity of aortic regurgitation. Treatment consists of excision of the membrane or fibrous ridge.

Supravalvular Aortic Stenosis This anomaly consists of a localized or diffuse narrowing of the ascending aorta originating just above the level of the coronary arteries at the superior margin of the sinuses of Valsalva. In contrast to other forms of aortic stenosis, the coronary arteries are subjected to elevated systolic pressures from theLV, are often dilated and tortuous, and are susceptible to premature atherosclerosis. New information indicates that a genetic defect for the anomaly is located in the same chromosomal subunit as elastin on chromosome 7.

COARCTATION OF THE AORTA

Narrowing or constriction of the lumen of the aorta may occur anywhere along its length but is most common distal to the origin of the left subclavian artery near the insertion of the ligamentum arteriosum. Coarctation occurs in ~7% of patients with congenital heart disease, is twice as common in males as in females, and is most frequent in patients with gonadal dysgenesis. Clinical manifestations depend on the site and extent of obstruction and the presence of associated cardiac anomalies, most commonly a bicuspid aortic valve. Aneurysmal arterial dilatation of the circle of Willis produces a high risk of sudden rupture and death.

Most children and young adults with isolated, discrete coarctation are asymptomatic. Headache, epistaxis, cold extremities, and claudication with exercise may occur, and attention is usually directed to the cardiovascular system when a heart murmur or hypertension in the upper extremities and absence, marked diminution, or delayed pulsations in the femoral arteries are detected on physical examination. Enlarged and pulsatile collateral vessels may be palpated in the intercostal spaces anteriorly, in the axillae, or posteriorly in the interscapular area. The upper extremities and thorax may be more developed than the lower extremities. A midsystolic murmur over the anterior part of the chest, back, and spinous processes may become continuous if the lumen is narrowed sufficiently to result in a high-velocity jet across the lesion throughout the cardiac cycle. Additional systolic and continuous murmurs over the lateral thoracic wall may reflect increased flow through dilated and tortuous collateral vessels.

TheECGusually revealsLVhypertrophy. Roentgenograms may show a dilated left subclavian artery high on the left mediastinal border and a dilated ascending aorta. Indentation of the aorta at the site of coarctation and pre- and poststenotic dilatation (the "3" sign) along the left paramediastinal shadow are almost pathognomonic. Notching of the ribs, an important radiographic sign, is due to erosion by dilated collateral vessels. Two-dimensional echocardiography from para- or suprasternal windows identifies the site and length of coarctation, while Doppler studies record and quantitate the pressure gradient. Transesophageal echocardiography and magnetic resonance imaging or digital angiography allow visualization of the length and severity of the obstruction and the associated collateral arteries. In adults, cardiac catheterization is indicated primarily to evaluate the coronary arteries.

The chief hazards result from severe hypertension and include the development of cerebral aneurysms and hemorrhage, rupture of the aorta, premature coronary arteriosclerosis,LVfailure, and infective endocarditis.

TREATMENT

Treatment is usually surgical; resection and end-to-end anastomosis or subclavian flap angioplasty are used commonly, although it may be necessary to use a tubular graft, patch, or bypass conduit if the narrowed segment is long. Systemic hypertension postoperatively, in the absence of residual coarctation, appears to be related to the duration of preoperative hypertension. Percutaneous balloon dilatation is controversial in native unoperated aortic coarctation but commonly successful for postsurgical recoarctation, often with deployment of a stent.

PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

Obstruction toRVoutflow may be localized to the supravalvular, valvular, or subvalvular levels or occur at a combination of these sites. Multiple sites of narrowing of the peripheral pulmonary arteries are a feature of *rubella embryopathy* and may occur with both the familial and sporadic forms of supravalvular aortic stenosis. Valvular pulmonic stenosis is the most common form of isolated RV obstruction.

The severity of the obstructing lesion, rather than the site of narrowing, is the most important determinant of the clinical course. In the presence of a normal cardiac output, a peak systolic transvalvular pressure gradient between 50 and 80 mmHg is considered to be moderate stenosis; levels below and above that range are classified as mild and severe, respectively. Patients with mild pulmonic stenosis are generally asymptomatic and demonstrate little or no progression in the severity of obstruction with age. In patients with more significant stenosis, the severity may increase with time. Symptoms vary with the degree of obstruction. Fatigue, dyspnea,RVfailure, and syncope may limit the activity of older patients, in whom moderate or severe obstruction may prevent an augmentation of cardiac output with exercise. In patients with severe obstruction, the systolic pressure in the RV may exceed that in theLV, since the ventricular septum is intact. RV ejection is prolonged with moderate or severe stenosis, and the sound of pulmonary valve closure is delayed and soft. RV hypertrophy reduces the compliance of that chamber, and a forcefulRAcontraction is necessary to augment RV filling. A fourth heart sound, prominent *a* waves in the jugular venous pulse, and, occasionally,

presystolic pulsations of the liver reflect vigorous atrial contraction. The clinical diagnosis is supported by a right parasternal lift and harsh systolic ejection murmur and thrill at the upper left sternal border, typically preceded by a systolic ejection sound, if the obstruction is valvular. The holosystolic decrescendo murmur of tricuspid regurgitation may accompany severe pulmonic stenosis, especially in the presence of congestive heart failure. Cyanosis usually reflects right-to-left shunting through a patent foramen ovale or atrial septal defect. In patients with supravalvular or peripheral pulmonary arterial stenosis, the murmur is systolic or continuous and is best heard over the area of narrowing, with radiation to the peripheral lung fields.

TheECG may be helpful in assessing the degree ofRVobstruction. In mild cases, the ECG is often normal, whereas moderate and severe stenoses are associated with right axis deviation and RV hypertrophy. A ventricular strain pattern, as well as high-amplitude P waves in leads II and V_1, indicatingRAenlargement, is associated with severe stenosis. The chest roentgenogram with mild or moderate pulmonic stenosis often shows a heart of normal size and normal vascularity of the lungs. In the presence of valvular stenosis, poststenotic dilatation of the main and left pulmonary arteries may be evident. With severe obstruction and resultant RV failure, RA and RV enlargement are generally evident. The pulmonary vascularity may be reduced with severe stenosis, RV failure, and/or a right-to-left shunt at the atrial level. Two-dimensional echocardiography visualizes pulmonary valve morphology; the outflow tract pressure gradient can be estimated by Doppler ultrasonography.

TREATMENT

The cardiac catheter technique of balloon valvuloplasty (Chap. 228) is usually effective. Direct surgical relief of moderate and severe obstruction may be accomplished at a low risk. Multiple stenoses of the peripheral pulmonary arteries are usually inoperable, but narrowing of a single branch or at the bifurcation of the main pulmonary trunk may be corrected.

CYANOTIC CONGENITAL HEART DISEASE WITH INCREASED PULMONARY BLOOD FLOW

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

In this condition the aorta arises from theRV to the right of and anterior to the pulmonary artery, which emerges from theLV(Fig. 234-1, *left panel*). This results in two separate and parallel circulations, and some communication between them must exist after birth to sustain life. Most patients have an interatrial communication, two-thirds have a patent ductus arteriosus, and about one-third have an associated ventricular septal defect. Transposition is more common in males and accounts for ~10% of cyanotic heart disease.

The course is determined by the degree of tissue hypoxia, the ability of each ventricle to sustain an increased work load in the presence of reduced coronary arterial oxygenation, the nature of the associated cardiovascular anomalies, and the status of the pulmonary vascular bed. Pulmonary vascular obstruction develops by 1 to 2 years of age in patients with an associated large ventricular septal defect or large patent ductus

arteriosus in the absence of obstruction toLVoutflow.

TREATMENT

The balloon or blade catheter or surgical creation or enlargement of an interatrial communication in the neonate is the simplest procedure for providing increased intracardiac mixing of systemic and pulmonary venous blood. Systemic-pulmonary artery anastomosis may be indicated in the patient with severe obstruction toLVoutflow and diminished pulmonary blood flow. Intracardiac repair may be accomplished by rearranging the venous returns (intra-atrial switch, i.e., Mustard or Senning operation) so that the systemic venous blood is directed to the mitral valve and thence to the LV and pulmonary artery, while the pulmonary venous blood is diverted through the tricuspid valve andRV to the aorta. The late survival after these repairs is good, but late sudden death is the most worrisome feature. Preferably, this malformation is corrected in infancy by transposing both coronary arteries to the posterior artery and transecting, contraposing, and anastomosing the aorta and pulmonary arteries (arterial switch operation). For those patients with a ventricular septal defect in whom it is necessary to bypass a severely obstructed LV outflow tract, corrective operation employs an intracardiac ventricular baffle and extracardiac prosthetic conduit to replace the pulmonary artery (Rastelli procedure).

SINGLE VENTRICLE

This is a family of complex lesions with both atrioventricular valves or a common atrioventricular valve opening to a single ventricular chamber. Associated anomalies include abnormal great artery positional relationships, pulmonic valvular or subvalvular stenosis, and subaortic stenosis.

Survival to adulthood depends on a relatively normal pulmonary blood flow and good ventricular function. Modifications of the Fontan approach are generally applied to these patients with creation of a pathway(s) from the systemic veins to the pulmonary arteries.

CYANOTIC CONGENITAL HEART DISEASE WITH DECREASED PULMONARY BLOOD FLOW

TRICUSPID ATRESIA

This malformation is characterized by atresia of the tricuspid valve, an interatrial communication, and, frequently, hypoplasia of theRV and pulmonary artery. The clinical picture is usually dominated by severe cyanosis due to obligatory admixture of systemic and pulmonary venous blood in theLV. TheECGcharacteristically showsRAenlargement, left axis deviation, and LV hypertrophy.

Atrial septostomy and palliative operations to increase pulmonary blood flow, often by anastomosis of a systemic artery or vein to a pulmonary artery, may allow survival to the second or third decade. A Fontan atriopulmonary connection may then allow functional correction in those patients with normal or low pulmonary arterial resistance pressure and good LVfunction.

EBSTEIN'S ANOMALY

Characterized by a downward displacement of the tricuspid valve into theRV, due to anomalous attachment of the tricuspid leaflets, the Ebstein tricuspid valve tissue is dysplastic and results in tricuspid regurgitation. The abnormally situated tricuspid orifice produces an "atrialized" portion of the RV lying between the atrioventricular ring and the origin of the valve, which is continuous with theRAchamber. Often the RV is hypoplastic. Although the clinical manifestations are variable, some patients come to initial attention because of progressive cyanosis from right-to-left atrial shunting, or symptoms due to tricuspid regurgitation and RV dysfunction, or paroxysmal atrial tachyarrhythmias. Diagnostic findings by two-dimensional echocardiography include the abnormal positional relation between the tricuspid and mitral valves with apical displacement of the septal tricuspid leaflet. Tricuspid regurgitation is quantitated by Doppler examination. Surgical approaches include prosthetic replacement of the tricuspid valve when the leaflets are tethered or repair of the native valve.

TETRALOGY OF FALLOT

The four components of the tetralogy of Fallot are ventricular septal defect, obstruction toRVoutflow, aortic override (straddle) of the ventricular septal defect, and RV hypertrophy (Fig. 234-1, right panel).

The severity ofRVoutflow obstruction determines the clinical presentation. The severity of hypoplasia of the RV outflow tract varies from mild to complete (pulmonary atresia). Pulmonary valve stenosis and supravalvular and peripheral pulmonary arterial obstruction may coexist; rarely there is unilateral absence of a pulmonary artery (usually the left). A right-sided aortic arch and descending aorta occur in ~25% of patients with tetralogy.

The relationship between the resistance to blood flow from the ventricles into the aorta and into the pulmonary vessels plays a major role in determining the hemodynamic and clinical picture. Thus, the severity of obstruction toRVoutflow is of fundamental significance. When the obstruction is severe, the pulmonary blood flow is reduced markedly, and a large volume of desaturated systemic venous blood is shunted from right to left across the ventricular septal defect. Severe cyanosis and erythrocytosis occur, and symptoms and sequelae of systemic hypoxemia are prominent. In many infants and children the obstruction is mild but progressive.

TheECGordinarily showsRV and, less often,RAhypertrophy. Radiologic examination characteristically reveals a normal-sized, boot-shaped heart (*coeur en sabot*) with prominence of the RV and a concavity in the region of the pulmonary conus. The pulmonary vascular markings are typically diminished, and the aortic arch and knob may be on the right side. Two-dimensional echocardiography from the parasternal or subcostal windows demonstrates the malalignment of the ventricular septal defect and the subpulmonary stenosis. Selective angiocardiography with RV injection provides architectural details of the RV outflow tract, pulmonary valve and annulus, and caliber of the main branches of the pulmonary artery; coronary arteriography identifies the anatomy and course of the coronary arteries.

TREATMENT

Factors that may complicate the treatment of patients with tetralogy of Fallot include infective endocarditis, paradoxic embolism, excessive erythrocytosis, coagulation defects, and cerebral infarction or abscess. Corrective operation is advisable at some point for almost all patients with this anomaly. Successful correction avoids progressive infundibular obstruction, delayed growth, and complications due to hypoxemia and excessive erythrocytosis. The size of the pulmonary arteries rather than the age or size of the infant or child is the most important determinant in establishing candidacy for primary repair. Pronounced hypoplasia of the pulmonary arteries is a relative contraindication for an early corrective surgical procedure. When this problem is present, a palliative operation, such as creation of a systemic arterial-pulmonary arterial shunt, is carried out and is usually followed by complete correction, which can be carried out at a lower risk later in childhood.

OTHER FORMS OF CONGENITAL HEART DISEASES

CONGENITALLY CORRECTED TRANSPOSITION

The two fundamental anatomic abnormalities in this malformation are transposition of the ascending aorta and pulmonary trunk and inversion of the ventricles. This arrangement results in desaturated systemic venous blood passing from theRAthrough the mitral valve to theLV and into the pulmonary trunk, whereas arterialized pulmonary venous blood flows from the left atrium (LA) through the tricuspid valve to theRV and into the aorta. Thus, the circulation is corrected functionally. The clinical presentation, course, and prognosis of patients with congenitally corrected transposition vary depending on the nature and severity of any complicating intracardiac anomalies. Ebstein-type anomalies of the left-side tricuspid atrioventricular valve, ventricular septal defect, obstruction to outflow from the venous ventricle, and congenital heart block are often associated with corrected transposition. The diagnosis of the malformation and associated lesions can often be established by two-dimensional echocardiography and Doppler examination.

MALPOSITIONS OF THE HEART

Positional anomalies refer to conditions in which the cardiac apex is in the right side of the chest (dextrocardia), or at the midline (mesocardia), or in which there is a normal location of the heart in the left side of the chest but abnormal position of the viscera (isolated levocardia). Knowledge of the position of the abdominal organs and of the branching pattern of the main stem bronchi is important in categorizing these malpositions. When dextrocardia occurs without situs inversus, when the visceral situs is indeterminate, or if isolated levocardia is present, associated, often complex, multiple cardiac anomalies are usually present. In contrast, mirror-image dextrocardia is usually observed with complete situs inversus, which occurs most frequently in individuals whose hearts are otherwise normal.

SURGICALLY MODIFIED CONGENITAL HEART DISEASE

Because of the enormous strides in cardiovascular surgical techniques that have

occurred in the past 20 years, a large number of long-term survivors of corrective operations in infancy and childhood have reached adulthood. These patients are often challenging because of the diversity of anatomic, hemodynamic, and electrophysiologic residua and sequelae of cardiac operations.

The proper care of the survivor of operation for congenital heart disease requires that the clinician understand the details of the malformation before operation; pay meticulous attention to the details of the operative procedure; and recognize the postoperative residua (conditions left totally or partially uncorrected), the sequelae (conditions caused by surgery), and the complications that may have resulted from the operation. With the exception of ligation and division of an uncomplicated patent ductus arteriosus, almost every other surgical repair of an anomaly leaves behind or causes some abnormality of the heart and circulation that may range from trivial to serious. Intraoperative transesophageal echocardiography assists in detecting unsuspected lesions, in monitoring the repair, and in verifying a satisfactory result or directing further repair. Thus, even with results that are considered clinically to be good to excellent, continued long-term postoperative follow-up is advisable.

Table 234-4 lists the categories of common late postoperative problems. Cardiac operations importantly involving the atria, such as closure of atrial septal defect, repair of total or partial anomalous pulmonary venous return, or venous switch corrections of complete transposition of the great arteries (the Mustard or Senning operations), may be followed years later by sinus node or atrioventricular node dysfunction or by atrial arrhythmias. Intraventricular surgery may also result in electrophysiologic consequences, including complete heart block necessitating pacemaker insertion to avoid sudden death. In addition, valvular problems may arise late after initial cardiac operation. An example is the progressive stenosis of an initially nonobstructive bicuspid aortic valve in the patient who underwent aortic coarctation repair. Such aortic valves may also be the site of infective endocarditis. After repair of the ostium primum atrial septal defect, the cleft mitral valve may become progressively incompetent. Tricuspid regurgitation may also be progressive in the postoperative patient with tetralogy of Fallot ifRVoutflow tract obstruction was not relieved adequately at initial surgery. In many patients with surgically modified congenital heart disease, inadequate relief of an obstructive lesion, or a residual regurgitant lesion, or a residual shunt will cause or hasten the onset of clinical signs and symptoms of myocardial dysfunction. Despite a good hemodynamic repair, many patients with a subaortic RV develop RV decompensation and signs of "left heart failure." In many patients, particularly those who were cyanotic for many years before operation, a preexisting compromise in ventricular performance is due to the original underlying malformation.

A final category of postoperative problems involves the use of prosthetic valves, patches, or conduits in the operative repair. The special risks include infective endocarditis, thrombus formation, and premature degeneration and calcification of the prosthetic materials. There are many patients in whom extracardiac conduits are required to correct the circulation functionally and often to carry blood to the lungs from theRA orRV. These conduits may develop intraluminal obstruction, and, if they include a prosthetic valve, it may show progressive calcification and thickening.

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235. RHEUMATIC FEVER - *Edward L. Kaplan*

In many parts of the world, especially in industrialized countries, acute rheumatic fever is less common than it was during the early and mid-years of the twentieth century. In the late 1940s, patients with rheumatic fever and rheumatic heart disease accounted for more than half of schoolchildren recognized to have cardiovascular problems in the United States. During the Second World War, there were more than 20,000 cases of acute rheumatic fever in U.S. Navy personnel alone. The incidence of rheumatic fever has declined remarkably in the industrialized countries of the world, where the disease has become rare. However, in many developing countries, which account for almost two-thirds of the world's population, streptococcal infections, rheumatic fever, and rheumatic heart disease remain a very significant public health problem. The magnitude of the problem in these countries today is similar to that in North America 50 years ago.

The decreased incidence of acute rheumatic fever and the low prevalence of rheumatic heart disease in industrialized countries have led many physicians and public health authorities to the incorrect conclusion that these conditions are no longer a problem. However, starting in the 1980s, unexpected scattered outbreaks of acute rheumatic fever among both adults and children in North America have confirmed the capacity for this potentially serious illness to reappear and pose significant public health problems. Neither antimicrobial agents nor other public health measures have been totally effective in the control of rheumatic fever in the industrialized or industrializing world.

EPIDEMIOLOGY

The epidemiology of acute rheumatic fever is identical to that of group A streptococcal upper respiratory tract infections (Chap. 140). As is the case for streptococcal sore throat, acute rheumatic fever most often occurs in children; the peak age-related incidence is between 5 and 15 years. Most initial attacks in adults take place at the end of the second and beginning of the third decades of life. Rarely, initial attacks occur as late as the fourth decade and recurrent attacks have been documented as late as the fifth decade.

Epidemiologic risk factors classically associated with individual attacks and especially with outbreaks of acute rheumatic fever include lower standards of living, especially crowding; the disease has been more common among socially and economically disadvantaged populations. However, the outbreaks in the United States in the late 1980s and early 1990s cannot be explained entirely by these factors. The large Utah outbreak of more than 500 cases during 13 years has affected primarily middle class patients with ready access to medical care. Therefore, one can conclude that the organism itself as well as the degree of host/herd immunity to the prevalent serotypes in an affected community are equally important risk factors.

Studies have shown that approximately 3% of individuals with untreated group A streptococcal pharyngitis will develop rheumatic fever. The epidemiology of rheumatic fever is also influenced by the serotypes of group A streptococci present in a population. The concept of "rheumatogenecity" of specific strains is largely based upon epidemiologic evidence associating certain serotypes with rheumatic fever (e.g., serotypes 1, 3, 5, 6, 18, etc.). Mucoid isolates are frequently associated with virulence

and with rheumatic fever.

PATHOGENESIS

More than half a century ago the pioneering studies of Lancefield differentiated beta-hemolytic streptococci into serologic groups. This ultimately led to the association of infection by the group A organism of the pharynx and tonsils (not of the skin) and the subsequent development of acute rheumatic fever. However, the mechanism(s) responsible for the development of rheumatic fever after an infection remains incompletely defined. Historically, approaches to understanding the pathogenesis of rheumatic fever have been grouped into three major categories: (1) direct infection by the group A streptococcus; (2) a toxic effect of streptococcal extracellular products on the host tissues; and (3) an abnormal or dysfunctional immune response to one or more as yet unidentified somatic or extracellular antigens produced by all (or perhaps only by some) group A streptococci.

There is insufficient evidence to support direct infection of the heart as the inciting event. Additionally, while toxins such as streptolysin O and others have been postulated to have a pathogenetic role, there is relatively little convincing evidence of this at the present time. Major efforts have focused on an abnormal immune response by the human host to one or more group A streptococcal antigens.

The hypothesis of "antigenic mimicry" between human and group A streptococcal antigens has been studied extensively and has concentrated on two interactions. The first is the similarity between the group-specific carbohydrate of the group A streptococcus and the glycoprotein of heart valves; the second involves the molecular similarity among the streptococcal cell membrane, streptococcal M protein sarcolemma, and other moieties of the human myocardial cell.

The possibility of a predisposing genetic influence in some individuals is one of the most tantalizing of the incompletely understood factors that might contribute to susceptibility to rheumatic fever. The precise genetic factors influencing the attack rate have never been adequately defined. Observations have been described that support the concept that this nonsuppurative sequel to a group A streptococcal upper respiratory tract infection results from an abnormal immune response by the human host. Thus, differences in immune responses to streptococcal antigens have been reported. Further, new data suggest that a unique surface marker on non-T lymphocytes in patients with rheumatic fever and rheumatic heart disease may prove helpful in defining which individuals are susceptible to developing rheumatic fever after a streptococcal infection because of abnormal immune responses.

DIAGNOSIS

There is no specific laboratory test that can establish a diagnosis of rheumatic fever. The diagnosis, therefore, is a clinical one but requires supporting evidence from the clinical microbiology and clinical immunology laboratories. Because of the variety of signs and symptoms associated with the rheumatic fever syndrome, in 1944 Jones first proposed criteria to assist the clinician in standardizing the diagnosis of rheumatic fever. The most recent modification of the *Jones criteria* (Updated Jones Criteria) was

published in 1992 by a Special Writing Group of the American Heart Association (Table 235-1).

There are five criteria termed *major* because they are most commonly found in patients with rheumatic fever: carditis, migratory polyarthritis, Sydenham's chorea, subcutaneous nodules, and erythema marginatum.

The *carditis* of acute rheumatic fever is a pancarditis involving the pericardium, myocardium, and endocardium. In most published series, between 40 and 60% of patients with acute rheumatic fever have evidence of carditis, which is characterized by one or more of the following: sinus tachycardia, the murmur of mitral regurgitation, an S_3gallop, a pericardial friction rub, and cardiomegaly. The introduction of echocardiography has assisted in the identification of subtle abnormalities of the mitral valve, and these may be present in an additional 20% of patients who do not have an audible heart murmur. A prolonged PR interval and evidence of heart failure may be present as well, but these are nonspecific and may be found in a number of other diseases.

Healing of the rheumatic valvulitis may cause fibrous thickening and adhesion, resulting in the most serious complication of rheumatic fever, i.e., valvular stenosis and/or regurgitation (Chap. 236). The mitral valve is involved most frequently, followed by the aortic valve. However, isolated aortic valve disease as a consequence of acute rheumatic fever is quite rare. In patients with aortic valve disease due to rheumatic fever, the mitral valve is almost always simultaneously affected. Even minor degrees of rheumatic valvular involvement can lead to susceptibilities to infective endocarditis (Chap. 126). Although rheumatic pericarditis can cause a serous effusion, fibrin deposits, and even pericardial calcification, it does not lead to constrictive pericarditis.

A *migratory polyarthritis* is present in as many as 75% of cases, most often affecting the ankles, wrists, knees, and elbows over a period of days. It usually does not affect the small joints of the hands or feet and seldom involves the hip joints. Since salicylates and other anti-inflammatory drugs usually cause prompt resolution of joint symptoms, it is important that the clinician *not* prescribe these medications until it is determined whether the arthritis is migratory. The arthritis of acute rheumatic fever is extremely painful. Pain can be controlled with codeine or similar analgesics until the diagnosis is established. The difference between arthralgia (subjective joint pain) and arthritis (joint pain and swelling) must be understood. Too often, arthralgia is used (incorrectly) as a major criterion.

Sydenham's chorea occurs in fewer than 10% of patients with rheumatic fever. The latent period between the onset of the initiating streptococcal infection and the onset of Sydenham's chorea may be as long as several months. While differing from the other manifestations, this central nervous system disorder is a part of the rheumatic fever complex and should be managed as such. Many patients who appear to have only chorea may present several decades later with evidence of typical rheumatic valvular disease. There is no definitive laboratory test for establishing a diagnosis of Sydenham's chorea, and the diagnosis is one of exclusion. Patients with Sydenham's chorea should be given secondary prophylaxis for prevention of recurrent attacks, even if they do not appear to have rheumatic heart disease.

Subcutaneous nodules and *erythema marginatum* are rare major manifestations, usually present in fewer than 10% of cases. Subcutaneous nodules are found over extensor surfaces of joints, are seen most often in patients with long-standing rheumatic heart disease, and are extremely rare in patients experiencing an initial attack. Erythema marginatum is an uncommon manifestation. It is an evanescent macular eruption with rounded borders -- usually concentrated on the trunk.

The *minor criteria* (Table 235-1) are nonspecific and may be present in many clinical conditions.

To fulfill the Jones criteria, either two major criteria, or one major criterion and two minor criteria, *plus* evidence of an antecedent streptococcal infection are required. The latter may be provided by recovery of the organism on culture or by evidence of an immune response to one of the commonly measured group A streptococcal antibodies (e.g., anti-streptolysin O, anti-deoxyribonuclease B, anti-hyaluronidase). Since the accurate diagnosis of rheumatic fever has future medical and financial implications, the clinician is obligated to evaluate any patient completely until the suspected diagnosis is either established or excluded.

Both the clinical microbiology and the clinical immunology laboratories have important roles in confirming the diagnosis of rheumatic fever. An attempt should be made to recover the organism from a throat culture, although group A streptococci can be recovered from the upper respiratory tract of only 25 to 40% of patients at the time the diagnosis is made. If a rapid antigen detection test is used but is negative, a confirmatory throat culture must be performed. It is helpful to obtain two or three cultures from the throat at the time the diagnosis is suspected but before initiating antibiotic therapy in order to confirm the presence of the organism.

At least 80% of patients with acute rheumatic fever have an elevated anti-streptolysin O titer at presentation. If one employs two additional streptococcal antibody tests such as the anti-DNAse B or anti-hyaluronidase test, the percentage of patients who show evidence of a preceding group A streptococcal infection will rise to more than 95%. While an initially elevated titer is convincing, being able to demonstrate a rise in titer from the acute to the convalescent phase is a more reliable means of documenting the recent infection. If three antibody tests are done and there is no evidence of a preceding infection, the diagnosis must be seriously reconsidered.

TREATMENT

There are two necessary therapeutic approaches to patients with acute rheumatic fever: anti-streptococcal antibiotic therapy and therapy for the clinical manifestations of the disease. At the time of diagnosis, *all* patients with acute rheumatic fever should be treated as if they have a group A streptococcal infection, whether or not the organism is recovered by culture. In addition to the relatively large percentage of such patients who may have a negative throat culture at the time of diagnosis, others may have only a few organisms present in the throat. Conventional antibiotic treatment should be started immediately: a complete 10-day course in adults of either oral penicillin V (500 mg twice daily), or erythromycin (250 mg four times daily) for those with penicillin allergy. Many

choose intramuscular benzathine penicillin G (a single intramuscular injection of 1.2 million units) for the treatment of the presumed streptococcal infection; this will also serve as the first dose of secondary prophylaxis for the prevention of recolonization of the upper respiratory tract in the future. Intramuscular benzathine penicillin G has been reported to result in a transient elevation of the erythrocyte sedimentation rate, which can prove confusing in the acute phase of the disease.

Following the initial anti-streptococcal therapy, secondary prophylaxis should be initiated to prevent subsequent colonization of the upper respiratory tract with group A streptococci. Recommendations of the American Heart Association and of the World Health Organization are for intramuscular injection of 1.2 million units of benzathine penicillin G every 4 weeks or for oral penicillin V (250 mg twice daily) or oral sulfadiazine (1.0 g daily). Recent studies have shown that in those individuals who are at high risk for recurrence of rheumatic fever, intramuscular benzathine penicillin G given every 3 weeks is more effective in reducing the risk of recurrence. Since it is known that the risk of recurrence of rheumatic fever is highest during the first 5 years after the attack, secondary prophylaxis is always given for at least this period. After that the decision to continue or discontinue secondary prophylaxis is dependent upon whether the patient has documented rheumatic heart disease and whether the patient is at high risk of exposure to streptococci (e.g., students, school teachers, medical and military personnel, etc.). Many believe that those with documented recurrences and/or documented rheumatic valvular heart disease should receive secondary prophylaxis for life. The duration of prophylaxis is often individualized for specific patients.

Medical therapy for the manifestations of rheumatic fever depends on the clinical status of the patient. For adult patients with the arthritis of rheumatic fever, salicylates in doses escalating to 2 g four times daily are very effective and will result in marked clinical improvement, often within 12 h. When this prompt relief does not occur, one should reexamine the original diagnosis. Salicylates may be given for 4 to 6 weeks and gradually tapered so as to prevent a rebound. The erythrocyte sedimentation rate is one method for determining the rate of taper for salicylates. Usually this requires at least 2 weeks. There are no conclusive data to support using nonsteroidal anti-inflammatory drugs for acute rheumatic fever. There is no indication for the use of steroids (usually prednisone) solely for the treatment of the arthritis of rheumatic fever.

Most experienced physicians believe that there is a role for steroids in patients with severe carditis accompanied by congestive heart failure. However, neither salicylates nor glucocorticoids influence the future development of valvular heart disease. In adults, prednisone can be started in doses as high as 30 mg four times daily in especially severe cases, and, as the patient improves, salicylates can be added during the tapering of the steroid dose; this may require 4 to 6 weeks.

In the presence of congestive heart failure, conventional medical measures (Chap. 232) are indicated. In the past, patients with acute rheumatic fever were kept at complete bed rest for months. This is inappropriate unless there is a specific reason such as persistent active carditis or severe heart failure. Patients with arthritis will begin to feel better very soon after anti-inflammatory therapy with salicylates is begun. They may be released from bed rest but should not resume full activity until signs of inflammatory process have abated and the acute-phase reactants have returned to normal.

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236. VALVULAR HEART DISEASE - *Eugene Braunwald*

The role of physical examination in the evaluation of patients with valvular disease is also considered in Chap. 225; of electrocardiography inChap. 226; of echocardiography inChap. 227; and of cardiac catheterization and angiography in Chap. 228.

MITRAL STENOSIS

ETIOLOGY AND PATHOLOGY

Two-thirds of all patients with mitral stenosis (MS) are female. MS is generally rheumatic in origin; very rarely, it is congenital. Pure or predominant MS occurs in approximately 40% of all patients with rheumatic heart disease. In others, lesser degrees of MS may accompany mitral regurgitation (MR) and aortic valve lesions. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and developed nations, the incidence of MS is declining. In rheumatic stenosis the valve leaflets are diffusely thickened by fibrous tissue and/or calcific deposits. The mitral commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid, and these changes, in turn, lead to narrowing at the apex of the funnel-shaped (fish-mouth) valve. Although the initial insult to the mitral valve is rheumatic, the later changes may be a nonspecific process resulting from trauma to the valve caused by altered flow patterns due to the initial deformity. Calcification of the stenotic mitral valve immobilizes the leaflets and narrows the orifice further. Thrombus formation and arterial embolization may arise from the calcific valve itself, but more frequently arise from the dilated left atrium (LA) in patients with atrial fibrillation (AF).

PATHOPHYSIOLOGY

In normal adults the mitral valve orifice is 4 to 6 cm^2. In the presence of significant obstruction, i.e., when the orifice is less than approximately 2 cm^2, blood can flow from theLA to the left ventricle (LV) only if propelled by an abnormally elevated left atrioventricular pressure gradient (seeFig. 228-2), the hemodynamic hallmark ofMS. When the mitral valve opening is reduced to 1 cm^2, a LA pressure of approximately 25 mmHg is required to maintain a normal cardiac output (CO). The elevated pulmonary venous and pulmonary arterial (PA) wedge pressures reduce pulmonary compliance, contributing to exertional dyspnea. The first bouts of dyspnea are usually precipitated by clinical events that increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure (see below). To assess the severity of obstruction, both the transvalvular pressure gradient and the flow rate must be measured (Chap. 228). The latter depends not only on the CO but on the heart rate as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of CO, tachycardia augments the transvalvular gradient and elevates further the LA pressure. (Similar considerations apply to the tricuspid valve.)

TheLVdiastolic pressure is normal in isolatedMS; coexisting aortic valve disease, systemic hypertension,MR, ischemic heart disease, and perhaps the residua of damage produced by rheumatic myocarditis are sometimes responsible for elevations that reflect impaired LV function and/or reduced LV compliance. LV dysfunction, as reflected in

reduced LV ejection fraction (EF), occurs in about one-fourth of patients with severe, chronic MS and may be a consequence of prolonged reduction of preload and/or extension of scarring from the valve into the adjacent myocardium. In pure MS and sinus rhythm, the elevatedLA andPA wedge pressures exhibit a prominent atrial contraction (*a* wave) and a gradual pressure decline after mitral valve opening (*y* descent) (seeFig. 228-4). In severe MS and whenever the pulmonary vascular resistance is significantly increased, the pulmonary arterial pressure (PAP) is elevated even when the patient is at rest, and in extreme cases it may approach the systemic arterial pressure. Further elevations of LA, PA wedge, and PAP occur during exercise. When the PA systolic pressure exceeds approximately 50 mmHg in patients with MS, or for that matter with any lesion affecting the left side of the heart, the increased right ventricle (RV) afterload impedes the emptying of this chamber, and the RV end-diastolic pressure and volume usually rise.

Cardiac Output The hemodynamic response to mitral obstruction ranges from a normalCO and a high left atrioventricular pressure gradient to a markedly reduced CO and low transvalvular pressure gradient. In most patients with moderateMS, the CO is normal or almost so at rest but rises subnormally during exertion. In patients with severe MS, particularly those in whom the pulmonary vascular resistance is strikingly elevated, the CO is subnormal at rest and may fail to rise or may even decline during activity.

Pulmonary Hypertension The clinical and hemodynamic features ofMS are influenced importantly by the level of thePAP. Pulmonary hypertension results from (1) passive backward transmission of the elevatedLApressure; (2) pulmonary arteriolar constriction, which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); (3) interstitial edema in the walls of the small pulmonary vessels; and (4) organic obliterative changes in the pulmonary vascular bed. Severe pulmonary hypertension results in tricuspid regurgitation (TR) and pulmonary incompetence as well as right-sided heart failure. The changes in the pulmonary vascular bed also may be considered to exert a protective effect; the elevated precapillary resistance reduces the likelihood of symptoms of pulmonary congestion by reducing the surge of blood into the pulmonary capillary bed during activity. However, this protection occurs at the expense of a reduced, fixedCO.

SYMPTOMS

In temperate climates the latent period between the initial attack of rheumatic carditis (in the increasingly rare circumstances in which a history of one can be elicited) and the development of symptoms due toMS is generally about two decades; most patients begin to experience disability in the fourth decade. Studies carried out before the development of mitral valvotomy revealed that once a patient with MS became seriously symptomatic, the disease progressed continuously to death within 2 to 5 years. In economically deprived areas, in tropical and subtropical climates, particularly on the Indian subcontinent, in Central America, and in the Middle East, MS tends to progress more rapidly and frequently causes serious symptoms in patients less than the age of 20 years. In contrast, slowly progressive MS in the elderly is being recognized with increasing frequency in the United States and western Europe.

When valvular obstruction is mild, the physical signs ofMS may be present without

symptoms. However, even in patients whose mitral orifices are large enough to accommodate a normal blood flow with only mild elevations ofLApressure, marked elevations of this pressure leading to dyspnea and cough may be precipitated by severe exertion, excitement, fever, severe anemia, paroxysmal tachycardia, sexual intercourse, pregnancy, and thyrotoxicosis. As MS progresses, lesser stresses precipitate dyspnea, and the patient becomes limited in daily activities. The redistribution of blood from the dependent portions of the body to the lungs, which occurs when the recumbent position is assumed, leads to orthopnea and paroxysmal nocturnal dyspnea. *Pulmonary edema* develops when there is a sudden surge in flow across a markedly narrowed mitral orifice. When moderately severe MS has existed for several years, *atrial arrhythmias* -- premature contractions, paroxysmal tachycardia, flutter, andAF -- occur with increasing frequency. The rapid ventricular rate associated with untreated or inadequately treated AF is frequently responsible for acute exacerbations of dyspnea. The development of permanent AF often marks a turning point in the patient's course and is generally associated with acceleration of the rate at which symptoms progress.

Hemoptysis (Chap. 33) results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension. It occurs most frequently in patients who have elevatedLApressures without markedly elevated pulmonary vascular resistances and is almost never fatal.

As the severity ofMSprogresses and the pulmonary vascular resistance rises or when tricuspid stenosis (TS) orTRdevelop, symptoms secondary to pulmonary congestion sometimes diminish, and the episodes of acute pulmonary edema and hemoptysis may become reduced in frequency and severity. The elevation of pulmonary vascular resistance further increasesRVsystolic pressure, leading to RV failure, fatigue, abdominal discomfort due to hepatic congestion, and edema.

Recurrent pulmonary emboli (Chap. 261), sometimes with infarction, are an important cause of morbidity and mortality late in the course ofMS. *Pulmonary infections*, i.e., bronchitis, bronchopneumonia, and lobar pneumonia, commonly complicate untreated MS. *Infective endocarditis* (Chap. 126) is rare in pure MS but is not uncommon in patients with combined MS andMR. *Chest pain* occurs in about 10% of patients with severe MS; it may be due to pulmonary hypertension or myocardial ischemia secondary to accompanying coronary atherosclerosis.

Pulmonary Changes In addition to the aforementioned changes in the pulmonary vascular bed, fibrous thickening of the walls of the alveoli and pulmonary capillaries occurs commonly inMS. The vital capacity, total lung capacity, maximal breathing capacity, and oxygen uptake per unit of ventilation are reduced (Chap. 250), and the latter fails to rise normally during exertion. Pulmonary compliance falls further as pulmonary capillary pressure rises during exercise. In some patients, airway resistance is abnormally increased. These alterations in pulmonary mechanics contribute to an increase in the work of breathing and dyspnea. The diffusing capacity may be reduced, particularly during exertion, as a result of structural changes in the diffusing surface and reduction of the pulmonary capillary blood volume. These changes in the lungs are due, in part, to increased transudation of fluid from the pulmonary capillaries into the interstitial and alveolar spaces. However, the increased capacity of the pulmonary lymphatic system to drain excess fluid retards the development of alveolar edema.

Thrombi and Emboli *Thrombi* may form in the left atria, particularly in the enlarged atrial appendages of patients withMS. If they *embolize*, they do so most commonly to the brain, kidneys, spleen, and extremities. Embolization occurs much more frequently in patients withAF or other unstable atrial arrhythmias, in older patients, and in those with a reduced cardiac output. However, systemic embolization may be the presenting complaint in otherwise asymptomatic patients with mild MS. At operation, thrombi are not found more frequently in theLA of patients with a past history of embolization than in those without this complication, indicating that usually the freshly formed clots are the ones that dislodge. Patients who have had one or more systemic emboli have an increased predilection for further embolic episodes. Rarely, a large pedunculated thrombus or a free-floating clot may suddenly obstruct the stenotic mitral orifice. Such "ball valve" thrombi produce syncope, angina, and changing auscultatory signs with alterations in position, findings that resemble those produced by an LA myxoma (Chap. 240).

PHYSICAL FINDINGS (See also Chap. 225)

Inspection and Palpation In patients with severeMS, there may be a malar flush with pinched and blue facies. In patients with sinus rhythm and severe pulmonary hypertension or associatedTS, the jugular venous pulse reveals prominent *a* waves due to vigorous right atrial systole. In patients withAF, the jugular pulse reveals only a single expansion during systole (*c-v* wave). The systemic arterial pressure is usually normal or slightly low. ARV tap along the left sternal border signifies an enlarged RV. A diastolic thrill is frequently present at the cardiac apex, particularly with the patient in the left lateral recumbent position.

Auscultation The first heart sound (S_1) is generally accentuated and snapping, and since the mitral valve does not close until theLVpressure reaches the level of the elevatedLApressure, this sound is often slightly delayed, causing a prolonged Q-S_1interval on the phonocardiogram. The pulmonary component of the second heart sound (P_2) is often accentuated, and the two components of the second heart sound (S_2) are closely split. A pulmonary systolic ejection click may be heard in patients with severe pulmonary hypertension. The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex but also may be easily heard along the left sternal edge or at the base of the heart. This sound generally follows the sound of aortic valve closure (A_2) by 0.05 to 0.12 s; that is, it follows P_2. Since the OS occurs when the LV pressure falls below the LA pressure, the time interval between A_2 and OS varies inversely with the severity of theMS. The intensities of the OS and S_1correlate with the mobility of the anterior mitral leaflet.

TheOS is followed by a low-pitched, rumbling, diastolic murmur, heard best at the apex with the patient in the left lateral recumbent position (seeFig. 225-4). It is accentuated by mild exercise (e.g., a few rapid sit-ups) carried out just before auscultation. In general, the duration of this murmur correlates with the severity of the stenosis. In patients with sinus rhythm, the murmur often reappears or becomes reaccentuated during atrial systole, as atrial contraction reelevates the rate of blood flow across the narrowed orifice. Soft (grade I or II/VI) systolic murmurs are commonly heard at the apex or along the left sternal border in patients with pure MSand do not necessarily signify the

presence ofMR. Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS andRVfailure.

Associated Lesions With severe pulmonary hypertension, a pansystolic murmur produced by functionalTR may be audible along the left sternal border. Characteristically, this murmur is accentuated by inspiration and diminishes during forced expiration (Carvallo's sign) or during performance of the Valsalva maneuver; it should not be confused with the apical pansystolic murmur ofMR.

The recognition of associatedMR is of considerable clinical importance in patients withMS. A presystolic murmur and an accentuated S_1 speak against the presence of serious associated MR, but when the $S_1$and/or theOS are soft or absent in a patient with mitral valve disease who also has an apical systolic murmur, it is likely that significant MR and/or serious calcification of the deformed mitral valve leaflets are present. A third heart sound (S_3) at the apex often signifies that the MR is serious; this sound is generally duller, is lower pitched, and follows the OS. Occasionally, in patients with pure MS, physical signs may falsely suggest MR. ARVS_3 and an enlarged RV that forms the cardiac apex may give the erroneous impression ofLVenlargement. The rumbling diastolic murmur of MS become less prominent or may even disappear and be replaced by the systolic murmur of functionalTR, which is mistaken for MR. WhenCO is markedly reduced in a patient with MS, the typical auscultatory findings, including the diastolic rumbling murmur, may not be detectable (silent MS), but they may reappear as compensation is restored. AssociatedTS also tends to obscure many of the physical signs of MS.

The Graham Steell murmur of pulmonary regurgitation (PR), a high-pitched, diastolic, decrescendo blowing murmur along the left sternal border, results from dilatation of the pulmonary valve ring and occurs in patients with mitral valve disease and severe pulmonary hypertension. This murmur may be indistinguishable from the more common murmur produced by aortic regurgitation (AR), except that it is rarely audible at the second right intercostal space and may disappear after successful surgical treatment of theMS.

LABORATORY EXAMINATION

Electrocardiogram InMS and sinus rhythm, the P wave usually suggestsLAenlargement (see Fig. 226-10). It may become tall and peaked in lead II and upright in lead V_1 when severe pulmonary hypertension orTScomplicates MS and right atrial (RA) enlargement occurs. The QRS complex is usually normal. However, with severe pulmonary hypertension, right axis deviation andRVhypertrophy are often present.

Roentgenogram The earliest changes are straightening of the left border of the cardiac silhouette, prominence of the main pulmonary arteries, dilatation of the upper lobe pulmonary veins, and backward displacement of the esophagus by an enlargedLA. In severeMS, however, all chambers and vessels upstream to the narrowed valve are prominent, including both atria, pulmonary arteries and veins,RV, and superior vena cava. Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and midlung fields and that result from distention of interlobular septa and

lymphatics with edema when the resting mean LA pressure exceeds approximately 20 mmHg.

Echocardiogram (See also Chap. 227) This is the most sensitive and specific noninvasive method for diagnosing MS. Transthoracic two-dimensional color flow Doppler echocardiographic imaging and Doppler ultrasound provide critical information, including an estimate of the transvalvular gradient and of mitral orifice size, the presence and severity of accompanying MR, the extent of restriction of valve leaflets, their thickness, and the degree of distortion of the subvalvular apparatus, and the anatomic suitability for balloon mitral valvotomy. In addition, echocardiography provides an assessment of the size of the cardiac chambers, an estimation of the PAP, and an indication of the presence and severity of associated TR and PR. Transesophageal echocardiography provides superior images and should be employed when transthoracic imaging is inadequate for guiding therapy.

DIFFERENTIAL DIAGNOSIS

Significant MR may also be associated with a prominent diastolic murmur at the apex, but this murmur commences slightly later in patients with MR than in patients with MS, and there is often clear-cut evidence of LV enlargement. An apical pansystolic murmur of at least grade III/VI intensity as well as an S_3 should arouse the suspicion of significant associated MR. Similarly, the apical middiastolic murmur associated with AR (Austin Flint murmur) may be mistaken for MS. TS, which occurs rarely in the absence of MS, may mask many of the clinical features of MS. Echocardiography is particularly useful in detecting MS in patients who have or are suspected of having other valve lesions and in defining the severity of the various lesions.

Primary pulmonary hypertension (Chap. 260) results in a number of the clinical and laboratory features of MS. It occurs most frequently in young women. However, the OS and diastolic rumbling murmur are absent, and the pulmonary artery wedge and LA pressures are normal, as is the size of the LA on echocardiography. *Atrial septal defect* (Chap. 234) also may be mistaken for MS; in both conditions there is often clinical, electrocardiographic, and roentgenographic evidence of RV enlargement and accentuation of the pulmonary vascularity. The widely split S_2 of atrial septal defect may be confused with the mitral OS, and the diastolic flow murmur across the tricuspid valve may be mistaken for the mitral diastolic murmur. However, the absence of LA enlargement and of Kerley B lines and the demonstration of fixed splitting of S_2 favor atrial septal defect over MS.

Left atrial myxoma (Chap. 240) may obstruct LA emptying, causing dyspnea, a diastolic murmur, and hemodynamic changes resembling those of MS. However, patients with an LA myxoma often have features suggestive of a systemic disease, such as weight loss, fever, anemia, systemic emboli, and elevated erythrocyte sedimentation rate and serum IgG concentration. Usually an OS is not audible, and the auscultatory findings may change markedly with body position. The diagnosis can be established by the demonstration of a characteristic echo-producing mass in the LA with two-dimensional echocardiography.

CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY

Left heart catheterization is useful for clarifying the picture when there is a discrepancy between clinical and echocardiographic findings (seeFig. 228-2). It is helpful in assessing associated lesions such as aortic stenosis (AS) andAR. Catheterization and coronary arteriography are not usually necessary to aid in the decision about surgery in younger patients with typical findings of severe obstruction on clinical examination and echocardiography. In males over 45 years of age, females over 55 years of age, and younger patients with coronary risk factors, especially those with positive noninvasive stress tests for myocardial ischemia, coronary angiography is usually advisable preoperatively to detect patients with critical coronary obstructions that should be bypassed at the time of operation. Catheterization andLVangiography are also indicated in most patients who have undergone balloon mitral valvotomy or previous mitral valve operations and who have redeveloped serious symptoms.

TREATMENT

In the asymptomatic adolescent with mitral valve disease, penicillin prophylaxis ofb-hemolytic streptococcal infections (Chap. 235) and prophylaxis for infective endocarditis (Chap. 126) are important. In symptomatic patients, some improvement usually occurs with restriction of sodium intake and maintenance doses of oral diuretics. Digitalis glycosides do not alter the hemodynamics and usually do not benefit patients with pureMS and sinus rhythm but are necessary for slowing the ventricular rate of patients withAF. Small doses of beta blockers (e.g., atenolol 25 to 50 mg/d) may be added when cardiac glycosides fail to control ventricular rate in such patients. Anticoagulants should be administered for at least 1 year to patients with MS who have suffered systemic and/or pulmonary embolization and permanently to those with AF.

IfAF is of relatively recent origin in a patient whoseMS is not severe enough to warrant balloon mitral valvotomy or surgical valvotomy, reversion to sinus rhythm pharmacologically or by means of electrical countershock is indicated. Usually this reversion should be undertaken after the patient has had 3 weeks of anticoagulant treatment. Conversion to sinus rhythm is rarely helpful in patients with severe MS, particularly those in whom theLA is especially enlarged or in whom AF has been present for more than 1 year, since sinus rhythm is rarely sustained.

Mitral Valvotomy Unless there is a specific contraindication, mitral valvotomy is indicated in the symptomatic patient with isolatedMS whose effective orifice is less than approximately 1.0 cm^2/m^2body surface area, or <1.6 cm^2 in normal-sized adults. Mitral valvotomy can be carried out by two techniques: percutaneous balloon mitral valvotomy and surgical valvotomy. In balloon mitral valvotomy (Figs. 236-1 and236-2), a catheter is directed into theLA after transseptal puncture and a balloon (Inoue balloon) is directed across the valve and inflated in the valvular orifice. This has become the procedure of choice for patients with uncomplicated MS.

An "open" valvotomy with cardiopulmonary bypass is usually preferable to closed valvotomy. In addition to opening the valve commissures, it is important to loosen any subvalvular fusion of papillary muscles and chordae tendineae and to remove large deposits of calcium, thereby improving valvular function, as well as to remove atrial thrombi.

Valvotomy, whichever technique is used, usually results in striking symptomatic and hemodynamic improvement and prolongs survival. In uncomplicated cases, the mortality rate is<2%. However, there is no evidence that the procedure improves the prognosis of patients with slight or no functional impairment unless they develop severe pulmonary hypertension on exertion. Therefore, unless recurrent systemic embolization has occurred, valvotomy is *not* recommended for patients who are entirely asymptomatic, regardless of hemodynamic findings. When there is little symptomatic improvement after valvotomy, it is likely that the procedure was ineffective, that it inducedMR, or that associated valvular or myocardial disease was present. The recurrence of symptoms several years after what appeared to be a satisfactory initial result is usually due to an inadequate valvotomy, but progression of other valvular lesions, mitral restenosis, or some combination of these conditions also may be responsible. About half of all patients undergoing mitral valvotomy require reoperation by 10 years. In the pregnant patient withMS, valvotomy should be carried out if pulmonary congestion occurs despite intensive medical treatment.

In patients withMS and significant associatedMR, those in whom the valve has been severely distorted by previous transcatheter or operative manipulation, or those in whom the surgeon does not find it possible to improve valve function significantly, mitral valve replacement (MVR) may have to be carried out. Since the operative mortality rate of isolated MVR is still approximately 6% (Table 236-1), and since there are long-term complications of valve replacement, patients in whom preoperative evaluation suggests the possibility that MVR may be required should be operated on only if they have critical MS, i.e., an orifice <0.6 cm^2/m^2body surface area and are in New York Heart Association class III, i.e., symptomatic with ordinary activity, despite optimal medical therapy. The overall 10-year survival of surgical survivors is approximately 70%. Long-term prognosis is worse in older patients and those with marked disability and striking depression of the cardiac index preoperatively.

MITRAL REGURGITATION

ETIOLOGY

Chronic rheumatic heart disease is the cause of severeMR in about one-third of cases. In contrast toMS, rheumatic MR occurs more frequently in males. The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. Mitral valve prolapse (MVP), an important cause of MR, is considered in the next section. MR also may occur as a congenital anomaly (Chap. 234), most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). MR may occur with fibrosis of a papillary muscle in patients with healed myocardial infarction as well as in patients with infarction involving the base of a papillary muscle. Transient MR also may occur during periods of ischemia involving a papillary muscle or the adjacent myocardium and may accompany bouts of angina pectoris. MR may occur with markedLVenlargement of any cause in which dilatation of the mitral annulus and lateral displacement of the papillary muscles interfere with coaptation of the valve leaflets. In hypertrophic cardiomyopathy, the anterior leaflet of the mitral valve is displaced anteriorly during systole, leading to regurgitation (Chap. 238). Calcification of the mitral annulus of unknown cause,

presumably degenerative, which occurs most commonly in elderly women, also can be responsible for significant MR. Acute MR may occur secondary to infective endocarditis involving the valve or chordae tendineae, in acute myocardial infarction with rupture of a papillary muscle or one of its heads, as a consequence of trauma, or after chordal rupture.

Regardless of cause, severeMR is often progressive, since enlargement of theLAplaces tension on the posterior mitral leaflet, pulling it away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, the dilatation of theLVincreases the regurgitation, which in turn enlarges the LA and LV further, causing chordal rupture and resulting in a vicious circle; hence the aphorism, "mitral regurgitation begets mitral regurgitation."

PATHOPHYSIOLOGY

The resistance toLVemptying is reduced in patients withMR. As a consequence, the LV is decompressed into theLAduring ejection, and with the reduction in LV size there is a rapid decline in LV tension. The initial compensation to acute MR is more complete LV emptying. However, LV volume increases progressively as the severity of the regurgitation increases and as LV function deteriorates. This increase in LV volume is often accompanied by a depressed forwardCO. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced profoundly by the extent of LV dilatation.

The *v* wave in the LApressure pulse is usually prominent (seeFig. 228-3). During early diastole, as the distended LA empties, there is a particularly rapid *y* descent (as long as there is no associatedMS). In chronicMR, there is often an increase inLVcompliance, so that LV volume rises with little elevation in LV diastolic pressure. The effective (forward)CO is usually reduced in seriously symptomatic patients. A brief, early diastolic atrioventricular pressure gradient may occur in patients with pure MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

The prompt appearance of contrast material in theLA after its injection into theLVsignifies the presence ofMR. The regurgitant volume can be measured by determining the difference between the total LV stroke volume, estimated angiocardiographically, and the effective forward stroke volume determined by the Fick method (Chap. 228). In severe cases, as much as 50% of the total LV stroke volume regurgitates with each beat. Qualitative, but clinically useful, estimates of the severity of regurgitation may be made by observation on cineangiograms of the degree of LA opacification after the injection of contrast material into the LV. Color flow Doppler imaging is most commonly used for this purpose (see below).

The compliance, i.e., the pressure-volume relationship, of theLA and pulmonary venous bed affects the clinical picture. Patients with acuteMRusually have *normal or reduced compliance*, little enlargement of the LA, but marked elevation of the LA pressure, particularly of the *v* wave. Pulmonary edema is common. Patients with a *marked increase in LA compliance* are at the opposite end of the spectrum, having long-standing, severe MR, marked enlargement of the LA, and normal or only slightly elevated LA and PApressures. These patients usually complain of severe fatigue and

exhaustion secondary to a lowCO, while symptoms resulting from pulmonary congestion are less prominent;AF is almost invariably present. Most common are patients whose clinical and hemodynamic features are between those in the two aforementioned groups, with variable degrees of enlargement of the LA and with significant elevation of the LA pressure. Symptoms are secondary to a combination of reduced forward CO and pulmonary congestion.

SYMPTOMS

Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic, severeMR. Systemic embolism occurs less frequently than inMS. Right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, andTR, occurs in patients with MR who have associated pulmonary vascular disease and marked pulmonary hypertension. In patients with acute, severe MR,LVfailure with acute pulmonary edema is common.

PHYSICAL FINDINGS

The arterial pressure is usually normal, and in patients with severeMR the arterial pulse may show a sharp upstroke. The jugular venous pulse shows abnormally prominent *a* waves in patients with sinus rhythm and marked pulmonary hypertension and prominent *v* waves in those with accompanying severeTR. A systolic thrill is often palpable at the cardiac apex, theLV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave, and the apex beat is often displaced laterally. AnRV tap and the shock of pulmonary valve closure may be palpable in patients with marked pulmonary hypertension.

Auscultation The $S_1$is generally absent, soft, or buried in the systolic murmur; indeed, an accentuated mitral closure sound is useful in excluding severeMR. In patients with severe MR, the aortic valve may close prematurely, resulting in wide splitting of the S_2. AnOSindicates associatedMS but does not exclude predominant regurgitation. A low-pitched S_3occurring 0.12 to 0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of theLV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets and is an important auscultatory feature of severe MR. The absence of an S_3indicates that if MR exists, it may not be severe. The S_3 may be followed by a short, rumbling, diastolic murmur, even in the absence of MS. A fourth heart sound (S_4) is often audible in patients with acute, severe MR of recent onset who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR but is present in patients with sinus rhythm and associated MS.

A systolic murmur of at least grade III/VI intensity, is the most characteristic auscultatory finding in severeMR. It is usually holosystolic (see Fig. 225-4), but it may be decrescendo and cease in late systole in patients with acute, severe MR when the tall *v* wave in the LApressure pulse reduces the late systolicLV-LA (reverse) pressure gradient. In MR due to papillary muscle dysfunction orMVP, the systolic murmur commences in midsystole (see below). The systolic murmur is usually most prominent at the apex and radiates into the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet, the regurgitant jet strikes

the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and therefore may be confused with the murmur ofAS. In patients with ruptured chordae tendineae the systolic murmur may have a cooing or "sea gull" quality, while a flail leaflet may cause a murmur with a musical quality. The systolic murmur of MR is intensified by isometric strain but is reduced during the Valsalva maneuver.

LABORATORY EXAMINATION

Electrocardiogram In patients with sinus rhythm there is evidence ofLAenlargement, butRAenlargement also may be present when pulmonary hypertension is severe. Chronic, severeMR is generally associated withAF. In many patients there is no clear-cut electrocardiographic evidence of enlargement of either ventricle. In others the signs ofLVhypertrophy are present.

Roentgenogram The LAand LVare the dominant chambers; in chronic cases, the former may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing combinedMR andMS. Calcification of the mitral annulus may be visualized.

Echocardiogram Color flow Doppler imaging is the most accurate noninvasive technique for the detection and estimation ofMR. Two-dimensional echocardiography is useful for assessingLVfunction from end systolic and end-diastolic volumes andEF. TheLA is usually enlarged and/or exhibits increased pulsations; the LV may be hyperdynamic. Findings that help to determine the etiology of MR can often be identified by two-dimensional echocardiography. Transesophageal imaging provides greater detail than transthoracic imaging. With ruptured chordae tendineae or a flail leaflet, coarse, errative motion of the involved leaflets may be noted. Vegetations associated with infective endocarditis, incomplete coaptation of the anterior and posterior mitral leaflets, and annular calcification, as well as MR secondary to LV dilatation, aneurysm, or dyskinesis may be recognized. The echocardiogram in patients withMVP is described in the next section.

TREATMENT

Medical The nonsurgical management of patients with severeMRbegins with restricting those physical activities that regularly produce dyspnea and excessive fatigue, reducing sodium intake, and enhancing sodium excretion with the appropriate use of diuretics (Chap. 232). Vasodilators and digitalis glycosides increase the forward output of the failingLV. Intravenous nitroprusside or nitroglycerin to reduce afterload and thereby the volume of regurgitant flow are useful in stabilizing patients with acute and/or severe MR. Angiotensin-converting enzyme inhibitors are useful in the treatment of chronic MR. The same considerations as in patients withMS apply to the reversion ofAF to sinus rhythm. In the late stages of heart failure anticoagulants and leg binders are used to diminish the likelihood of venous thrombi and pulmonary emboli.

Surgical In the selection of patients with severeMR for surgical treatment, the chronic,

often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with valve reconstruction or replacement. Patients with MR who are asymptomatic or who are limited only during strenuous exertion are not considered to be candidates for surgical treatment, since their condition may remain stable for many years. By contrast, unless there are contraindications, surgical treatment should be offered to patients with severe MR whose limitations do not allow full time employment or the performance of normal household activities despite optimal medical management. Surgical treatment of severe MR is indicated even for asymptomatic patients or those with mild symptoms whenLVdysfunction is progressive, with LV ejection fraction declining below 60% and/or end-systolic cavity dimension on echocardiography rising above 50 mm. In patients with impaired LV function, the risk of surgery rises sharply, the recovery of LV performance is incomplete, and the long-term survival is reduced (Fig. 236-3). However, conservative management has little to offer these patients, so operative treatment may be indicated even at an advanced stage of the disease; and occasionally, the clinical and hemodynamic improvement that follows surgical treatment of patients with advanced disease is dramatic. Though most patients who survive surgery appear to be greatly improved, some degree of myocardial dysfunction may persist.

When surgical treatment is contemplated, left-sided heart catheterization and angiocardiography may be helpful in confirming the presence of severeMR in patients in whom there is a discrepancy between the clinical picture and the echocardiographic findings; these procedures may also aid in detecting and assessing the severity of associated valve lesions. Importantly, coronary arteriography identifies patients who require concomitant coronary revascularization.

Surgical treatment ofMR, especially that caused by valves that are markedly deformed, with shrunken, calcified leaflets secondary to rheumatic fever, requiresMVR with a prosthesis. However, in an increasing fraction of patients, particularly those with severe annular dilatation, flail leaflets,MVP, ruptured chordae, or infective endocarditis, reconstruction of the mitral valve apparatus (mitral valvuloplasty) and/or mitral annuloplasty with an annuloplasty ring may be successful. Valve reconstruction should be carried out whenever feasible since the operative risk is about half (~3%) of that associated with MVR (Table 236-1). Also, reconstruction spares the patient the long-term adverse consequences of valve replacement (i.e., thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses). In addition, by preserving the integrity of the papillary muscles and subvalvular apparatus, mitral valvuloplasty maintainsLVfunction.

MITRAL VALVE PROLAPSE

MVP, also variously termed the *systolic click-murmur syndrome*, *Barlow's syndrome*, *floppy-valve syndrome*, and *billowing mitral leaflet syndrome*, is a relatively common, but highly variable, clinical syndrome resulting from diverse pathogenic mechanisms of the mitral valve apparatus. Among these are excessive or redundant mitral leaflet tissue, which is commonly involved with myxomatous degeneration and greatly increased concentration of acid mucopolysaccharide. It is a frequent finding in patients with heritable disorders of connective tissue, including the Marfan syndrome (Chap.

351), osteogenesis imperfecta, and the Ehler-Danlos syndrome. In most patients with MVP, however, myxomatous degeneration is confined to the mitral (or less commonly the tricuspid or aortic) valves without other clinical or pathologic manifestations of disease; the posterior leaflet is usually more affected than the anterior, and the mitral valve annulus is often greatly dilated. In many patients, elongated redundant chordae tendineae cause or contribute to the regurgitation.

In most patients withMVP, the cause is unknown, but in some it appears to be a genetically determined collagen tissue disorder. A reduction in the production of type III collagen has been incriminated, and electron microscopy has revealed fragmentation of collagen fibrils. MVP may be associated with thoracic skeletal deformities similar to but not as severe as those in the Marfan syndrome, including a high arched palate and alterations of the chest and thoracic spine, including the so-called straight back syndrome. MVP also may occur as a sequel of acute rheumatic fever, in ischemic heart disease, and in cardiomyopathies, as well as in 20% of patients with ostium secundum atrial septal defect.

MVPmay lead to excessive stress on the papillary muscles, which in turn leads to dysfunction and ischemia of the papillary muscles and subjacent ventricular myocardium; rupture of chordae tendineae and progressive annular dilatation and calcification also contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious cycle. The electrocardiographic changes (see below) and ventricular arrhythmias appear to result from regional ventricular dysfunction related to increased stress placed on the papillary muscles.

CLINICAL FEATURES

MVPis more common in females. It affects individuals in a wide age range but most commonly between the ages of 14 and 30 years. The clinical course is often benign. MVP may also be observed in older (>50 years) patients, often males, and in themMR is more often severe and requires surgical treatment. There is an increased familial incidence for some patients, suggesting an autosomal dominant form of inheritance. MVP encompasses a broad spectrum of severities in patients, ranging from only a systolic click and murmur and mild prolapse of the posterior leaflet of the mitral valve to severe MR due to chordal rupture and massive prolapse of both leaflets. In many patients, this condition progresses over years or decades.

Most patients are asymptomatic and remain so for their entire lives. However,MVP is now the most common cause of isolated severeMRrequiring surgical treatment in North America. Arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia, have been reported and may cause palpitations, light-headedness, and syncope. Sudden death has been noted but is a very rare complication. Many patients have chest pain that is difficult to evaluate. It is often substernal, prolonged, poorly related to exertion, and rarely resembles typical angina pectoris. Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported. Infective endocarditis may occur in patients with MR associated with MVP.

Auscultation The most important finding is the mid- or late (nonejection) systolic click, which occurs 0.14 s or more after the S_1 and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximum excursion. Systolic clicks may be multiple and may be followed by a high-pitched, late systolic crescendo-decrescendo murmur, which occasionally is "whooping" or "honking," and is heard best at the apex. The click and murmur occur earlier with standing, during the strain of the Valsalva maneuver, and any intervention that decreasesLVvolume, exaggerating the propensity of mitral leaflet prolapse. Conversely, squatting and isometric exercise, which increase LV volume, diminish mitral prolapse, and the click-murmur complex is delayed and may even disappear. Some patients have a midsystolic click without the murmur; others have the murmur without a click. Still others have both sounds at different times.

LABORATORY EXAMINATION

The *electrocardiogram* most commonly is normal but may show biphasic or inverted T waves in leads II, III, and aVF, and occasionally supraventricular or ventricular premature contractions. *Two-dimensional echocardiography* is particularly effective in identifying the abnormal position and prolapse of the mitral valve leaflets; a useful echocardiographic definition ofMVP is systolic displacement (in the parasternal view) of the mitral valve leaflets by at least 2 mm into theLAsuperior to the plane of the mitral annulus. Thickening of the mitral valve leaflets identifies a subgroup of patients at higher risk of infective endocarditis and the development of severeMR. Prolapse of the tricuspid and/or aortic valve may be found. *Color-imaging* and *Doppler studies* are helpful in revealing and evaluating accompanying MR. *Angiocardiography* generally shows prolapse of the posterior and sometimes of both mitral valve leaflets.

TREATMENT

The management of patients withMVPconsists of reassurance of the asymptomatic patient without severeMR or arrhythmias and the prevention of infective endocarditis with antibiotic prophylaxis in patients with a systolic murmur and/or thickening of mitral valve leaflets on endocardiography. Beta blockers have been found to relieve chest pain. If symptomatic tachyarrhythmias have occurred, antiarrhythmic agents as dictated by electrophysiologic studies should be administered. If the patient is symptomatic from severe MR, mitral valve repair (or rarely, replacement) is indicated. Antiplatelet aggregation agents such as aspirin should be given to patients with transient ischemic attacks, and if these are not effective, anticoagulants should be used.

AORTIC STENOSIS

ASoccurs in about one-fourth of all patients with chronic valvular heart disease; approximately 80% of adult patients with symptomatic valvular AS are male.

ETIOLOGY

ASin adults may be congenital in origin, it may be secondary to rheumatic inflammation of the aortic valve, or it may be due to degenerative calcification of the aortic cusps of unknown cause. The *congenitally affected valve* may already be stenotic at birth (Chap.

234) and may become progressively more fibrotic, calcified, and stenotic. In other cases the valve may be congenitally deformed, usually bicuspid, without serious narrowing of the aortic orifice during childhood; its abnormal architecture makes its leaflets susceptible to otherwise ordinary hemodynamic stresses, which ultimately lead to valvular thickening, calcification, increased rigidity, and narrowing of the aortic orifice.

Rheumatic endocarditis of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid valve. This condition in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time the obstruction toLVoutflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine the etiology of the underlying process. RheumaticAS is almost always associated with rheumatic involvement of the mitral valve. A rheumatic etiology is favored by a history of active rheumatic fever and by associated severeAR.

*Age-related degenerative calcific**AS*(also known as senile or sclerocalcific AS) is now the most common cause of AS in adults in North America and Western Europe. About 30% of persons>65 years exhibit aortic valve sclerosis, many of whom have a systolic murmur of AS but without obstruction, while an additional 2% exhibit frank stenosis.

OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

Besides valvularAS, three other lesions may be responsible for obstruction toLVoutflow.

1. *Hypertrophic cardiomyopathy* (Chap. 238). This condition is characterized by marked hypertrophy of theLV and involves in particular the interventricular septum; it may cause subaortic obstruction.

2. *Discrete congenital subvalvular**AS*(Chap. 234). This congenital anomaly is produced by either a membranous diaphragm or a fibrous ridge just below the aortic valve.

3. *Supravalvular**AS*(Chap. 234). This uncommon congenital anomaly is produced by narrowing of the ascending aorta or by a fibrous diaphragm with a small opening just above the aortic valve.

PATHOPHYSIOLOGY

The obstruction toLVoutflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilatation and reduction of stroke volume. However, in patients the obstruction may be present at birth and/or increases gradually over the course of many years, and LV output is maintained by the presence of concentric LV hypertrophy. This serves as a useful compensatory mechanism because it reduces toward normal the systolic stress developed by the myocardium. A large transaortic valvular pressure gradient may exist for many years without a reduction ofCO or LV dilatation; ultimately, however, these changes occur.

A peak systolic pressure gradient>50 mmHg in the face of a normal cardiac output or an effective aortic orifice less than approximately 0.5 cm^2/m^2body surface area, i.e., less

than approximately one-third of the normal orifice, is generally considered to represent critical obstruction toLVoutflow. The elevated LV end-diastolic pressure observed in many patients with severeASsignifies the presence of LV dilatation and/or diminished compliance of the hypertrophied LV wall. A large *a* wave in theLApressure pulse is usually present. Loss of an appropriately timed, vigorous atrial contraction, as occurs inAF or atrioventricular dissociation, may result in a rapid aggravation of symptoms. Although theCO at rest is within normal limits in most patients with severe AS, it usually fails to rise normally during exercise. Late in the course the CO and LV-aortic pressure gradient decline, and the mean LA,PA, andRVpressures rise.

The hypertrophiedLVmuscle mass elevates myocardial oxygen requirements. In addition, even in the absence of obstructive coronary artery disease, there may be interference with coronary blood flow, because the pressure compressing the coronary arteries exceeds the coronary perfusion pressure, often causing ischemia, especially in the subendocardium and during tachycardia both in the presence and in the absence of coronary arterial narrowing.

A significant fraction of patients with rheumaticAS has associated mitral valve disease. AS intensifies the severity of accompanyingMR by increasing the pressure driving blood from theLV to theLA.

SYMPTOMS

ASis rarely of hemodynamic or clinical importance until the valve orifice has narrowed to approximately 0.5 cm^2/m^2body surface area in adults. Even critical AS may exist for many years without producing any symptoms because of the ability of the hypertrophiedLV to generate the elevated intraventricular pressures required for a normal stroke volume.

Most patients with pure or predominantAS have gradually increasing obstruction for years but do not become symptomatic until the sixth to eighth decades. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities. *Dyspnea* results primarily from elevation of the pulmonary capillary pressure caused by elevations ofLA andLVdiastolic pressures secondary to reduced compliance and/or LV dilatation. *Angina pectoris* usually develops somewhat later and reflects an imbalance between the augmented myocardial oxygen requirements and reduced oxygen availability; the former results from the increased myocardial mass and intraventricular pressure, while the latter may result from accompanying coronary artery disease, which is not uncommon in patients with AS, as well as from compression of the coronary vessels by the hypertrophied myocardium. Therefore, angina may occur in severe AS even without obstructive epicardial coronary artery disease. *Exertional syncope* may result from a decline in arterial pressure caused by vasodilatation in the exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixedCO or from a sudden fall in CO produced by an arrhythmia.

Since theCO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, and other clinical manifestations of a low CO

are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV failure and systemic venous hypertension, hepatomegaly, AF, and TR are usually late findings in patients with isolated, severe AS.

When AS and MS coexist, the reduction of cardiac output induced by MS lowers the pressure gradient across the aortic valve and thereby masks many of the clinical findings produced by AS. Left heart catheterization is helpful in defining the relative importance of each valvular abnormality.

PHYSICAL FINDINGS

The rhythm is generally regular until very late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. The systemic arterial pressure is usually within normal limits. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. Systemic hypertension is unusual in patients with marked AS, and a basal systolic arterial pressure >200 mmHg essentially excludes severe narrowing of this valve. The peripheral arterial pulse, as palpated in the carotid or brachial arteries, rises slowly to a delayed sustained peak (pulsus parvus et tardus) (see Fig. 225-2*B*). In the elderly, the stiffening of the arterial wall may mask this important physical sign. A palpable double systolic arterial pulse, the so-called bisferiens pulse, excludes pure or predominant AS and signifies dominant AR. In the late stages of AS, when the pulse pressure is reduced, the pulse amplitude may be so small that the anacrotic nature of the pulse and the delay in its upstroke may become difficult to appreciate. In many patients the *a* wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the bulging, hypertrophied interventricular septum.

The LV impulse is usually active and displaced laterally, reflecting the presence of LV hypertrophy. A double apical impulse may be recognized, particularly with the patient in the left lateral recumbent position. A systolic thrill is generally present at the base of the heart, in the jugular notch, and along the carotid arteries. In patients who do not have marked pulmonary emphysema, a thick chest wall, thoracic deformity, or heart failure, the absence of a systolic thrill suggests that the AS is relatively mild.

Auscultation An early systolic ejection sound, actually the OS of the aortic valve, is frequently audible in children and adolescents with congenital noncalcific valvular AS. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxic splitting of the S_2 (Chap. 225). The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves, and calcification diminishes the intensity of this sound. Frequently, an S_4 is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an S_3 generally occurs when the LV dilates.

The murmur of AS is characteristically an ejection (mid) systolic murmur that

commences shortly after the S_1, increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure (seeFig. 225-4). It is characteristically low-pitched, rough, and rasping in character, loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally, it is transmitted downward and to the apex where it may be confused with the systolic murmur ofMR; the latter, however, is usually holosystolic. In almost all patients with severe obstruction, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure in whom the stroke volume and therefore the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

LABORATORY EXAMINATION

Electrocardiogram The main finding in most patients with severeAS isLVhypertrophy (see Fig. 226-10). In advanced cases, ST-segment depression and T-wave inversion (LV "strain") in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the electrocardiogram and the hemodynamic severity of obstruction, and the absence of electrocardiographic signs of LV hypertrophy does not exclude severe obstruction. The presence ofLAenlargement should suggest the possibility of associated mitral valve disease.

Roentgenogram The chest roentgenogram may show no or little overall cardiac enlargement for many years, since the development of concentricLVhypertrophy is the initial response to obstruction to LV outflow. Hypertrophy without dilatation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view; criticalAS is often associated with poststenotic dilatation of the ascending aorta. Aortic calcification is usually readily apparent on fluoroscopic examination or by echocardiography; *the absence of valvular calcification in an adult suggests that severe valvular AS is not present*. In later stages of the disease as the LV dilates, there is increasing roentgenographic evidence of LV enlargement; pulmonary congestion; and enlargement of theLA,PA, and right side of the heart.

Echocardiogram The key findings areLVhypertrophy and, in patients with valvular calcification (i.e., most adult patients with symptomaticAS), multiple, bright, thick, echoes from within the aortic root. Eccentricity of the aortic valve cusps is characteristic of congenitally bicuspid valves (Plate I-3). Transesophageal imaging displays the obstructed orifice extremely well. LV dilatation and reduced systolic shortening reflect impairment of LV function. The transaortic valvular gradient can be estimated by Doppler echocardiography. Echocardiography is particularly useful for identifying valvular abnormalities such asMS andAR, which sometimes accompany AS, and for differentiating valvular AS from obstructive hypertrophic cardiomyopathy.

Catheterization Catheterization of the left side of the heart and coronary arteriography should generally be carried out in patients suspected of having severeAS who are being considered for operative treatment. These investigations are especially indicated in the following:

1. Patients with clinical signs ofAS and symptoms of myocardial ischemia, in whom associated coronary artery disease is suspected. An effort should be made to determine

whether AS or coronary atherosclerosis is primarily responsible for the symptoms, and coronary arteriography should be carried out in an effort to identify patients who require coronary bypass grafting at the time of aortic valve surgery.

2. Patients with multivalvular disease, in whom the role played by each valvular deformity should be defined to aid in the planning of definitive operative treatment.

3. Young, asymptomatic patients with noncalcific congenital AS, to define the severity of obstruction toLVoutflow, since operation [which does not usually require aortic valve replacement (AVR)] or balloon valvotomy may be indicated for them if severeAS is present, even in the absence of symptoms. Balloon valvotomy may follow left heart catheterization immediately.

4. Patients in whom it is suspected that the obstruction toLVoutflow may not be at the aortic valve but rather in the sub- or supravalvular regions.

NATURAL HISTORY

Death in patients with severeASoccurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients not treated surgically, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; and congestive heart failure, 1.5 to 2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Congestive heart failure was considered to be the cause of death in one-half to two-thirds of patients. Among adults dying with valvular AS, sudden death, which presumably results from an arrhythmia, occurred in 10 to 20% and at an average age of 60 years. However, most sudden deaths occur in patients who had previously been symptomatic.

TREATMENT

All patients with moderate or severeASrequire careful periodic follow-up. In patients with severe AS, strenuous physical activity should be avoided even in the asymptomatic stage. Digitalis glycosides, sodium restriction, and the cautious administration of diuretics are indicated in the treatment of congestive heart failure, but care must be taken to avoid volume depletion since this may cause a marked reduction ofCO. While nitroglycerin is helpful in relieving angina pectoris, vasodilator therapy for heart failure is usually of little value and may, in fact, be harmful.

Surgical Treatment The most critical decision in the management ofASconcerns the advisability of surgical treatment which, in most adults with calcific AS and critical obstruction (aortic orifice<0.5 cm^2/m^2body surface area), consists ofAVR. In most instances, it is prudent to postpone operation in patients with severe calcific AS who are asymptomatic (unless they exhibitLVdysfunction), since their future course is difficult to predict and they may continue to do well for many years. However, they should be followed carefully by clinical examination for the development of symptoms and by serial echocardiograms for evidence of deteriorating LV function. Operation is generally indicated in patients with severe AS who are asymptomatic, irrespective of their LV function, as well as those who exhibit LV dysfunction, even if they are asymptomatic. In

patients without heart failure, the operative risk of AVR is approximately 4% (Table 236-1).

When angina pectoris, syncope, orLVdecompensation develops in adults with severe valvularAS, the outlook, despite medical treatment, is very poor and can be improved significantly byAVR. The operative risk is considerably lower than the risk of nonoperative treatment; moreover, the symptomatic improvement in some survivors of operation has been remarkable. Regression of LV hypertrophy may occur after relief of obstruction.

Operation should, if possible, be carried out before frankLVfailure develops; at this late stage, the operative risk is high (15 to 20%), and evidence of myocardial disease may persist even when the operation is technically successful. Furthermore, long-term postoperative survival also correlates inversely with preoperative LV dysfunction. Nonetheless, in view of the very poor prognosis of such patients when they are treated medically, there is usually little choice but to advise surgical treatment. In patients in whom severeAS and coronary artery disease coexist, relief of the AS and revascularization of the myocardium by means of aortocoronary bypass grafting may result in striking clinical and hemodynamic improvement.

Because many patients with calcificAS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function beforeAVR is recommended. The mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. The 10-year survival rate of patients with AVR is approximately 60%. Approximately 30% of bioprosthetic valves evidence primary valve failure in 10 years, requiring re-replacement, and an approximately equal percentage of patients with mechanical prostheses develop significant hemorrhagic complications as a consequence of treatment with anticoagulants.

Percutaneous Balloon Aortic Valvuloplasty This procedure is preferable to operation in children and young adults with congenital, noncalcificAS. It is not commonly used in elderly patients with severe calcific AS because of a high restenosis rate. Nonetheless, this procedure has been used successfully in patients who are too ill or frail to undergo operation, in patients with life-threatening AS and advanced extracardiac disease, and as a "bridge to operation" in patients with severeLVdysfunction.

AORTIC REGURGITATION

ETIOLOGY

ARmay be caused by primary valve disease or by primary aortic root disease.

Primary Valve Disease Approximately three-fourths of patients with pure or predominant valvularAR are males; females predominate among patients with AR who have associated mitral valve disease. In approximately two-thirds of patients with AR the disease is rheumatic in origin, resulting in thickening, deformity, and shortening of the individual aortic valve cusps, changes that prevent their proper opening during systole and closure during diastole. A rheumatic origin is less common in patients with isolated AR. Acute AR may result from infective endocarditis, which can develop on a

valve previously affected by rheumatic disease, a congenitally deformed valve, or, rarely, a normal aortic valve, and perforate or erode one or more of the leaflets. Patients with congenital membranous subaortic stenosis often develop thickening of the aortic valve leaflets, which makes the valves particularly susceptible to endocarditis. AR also may occur in patients with congenital bicuspid aortic valves. Prolapse of an aortic cusp, resulting in progressive chronic AR, occurs in approximately 15% of patients with ventricular septal defect (Chap. 234). Congenital fenestrations of the aortic valve occasionally produce mild AR. Although traumatic rupture of the aortic valve is an uncommon cause of acute AR, it does represent the most frequent serious lesion in patients surviving nonpenetrating cardiac injuries. The coexistence of hemodynamically significantAS with AR usually excludes all the rarer forms of AR because it occurs almost exclusively in patients whose AR is rheumatic or congenital in origin. In patients with AR due to primary valvular disease, dilatation of the aortic annulus may occur secondarily and intensify the regurgitation.

Primary Aortic Root Disease AR, both acute and chronic, also may be due entirely to marked aortic dilatation, i.e., aortic root disease, without primary involvement of the valve leaflets; widening of the aortic annulus and separation of the aortic leaflets are responsible for the AR (Chap. 247). Cystic medial necrosis of the ascending aorta, which may or may not be associated with other manifestations of the Marfan syndrome, idiopathic dilatation of the aorta, osteogenesis imperfecta, and severe hypertension all may widen the aortic annulus and lead to progressive AR. Occasionally, AR is caused by retrograde dissection of the aorta involving the aortic annulus. Syphilis and ankylosing rheumatoid spondylitis may be associated with cellular infiltration and scarring of the media of the thoracic aorta, leading to aortic dilatation, aneurysm formation, and severe regurgitation. In syphilis of the aorta, the involvement of the intima may narrow the coronary ostia, which in turn may be responsible for myocardial ischemia.

PATHOPHYSIOLOGY

The total stroke volume ejected by theLV(i.e., the sum of the effective forward stroke volume and the volume of blood that regurgitates back into the LV) is increased in patients withAR. In patients with wide-open (free) AR, the volume of regurgitant flow may equal the effective forward stroke volume. In contrast toMR, in which a fraction of the LV stroke volume is delivered into the low-pressureLA, in AR the entire LV stroke volume is ejected into a high-pressure zone, the aorta. An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for AR. The dilatation of the LV allows this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril. Therefore, severe AR may occur with a normal effective forward stroke volume and a normal left ventricular/ejection fraction (EF) [total (forward plus regurgitant) stroke volume/end-diastolic volume], together with an elevated LV end-diastolic pressure and volume. However, through the operation of Laplace's law (which holds that myocardial wall tension is the product of intracavitary pressure and LV radius), LV dilatation increases the LV systolic tension required to develop any given level of systolic pressure. As LV function deteriorates, the end-diastolic volume rises and the forward stroke volume and EF decline. Deterioration of LV function often precedes the development of symptoms. Considerable thickening of the LV wall also occurs with

chronic AR, and at autopsy the hearts of these patients may be among the largest encountered, sometimes weighing >1000 g.

The reverse pressure gradient from aorta toLV, which is responsible for theAR flow, falls progressively during diastole (seeFig. 228-4), accounting for the decrescendo nature of the diastolic murmur. Equilibration between aortic and LV pressures may occur toward the end of diastole in patients with severe AR, particularly when the heart rate is slow, and the LV end-diastolic pressure may be elevated, occasionally to extremely high levels (>40 mmHg). Rarely, in acute, severe AR, the LV pressure exceeds theLApressure toward the end of diastole, and this reversed pressure gradient closes the mitral valve prematurely or causes diastolic MR.

In patients with severeAR, the effective forwardCOusually is normal or only slightly reduced at rest, but often it fails to rise normally during exertion. Early signs of LV dysfunction include reduction in theEF, determined by echocardiography or radionuclide angiography. In advanced stages there may be considerable elevation of theLA,PAwedge, PA, andRVpressures and lowering of the forward CO at rest.

Myocardial ischemia may occur in patients withARbecause myocardial oxygen requirements are elevated by bothLVdilatation and elevated LV systolic tension. However, the major portion of coronary blood flow occurs during diastole, when arterial pressure is subnormal, thereby reducing coronary perfusion pressure. This combination of increased oxygen demand and reduced supply may cause myocardial ischemia, particularly of the subendocardium.

HISTORY

A family history may frequently be elicited from patients withARassociated with the Marfan syndrome. A history compatible with infective endocarditis may sometimes be elicited from patients with rheumatic or congenital involvement of the aortic valve, and the infection often precipitates or seriously aggravates preexisting symptoms. Ankylosing spondylitis is usually self-evident.

Chronic, severeAR may have a long latent period, and patients may remain relatively asymptomatic for as long as 10 to 15 years. However, uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint. Sinus tachycardia during exertion or with emotion or premature ventricular contractions may produce particularly uncomfortable palpitations, as well as head pounding. These complaints may persist for many years before the development of exertional dyspnea, usually the first symptom of diminished cardiac reserve. The dyspnea is followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive diaphoresis. Chest pain occurs frequently, even in younger patients, and it is not necessary to invoke the presence of coronary artery disease to explain this symptom in patients with severe AR. Anginal pain may develop at rest as well as during exertion. Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis. The anginal episodes can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin. Systemic fluid accumulation, including congestive hepatomegaly and ankle edema may develop late in the course of the disease.

In patients with acute, severeAR, as may occur in infective endocarditis or trauma, theLVcannot dilate sufficiently to maintain stroke volume, and LV diastolic pressure rises rapidly with associated elevations ofLA andPA wedge pressures. Pulmonary edema and/or cardiogenic shock may develop rapidly.

PHYSICAL FINDINGS

In severeAR, the jarring of the entire body and the bobbing motion of the head with each systole can be appreciated, and the abrupt distention and collapse of the larger arteries are easily visible. The examination should be directed toward the detection of conditions predisposing to AR, such as the Marfan syndrome, rheumatoid spondylitis, and ventricular septal defect.

Arterial Pulse A rapidly rising "water-hammer" pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan's pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke's pulse), are characteristic of freeAR. A booming, "pistol-shot" sound can be heard over the femoral arteries (Traube's sign), and a to-and-fro murmur (Duroziez's sign) is audible if the femoral artery is lightly compressed with a stethoscope.

The arterial pulse pressure is widened, with an elevation of the systolic pressure, sometimes to as high as 300 mmHg, and a depression of the diastolic pressure. The measurement of arterial diastolic pressure with a sphygmomanometer may be complicated by the fact that systolic sounds are frequently heard with the cuff completely deflated. However, the level of cuff pressure at the time of muffling of the Korotkoff sounds generally corresponds fairly closely to the true intraarterial diastolic pressure. The severity ofAR does not always correlate directly with the arterial pulse pressure, and severe regurgitation may exist in patients with arterial pressures in the range of 140/60 mmHg. As the disease progresses and theLVend-diastolic pressure rises markedly, the arterial diastolic pressure may actually rise also, since the aortic diastolic pressure cannot fall below the LV end-diastolic pressure.

Palpation TheLVimpulse is heaving and displaced laterally and inferiorly. The systolic expansion and diastolic retraction of the apex are prominent and contrast with the sustained systolic thrust characteristic of severeAS. A diastolic thrill is often palpable along the left sternal border, and a prominent systolic thrill may be palpable in the jugular notch and transmitted upward along the carotid arteries. This thrill and the accompanying systolic murmur are due to the markedly increased blood flow across the aortic orifice and do not necessarily signify the coexistence of AS. In many patients with pureAR or with combined AS and AR, the carotid arterial pulse is bisferiens, i.e., with two systolic waves separated by a trough.

Auscultation In patients with severeAR, the aortic valve closure sound is usually absent. An S_3 and systolic ejection sound are frequently audible, and occasionally, an S_4 also may be heard. The murmur of AR is typically a high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border (see Fig. 225-4). In patients with mild AR, this murmur is brief, but as the severity increases, generally becomes louder and longer, indeed holodiastolic. When

the murmur is soft, it can be heard best with the diaphragm of the stethoscope and with the patient sitting up, leaning forward, and with the breath held in forced expiration. In patients in whom the AR is caused by primary valvular disease, the diastolic murmur is usually louder along the left than the right sternal border. However, when the murmur is heard best along the right sternal border, it suggests that the AR is caused by aneurysmal dilatation of the aortic root. "Cooing" or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream. Unless it is trivial in magnitude, the AR is usually accompanied by peripheral signs such as a widened pulse pressure or a collapsing pulse. By contrast, with the Graham Steell murmur of pulmonary regurgitation, which may be confused with the diastolic murmur of AR, there usually is clinical evidence of severe pulmonary hypertension, including a loud and palpable pulmonary component of the S_2.

A midsystolic ejection murmur is frequently audible in AR. It is generally heard best at the base of the heart and is transmitted along the carotid vessels. This murmur may be quite loud without signifying aortic obstruction; it is often higher pitched, shorter, and less rasping in quality than the ejection systolic murmur heard in patients with predominant AS. A third murmur frequently heard in patients with severe AR is the Austin Flint murmur, a soft, low-pitched, rumbling middiastolic bruit. It is probably produced by the displacement of the anterior leaflet of the mitral valve by the AR stream but does not appear to be associated with hemodynamically significant mitral obstruction. Both the Austin Flint murmur and the rumbling diastolic murmur of MS are loudest at the apex, but the murmur of MS is usually accompanied by a loud S_1 and immediately follows the OS of the mitral valve, whereas the Austin Flint murmur is often shorter in duration than the murmur of MS; in patients with sinus rhythm the latter exhibits presystolic accentuation. The auscultatory features of AR are intensified by isometric exercise such as strenuous handgrip, which augments systemic resistance, and reduced by inhalation of amyl nitrite. A blowing holosystolic murmur at the apex, which is transmitted to the axilla, also may be heard in patients with AR who have marked LV dilatation and functional MR.

In acute, severe AR, the elevation of LV end-diastolic pressure may lead to early closure of the mitral valve, an associated middiastolic sound, a soft or absent S_1, a pulse pressure that is not particularly wide, and a soft, short diastolic murmur.

LABORATORY EXAMINATION

Electrocardiogram In patients with mild AR, there may be no electrocardiographic abnormalities, but with severe, chronic AR, the electrocardiographic signs of LV hypertrophy become manifest (Chap. 226). In addition, these patients frequently exhibit ST-segment depression and T-wave inversion in leads I, aVL, V_5, and V_6 ("LV strain"). Left axis deviation and/or QRS prolongation denote diffuse myocardial disease, generally associated with patchy fibrosis, and usually signify a poor prognosis.

Roentgenogram In severe chronic AR, the apex is displaced downward and to the left in the frontal projection, and frequently the cardiac shadow extends below the left diaphragm. LV enlargement also may be apparent in the left anterior oblique and lateral projections, in which the LV is displaced posteriorly and encroaches on the spine. In patients in whom primary valvular disease is responsible for the AR, the ascending

aorta and aortic knob may be moderately dilated. When AR is caused by primary disease of the aortic wall, aneurysmal dilatation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view.

Echocardiogram Increased systolic excursion of the posterior left ventricular wall is evident; the extent and velocity of wall motion are normal or even supernormal, until myocardial contractility declines. A rapid, high-frequency fluttering of the anterior mitral leaflet produced by the impact of the regurgitant jet is a characteristic finding. The echocardiogram is also useful in determining the cause ofAR, by detecting dilatation of the aortic annulus (Plate I-3). Thickening and failure of coaptation of the leaflets also may be noted. Color flow Doppler echocardiographic imaging is very sensitive in the detection of AR, and Doppler echocardiography is helpful in assessing its severity. Serial two-dimensional echocardiography is valuable in evaluatingLVperformance and in detecting progressive myocardial dysfunction.

Cardiac Catheterization and Angiography In addition to providing an accurate confirmation of the magnitude of regurgitation and the status ofLVfunction, the condition of the coronary arterial bed may be evaluated preoperatively.

TREATMENT

Although operation constitutes the principal treatment ofAR and should be carried out before the development of heart failure, the latter usually responds briefly to treatment with digitalis glycosides, salt restriction, diuretics, and vasodilators, especially ACE inhibitors. Digitalis also may be indicated in patients with severe regurgitation and dilated left ventricles without frankLVfailure. Cardiac arrhythmias and infections are poorly tolerated in patients with free AR and must be treated promptly and vigorously. Although nitroglycerin and long-acting nitrates are not as helpful in relieving anginal pain as in patients with ischemic heart disease, they are worth a trial. Long-acting nifedipine has been found to delay the need for operation. Patients with syphilitic aortitis should receive a full course of penicillin therapy (Chap. 172).

Surgical Treatment In deciding on the advisability and proper timing of surgical treatment, two points should be kept in mind: (1) patients with chronicARusually do not become symptomatic until after the development of myocardial dysfunction, and (2) surgical treatment often does not restore normalLVfunction. Therefore, in patients with severe AR, careful clinical follow-up and noninvasive testing with echocardiography at approximately 6-month intervals are necessary if operation is to be undertaken at the optimal time, i.e., *after* the onset of LV dysfunction but *prior* to the development of severe symptoms. Operation can be deferred as long as the patient both remains asymptomatic and retains normal LV function. In general, operation should be carried out even in asymptomatic patients with progressive LV dysfunction and an LVEF<55% or a LV end-systolic volume>55 mL/m^2. (The latter has been referred to as the "55/55 rule.")

AVRwith a suitable mechanical or tissue prosthesis is generally necessary in patients with rheumaticAR and in many patients with other forms of regurgitation. Rarely, when a leaflet has been perforated during an episode of infective endocarditis or torn from its attachments to the aortic annulus, surgical repair may be possible. When AR is due to

aneurysmal dilatation of the annulus and ascending aorta rather than to primary valvular involvement, it may be possible to reduce the regurgitation by narrowing the annulus or by excising a portion of the aortic root without replacing the valve. More frequently, however, regurgitation can be eliminated only by replacing the aortic valve, excising the dilated or aneurysmal ascending aorta responsible for the regurgitation, and replacing the latter with a graft. This formidable procedure entails a higher risk than isolated AVR.

As in patients with other valvular abnormalities, both the operative risk and the late mortality are largely dependent on the stage of the disease and on myocardial function at the time of operation. The overall operative mortality for isolatedAVR is 4.3% (Table 236-1). However, patients with marked cardiac enlargement and prolongedLVdysfunction experience an operative mortality rate of approximately 10% and a late mortality rate of approximately 5% per year due to LV failure despite a technically satisfactory operation. Nonetheless, because of the very poor prognosis with medical management, even patients with LV failure should be considered for operation.

ACUTE AORTIC REGURGITATION

Infective endocarditis, aortic dissection, and trauma are the most common causes of severe, acuteAR. Since theLV has not had time to dilate in this condition, stroke volume declines and ventricular diastolic pressure rises markedly; the arterial pulse pressure is often not markedly widened, and the physical signs characteristic of severe chronic AR may be absent. Premature closure of the mitral valve is common and can be recognized by echocardiography. The S_1 is soft or absent; the aortic diastolic murmur is characteristically brief. Patients present with pulmonary congestion and edema, as well as hypotension secondary to a low cardiac output. Acute, severe AR requires prompt surgical treatment, which may be lifesaving.

TRICUSPID STENOSIS

TS, a relatively uncommon valvular lesion in North America and western Europe, is more common in tropical and subtropical climates, especially on the Indian subcontinent, and in Latin America. It is generally rheumatic in origin and is more common in women than in men. It does not occur as an isolated lesion but is usually associated withMS. Hemodynamically significant TS occurs in 5 to 10% of patients with severe MS; rheumatic TS is commonly associated with some degree ofTR.

PATHOPHYSIOLOGY

A diastolic pressure gradient between theRA andRV can be recorded with a double-lumen cardiac catheter. It is augmented when the transvalvular blood flow increases during inspiration and declines during expiration. A mean diastolic pressure gradient >4 mmHg is usually sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion and, unless sodium intake has been restricted and diuretics administered, it is associated with ascites and edema, sometimes severe. In patients with sinus rhythm, the RA *a* wave may be extremely tall and may even approach the level of the RV systolic pressure. The restingCO is usually depressed and fails to rise during exercise. The low CO is responsible for the normal or only slightly elevatedLA,PA, and RV systolic pressures despite the presence ofMS.

SYMPTOMS

Since the development ofMSgenerally precedes that ofTS, many patients initially have symptoms of pulmonary congestion. Amelioration of these symptoms should raise the possibility that TS may be developing. Characteristically, patients complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have. Fatigue secondary to a low cardiac output and discomfort due to refractory edema, ascites, and marked hepatomegaly are common in patients with TS and/orTR. In some patients, TS may be suspected for the first time when symptoms ofRVfailure persist after an adequate mitral valvulotomy.

PHYSICAL FINDINGS

SinceTSusually occurs in the presence of other obvious valvular disease, the diagnosis may be missed unless it is specifically considered and searched for. Severe TS is associated with marked hepatic congestion, often resulting in cirrhosis, jaundice, serious malnutrition, anasarca, and ascites. Congestive hepatomegaly and, in cases of severe tricuspid valve disease, splenomegaly are present. The jugular veins are distended, and in patients with sinus rhythm there may be giant *a* waves. The *v* waves are less conspicuous, and since tricuspid obstruction impedesRAemptying during diastole, there is a slow *y* descent. In patients with sinus rhythm there may be prominent presystolic pulsations of the enlarged liver as well.

On auscultation, the pulmonic valve closure sound is not accentuated, and occasionally, anOS of the tricuspid valve may be heard approximately 0.06 s after pulmonic valve closure. The diastolic murmur ofTS has many of the qualities of the diastolic murmur ofMS, and since TS almost always occurs in the presence of MS, the less common valvular lesion may be missed. However, the tricuspid murmur is generally heard best along the left lower sternal margin and over the xiphoid process and is most prominent during presystole in patients with sinus rhythm. The diastolic murmur is reduced in amplitude as the stethoscope is inched laterally, only to intensify or reappear as the mitral murmur at the apex. The murmur of TS is augmented during inspiration, and it is reduced during expiration and particularly during the strain of Valsalva maneuver, when tricuspid blood flow is reduced. This finding is often most easily elicited when the patient is in the erect position.

LABORATORY EXAMINATION

The electrocardiographic features ofRAenlargement (Chap. 226) include tall, peaked P waves in lead II, as well as prominent, upright P waves in lead V_1. The *absence* of electrocardiographic evidence of renovascular hypertension (RVH) in a patient with right-sided heart failure who is believed to haveMSshould suggest associated tricuspid valve disease. The chest roentgenogram in patients with combinedTS and MS show particular prominence of the RA and superior vena cava without much enlargement of thePA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS. On echocardiographic examination, the tricuspid valve is usually thickened; the transvalvular gradient can be estimated by Doppler echocardiography.

TREATMENT

Patients with TSgenerally exhibit marked systemic venous congestion; intensive salt restriction and diuretic therapy are required during the preoperative period. Such a preparatory period may diminish hepatic congestion and thereby improve hepatic function sufficiently so that the risks of operation are diminished. Surgical relief of the TS should be carried out, preferably at the time of mitral valvotomy, in patients with moderate or severe TS who have mean diastolic pressure gradients exceeding approximately 4 mmHg and tricuspid orifices less than 1.5 to 2.0 cm^2. TS is almost always accompanied by significantTR. Open-heart repair may permit substantial improvement of tricuspid valve function. If this cannot be accomplished, the tricuspid valve may have to be replaced with a prosthesis, preferably a large bioprosthetic valve.

TRICUSPID REGURGITATION

Most commonly,TR is functional and secondary to marked dilatation of theRV and the tricuspid annulus. Functional TR may complicate RV enlargement of any cause, including inferior wall infarcts that involve the RV, and it is commonly seen in the late stages of heart failure due to rheumatic or congenital heart disease with severe pulmonary hypertension, as well as in ischemic heart disease, cardiomyopathy, and cor pulmonale. It is in part reversible if pulmonary hypertension is relieved. Rheumatic fever may produce organic TR, often associated withTS. Infarction of RV papillary muscles, tricuspid valve prolapse, carcinoid heart disease, endomyocardial fibrosis, infective endocarditis, and trauma all may produce TR. Less commonly, TR results from congenitally deformed tricuspid valves, and it occurs with defects of the atrioventricular canal as well as with Ebstein's malformation of the tricuspid valve (Chap. 234).

As is the case forTS, the clinical features ofTRresult primarily from systemic venous congestion and reduction ofCO. With the onset of TR in patients with pulmonary hypertension, symptoms of pulmonary congestion diminish, but the clinical manifestations of right-sided heart failure become intensified. The neck veins are distended with prominent *v* waves; and marked hepatomegaly, ascites, pleural effusions, edema, systolic pulsations of the liver, and positive hepatojugular reflux are common. A prominentRVpulsation along the left parasternal region and a blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration and reduced during expiration or the strain of the Valsalva maneuver, are characteristic findings;AF is usually present.

The electrocardiogram usually shows changes characteristic of the lesion responsible for the enlargement of the RVthat leads toTR. Roentgenographic examination usually reveals enlargement of both theRA and RV. Echocardiography may be helpful by demonstrating RV dilatation and prolapsing or flail tricuspid leaflets; the diagnosis of TR can be made by color flow Doppler echocardiography, and the severity estimated by Doppler examination. The latter is also useful in estimatingPApressure.

In patients with severeTR, theCO is usually markedly reduced, and theRApressure pulse may exhibit no *x* descent during early systole but a prominent *c-v* wave with a rapid *y* descent. The mean RA and the RV end-diastolic pressures are often elevated.

TREATMENT

IsolatedTR, in the absence of pulmonary hypertension, such as that occurring as a consequence of infective endocarditis or trauma, is usually well tolerated and does not require operation. Indeed, even total excision of an infected tricuspid valve is often well tolerated if thePApressure is normal. Treatment of the underlying cause of heart failure usually reduces the severity of functional TR. In patients with mitral valve disease and TR secondary to pulmonary hypertension and massiveRVenlargement, effective surgical correction of the mitral valvular abnormality results in lowering of the PA pressures and gradual reduction or disappearance of the TR without direct treatment of the tricuspid valve. However, recovery may be much more rapid in patients with severe secondary TR if, at the time of mitral valve surgery, tricuspid annuloplasty (generally with the insertion of a plastic ring), open tricuspid valve repair, or, in the rare instance of severe organic tricuspid valve disease, tricuspid valve replacement is performed. Surgical treatment of the TR also should be carried out in patients with severe regurgitation secondary to deformity of the tricuspid valve due to rheumatic fever, particularly those *without* severe pulmonary hypertension.

PULMONIC VALVE DISEASE

The pulmonic valve is affected by rheumatic fever far less frequently than are the other valves, and it is uncommonly the seat of infective endocarditis. The most common *acquired* abnormality affecting the pulmonic valve is regurgitation secondary to dilatation of the pulmonic valve ring as a consequence of severe pulmonary hypertension. This produces the Graham Steell murmur, a high-pitched, decrescendo, diastolic blowing murmur along the left sternal border, which is difficult to differentiate from the far more common murmur produced byAR. It is usually of little hemodynamic significance; indeed, surgical removal or destruction of the pulmonic valve by infective endocarditis does not produce heart failure unless serious pulmonary hypertension is also present. The *carcinoid syndrome* may cause pulmonic stenosis and/or regurgitation.**Congenital pulmonic stenosis* is discussed in Chap. 234.

VALVE REPLACEMENT

The results of replacement of any valve are dependent primarily on (1) the patient's myocardial function and general medical condition at the time of operation, (2) the technical abilities of the operative team and the quality of the postoperative care, and (3) the durability, hemodynamic characteristics, and thrombogenicity of the prosthesis. Increased operative mortality is associated with the higher levels of preoperative functional disability and pulmonary hypertension. Late complications of replacement of any valve, which are declining in incidence, include paravalvular leakage, thromboemboli, bleeding due to anticoagulants, mechanical dysfunction of the prosthesis, and infective endocarditis.

The considerations involved in the choice between a bioprosthetic (tissue) and artificial mechanical valve are similar in the mitral and aortic positions and in the treatment of stenotic, regurgitant, or mixed lesions. All patients who have undergone replacement of any valve with a mechanical prosthesis must be maintained permanently on anticoagulants, but this treatment imposes a hazard of hemorrhage. The primary

advantage of bioprostheses over mechanical prostheses is the reduction of thromboembolic complications; and except for patients with chronicAF, few such instances have been associated with their use. The major disadvantage of bioprosthetic valves is their mechanical deterioration, the incidence of which is inversely proportional with age. This results in the need to replace the prosthesis in 30% of patients by 10 years and in 50% by 15 years. Bioprostheses are ordinarily not used in younger patients (<35 years) because of accelerated deterioration but are particularly useful in the elderly (>70 years), in whom there is more concern about chronic anticoagulation than about long-term (>15 years) valve durability. These valves are also indicated in women who expect to become pregnant, as well as others in whom anticoagulation may be contraindicated. Alternative bioprostheses are homograft (allograft) aortic valves obtained from cadavers and cryopreserved, pericardial autografts as well as pulmonary autograft transplanted into the aortic position. In patients without contraindications to anticoagulants, particularly those under 65 years, a mechanical prosthesis may be preferable. Many surgeons now select the St. Jude prosthesis, a double-disk tilting prosthesis, for replacement of both aortic and mitral valves because of somewhat more favorable hemodynamic characteristics and a suggestion of lower thrombogenicity.

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237. COR PULMONALE - *Eugene Braunwald*

DEFINITIONS

Cor pulmonale is defined as enlargement of the right ventricle (RV) secondary to abnormalities of the lungs, thorax, pulmonary ventilation, or circulation. It sometimes leads to RV failure, with an elevation of transmural RV end-diastolic pressure. Cor pulmonale and RV failure may be acute, as in pulmonary thromboembolism; or chronic, as in stable, severe chronic obstructive lung disease (COLD); or "acute on chronic," as in COLD with a superimposed infection and intensification of hypoxia. Approximately 20% of hospital admissions for heart failure are caused by RV failure associated with cor pulmonale. More than half of the patients with COLD have cor pulmonale, and this condition constitutes between 5 and 10% of all adult heart diseases in the United States. Cor pulmonale constitutes a higher percentage of all forms of heart disease in countries where the incidence of COLD is higher, such as the United Kingdom, and in areas such as Mexico City where air pollution is severe.

NORMAL FUNCTION OF THE PULMONARY CIRCULATION

The pulmonary circulation is interposed between the right and left ventricles for the purpose of gas exchange, the filtering out of particles, and the chemical modification of the blood, such as the conversion of angiotensin I to angiotensin II. Normally, flow through the pulmonary vascular bed depends not only on the pumping action of theRV but also on respiratory movements and on the filling and contraction of the left ventricle. Respiratory motion facilitates pulmonary blood flow by enhancing venous return into the thorax on inhalation; the positive pressure of exhalation then aids in propelling blood into the systemic vascular bed.

The stroke volume of theRV, as of the left, is regulated by its preload, contractility, and afterload (Chap. 231). Since the RV is a relatively thin, compliant reservoir, acute changes in venous return (e.g., an increase with inhalation and decline with exhalation) can occur with little change in transmural RV pressure. However, the ability of the RV to increase its systolic pressure is limited. Normally, the RV afterload, which is closely related to the pulmonary artery pressure, is low. The pulmonary artery pressure normally rises slightly when blood is displaced into the chest at the start of exercise; on assuming recumbency; or with cold, anxiety, or pain. A driving pressure of only about 5 cmH_2O between the pulmonary artery (15 cmH_2O) and the left atrium (10 cmH_2O) normally propels the entire cardiac output of approximately 5 L/min at rest through the lungs, and only a modest increase in pressure is necessary to drive a flow of up to 25 L/min through the pulmonary capillary bed during maximal exercise.

The resistance of the pulmonary circulation (*R*), i.e., the pulmonary vascular resistance (Chap. 228), is calculated as the intravascular driving pressure (*DP*), i.e., pulmonary artery pressure minus pulmonary venous or left atrial pressure, divided by the pulmonary blood flow rate (). The caliber of a distensible vessel depends on its transmural pressure. Calculated *R* increases when vessels collapse, narrow, or lengthen, or when the viscosity of the blood increases.

where *K*= constant; *l* =length; *r* = radius; andm = viscosity. Calculated *R* decreases with increasing pulmonary blood flow because pulmonary vessels are distended and collapsed vessels are recruited.

PATHOPHYSIOLOGY

The severity ofRVenlargement in cor pulmonale is a function of the increase in afterload. When the pulmonary vascular resistance is elevated and relatively fixed, as in pulmonary vascular or severe parenchymal lung disease, an elevation in cardiac output as occurs with physical exertion can elevate pulmonary artery pressure markedly. RV afterload may be augmented when the lungs are hyperinflated, as inCOLD, due to the compression of the alveolar capillaries and the lengthening of the pulmonary vessels. RV afterload can also increase when lung volume is reduced following extensive pulmonary resection, as well as in restrictive lung diseases in which pulmonary vessels are compressed and distorted. RV afterload rises with hypoxic pulmonary vasoconstriction caused by hypoxia or acidosis, which are important causes of pulmonary hypertension. Hypoxic vasoconstriction in regions of the lung affected by disease distributes blood flow to normally ventilated regions. Hypoxic vasoconstriction results from alveolar, rather than intravascular, hypoxia and is exaggerated by hypercapnia, probably because of the associated acidosis. When the hematocrit becomes markedly elevated with chronic hypoxemia (secondary polycythemia), the increase in blood viscosity can also aggravate the pulmonary hypertension. Chronic hypoxic pulmonary vasoconstriction may cause pulmonary vascular disease with endothelial swelling and medial hypertrophy (see below).

The elevation ofRVafterload responsible for cor pulmonale is caused principally by pulmonary vascular or parenchymal disease. The principal syndromes and their pathophysiologic mechanisms are summarized inTable 237-1.

PULMONARY VASCULAR DISEASES

In these conditions theRVafterload is elevated as a consequence of restriction to pulmonary blood flow. In cor pulmonale secondary to pulmonary vascular disease, pulmonary hypertension is usually more severe than in pulmonary parenchymal disease. Chronic cor pulmonale secondary to pulmonary vascular disease may result from repeated pulmonary emboli, pulmonary vasculitis, pulmonary vasoconstriction secondary to high altitude, congenital heart disease with left-to-right shunting (e.g., atrial or ventricular septal defect, patent ductus arteriosus;Chap. 234), as well as pulmonary venoocclusive disease. When the cause of elevated pulmonary vascular resistance responsible for cor pulmonale cannot be defined, the condition is referred to as *primary pulmonary hypertension* (Chap. 260).

COR PULMONALE DUE TO PULMONARY EMBOLI

This condition is associated with two distinct syndromes.

Acute Cor Pulmonale It has been estimated that in the United States about 50,000 people die each year from pulmonary thromboembolism (Chap. 261). Probably half die

within the first hour from acute right heart failure due to massive or multiple emboli. A sudden, large embolic burden causes a low-output state resulting from theRV's inability to generate the pressure necessary to drive blood through the acutely compromised pulmonary vascular bed. Depression of cardiac output can also occur with a moderate-sized embolism if the pulmonary circulation has been critically compromised by previous pulmonary vascular or parenchymal disease. The RV begins to fail when systolic pressure is forced to double acutely, i.e., to exceed approximately 50 mmHg. Acute RV failure secondary to pulmonary embolism is suggested by the history of the sudden onset of severe dyspnea and cardiovascular collapse in a patient with, or predisposed to, venous thrombosis.

Clinical Manifestations Acute RVfailure causes pallor, sweating, hypotension, and a rapid pulse of small amplitude. The neck veins are distended and often exhibit prominent *v* waves secondary to tricuspid regurgitation. The liver may be pulsatile, distended, and tender. A systolic murmur of tricuspid regurgitation along the left sternal border may be accompanied by a presystolic (S_4) gallop sound. Arterial blood gas frequently shows reduced Pa_{O_2} due to ventilation/perfusion mismatching and a low Pa_{CO_2}due to hyperventilation.

TREATMENT

If the cardiac output remains adequate to sustain the patient during the critical first 2 or 3 h, endogenous thrombolysis usually results in fragmentation of the clot and the pulmonary artery pressure returns to normal rapidly. Although it has been shown that treatment with thrombolytic agents lyses clots more rapidly than does heparin (Chap. 261), this therapy is probably indicated only when cardiac output is critically reduced and theRVfails. In acute cor pulmonale [and in RV failure due to acute RV infarction (Chap. 243)], an increase in RV preload can be achieved by a cautious expansion of blood volume, which helps to maintain cardiac output. When hypoxic pulmonary vasoconstriction contributes to pulmonary hypertension, inhalation of 100% O_2reduces RV afterload.

Chronic Cor Pulmonale Secondary to Pulmonary Vascular Disease In contrast to acute, massive thromboembolism, when the elevation in pulmonary vascular resistance and theRVhypertrophy develop gradually, higher pulmonary vascular pressures, sometimes even approaching systemic arterial levels, may be generated. Chronic cor pulmonale can be caused by recurrent, medium-sized emboli that fail to lyse, but organize, resulting in chronic thromboembolic pulmonary hypertension. Particles from intravenous drug abuse, parasites, or tumor tissue that embolizes into the pulmonary vascular bed may also cause persistent pulmonary hypertension. Chronic cor pulmonale can also be caused by *primary pulmonary hypertension* (Chap. 260) or any chronic widespread vasculitis, such as occurs in association with collagen vascular disorders and that may affect the pulmonary vascular bed, particularly the CREST syndrome (Chap. 313).

Clinical Manifestations Dyspnea and tachypnea are characteristic features of pulmonary hypertension secondary to pulmonary vascular disease. They may be distressing during mild exertion or even at rest and are *not* relieved by sitting upright. An unproductive cough is another frequent complaint. Anterior chest pain, due to acute

dilation of the root of the pulmonary artery orRVischemia, can occur. The elevation in systemic venous pressure can cause hepatomegaly and ankle edema.

Occasionally there is cyanosis due to arterial hypoxemia and low cardiac output. ARV heave may be palpable along the left sternal border or in the epigastrium, and a high-pitched pulmonary ejection click may be audible to the left of the upper sternum. The second (pulmonary) component of the second heart sound is intensified and may be palpable; fixed narrow splitting of the second heart sound and a right ventricular protodiastolic gallop (S_3) that may increase during inspiration can be present. A systolic murmur of tricuspid regurgitation, which is augmented by inspiration, is often audible; occasionally, a diastolic murmur of pulmonary regurgitation is also heard. Prominent *a* (and sometimes also *v*) waves in the jugular venous pulse are evident. The onset of RV failure is reflected by an increase of venous pressure, the development of larger *v* waves associated with increasing tricuspid regurgitation, a positive hepatojugular reflux, and a gallop rhythm with both third and fourth heart sounds. These physical findings of RV failure can disappear rapidly when pulmonary artery pressure is reduced by relief of hypoxemia.

Hypocapnia due to alveolar hyperventilation is an important feature of chronic pulmonary hypertension secondary to pulmonary vascular disease. Usually there are no abnormalities on spirometry, but the ratio of dead space to tidal volume may be high, particularly when large-vessel obstruction is present. The diffusing capacity of the lung is reduced when the pulmonary vascular disease is associated with a capillary vasculitis and/or loss of capillary blood volume. Typically, exertion causes a marked fall in Pa_{O_2}. The assessment of exercise capacity may be a useful way of following changes in the severity of pulmonary vascular disease in patients with chronic cor pulmonale, because exercise ability is limited by cardiac output and the latter, in turn, by the severity of the pulmonary vascular obstruction.

Laboratory Examination On *radiologic examination* the pulmonary trunk and hilar vessels are enlarged, as is the descending right pulmonary artery. Ventilation and perfusion lung scans and systemic venography showing deep vein thrombosis in the lower extremities are helpful in confirming the diagnosis of embolic pulmonary vascular disease. In the presence of severe pulmonary hypertension, the *electrocardiogram* (ECG) shows P pulmonale, right axis deviation, andRVhypertrophy (Chap. 226).

Echocardiography allows measurement of the thickness of theRV wall and may show enlargement of the RV cavity in relation to the left. The interventricular septum may be displaced leftward and may move paradoxically during the cardiac cycle. Pulmonary artery and RV systolic pressure can be estimated from measurement of the peak tricuspid regurgitant flow and pulmonic regurgitant flow with Doppler echocardiography.

*Magnetic resonance imaging*is useful for measuringRV mass, wall thickness, cavity volume, and ejection fraction.

Failure of theRVejection fraction (measured by radionuclide ventriculography) to increase on exercise is a good indicator of pulmonary hypertension and/or intrinsic RV dysfunction. *Myocardial perfusion scintigraphy* with thallium 201 or sestamibi is also useful in diagnosing cor pulmonale, since the hypertrophied RV is visualized by these

radionuclides. (Normally the RV is not imaged by these radionuclides because of the much greater uptake by the left ventricle.)

Cardiac catheterization provides precise measurement of pulmonary vascular pressures, calculation of pulmonary vascular resistance, and their responses to oxygen and vasodilators. Catheterization is sometimes helpful in patients with cor pulmonale to exclude congenital and left heart diseases, and it allows pulmonary angiography to be carried out to confirm the nature of the pulmonary vascular obstruction. Measurements of pulmonary vascular pressure and flow during exercise may reveal abnormal pressure increments of pulmonary artery systolic and diastolic andRVdiastolic pressures and an inadequate responses of cardiac output.

Lung biopsy can be useful in demonstrating vasculitis in some types of pulmonary vascular disease such as the collagen vascular diseases, rheumatoid arthritis, and Wegener's granulomatosis.

PARENCHYMAL PULMONARY DISEASES

The pathogenesis of cor pulmonale in patients with chronic parenchymal pulmonary disease is shown inFig. 237-1. Cor pulmonale may be caused by both obstructive and restrictive lung diseases, more frequently the former. In these conditions there are usually only modest elevations of pulmonary artery pressure. The development of cor pulmonale confers a poor prognosis on patients with respiratory disease, not becauseRVfailure cannot be treated, but because it reflects the seriousness of the underlying pulmonary disease.

CHRONIC OBSTRUCTIVE LUNG DISEASE (See alsoChap. 258)

This is the most common cause of chronic cor pulmonale. The enlargement of theRV is attributed to the mild-to-moderate pulmonary hypertension that is common in severe obstructive bronchitis and emphysema. Pulmonary artery systolic pressure is typically in the range of 50 to 60 mmHg, far below the systemic levels that may occur in patients with congenital heart disease and in those with primary pulmonary hypertension. Patients with cor pulmonale due toCOLDusually have an advanced form of the disease with FEV_1< 1.0 L and Pa_{O2}< 60 mmHg (Chap. 250). RV failure secondary to COLD often occurs when there is "acute-on-chronic" respiratory failure with intensification of hypoxemia.

Pulmonary hypertension inCOLD is caused by one or more of the following:

1. Pulmonary vasoconstriction secondary to alveolar hypoxia, acidemia, and hypercapnia. When these vasoconstrictor stimuli persist, medial thickening of the smaller muscular arteries develops by the mechanical effects of the high lung volume on the pulmonary vessels.

2. The loss of small vessels in the vascular bed in regions of emphysema and lung destruction.

3. The increased cardiac output and blood viscosity caused by polycythemia secondary

to hypoxia.

Of these causes, hypoxia is the most important. Pulmonary artery pressure rises further on exercise and often falls acutely on inspiration of 100% O_2. Cardiac output tends to be high in the absence of heart failure if hypoxia and hypercapnia are present. Because of the importance of hypoxic pulmonary vasoconstriction in causing pulmonary hypertension, the hypoventilating "blue bloater" with alveolar hypoxia and hypercapnia more frequently suffers from pulmonary hypertension and consequent cor pulmonale than does the emphysematous "pink puffer" without alveolar hypoxia. Ischemic left ventricular dysfunction is a frequent accompaniment since patients with cor pulmonale secondary to COLD usually have a history of heavy cigarette smoking, a major risk factor for ischemic heart disease. The elevation of pulmonary artery pressure may be secondary, in part, to the increase in left atrial pressure resulting from left heart dysfunction. Almost half of all patients who die with cor pulmonale due to COLD also have left ventricular hypertrophy on postmortem examination.

Right ventricular failure often complicates cor pulmonale when patients withCOLDdevelop ventilatory failure and/or a superimposed acute respiratory infection with hypoxia and hypercapnia, and worsening of pulmonary hypertension. Both supraventricular and ventricular arrhythmias may occur. The liver is engorged, tender, and displaced downward by the low diaphragm; a hepatojugular reflux may be present.

An exacerbation of airway obstruction elevates intrathoracic pressure, which impedes venous return, raises jugular venous pressure, and may cause peripheral edema. The venous hypertension due to airflow obstruction declines, sometimes very rapidly, with relief of the obstruction.

Pathology TheRVhypertrophies progressively inCOLD. The main pulmonary arteries are enlarged, and the muscular pulmonary arteries show prominent longitudinal muscle, fibrosis, and elastic changes that continue into the arterioles, where the media becomes muscularized. The small vessels and capillaries are distorted or disappear in regions of lung hyperinflation.

Clinical Manifestations A history of a productive cough and dyspnea, perhaps with wheezing, is frequently elicited. Breathlessness limits the patient's ability in the minor stresses of daily living. Frequently there is a history of emergency hospital admissions because of respiratory infection, sometimes necessitating mechanical ventilation. In breathing oxygen, there may be increasing somnolence or other symptoms of hypercapnia such as recurring headaches, confusion, and even vomiting which, when combined with blurred optic discs (also due to cerebral vasodilation), constitutes the "pseudo tumor cerebri" syndrome. Hypoxia due to hypoventilation is usually worse at night.

Physical Findings Often there is nicotine staining of the fingers, a tell-tale sign reflecting many years of heavy cigarette smoking. The skin may be warm and the arterial pulse bounding in the high cardiac output state induced by hypoxia and hypercapnia. The distention of the chest due to the airflow obstruction and the presence of rhonchi and wheezes secondary to chronic bronchitis usually make cardiac auscultation difficult. A right-sided protodiastolic gallop sound (S_3) and a systolic murmur of tricuspid regurgitant

may be audible. Signs of right heart failure are, as discussed above, difficult to separate from those due to severe airflow obstruction. Peripheral edema may worsen with elevation of systemic venous pressure when atrial fibrillation occurs or when pulmonary infection supervenes. A positive hepatojugular reflux suports the diagnosis ofRVfailure.

Laboratory Examination *Pulmonary function studies* show marked airflow obstruction with hypoxemia and hypercapnia. Exercise is limited by ventilatory rather than cardiac dysfunction untilRVfailure develops. The *chest roentgenogram* reveals hyperinflation, which makes the degree of right heart enlargement difficult to assess. The central pulmonary arteries are large, but at the periphery the vessels are narrowed and disappear, particularly in regions of the lungs that are markedly emphysematous. The ECGis relatively insensitive in demonstrating right heart enlargement because the enlarged lungs are poor electrical conductors and the inspiratory position of the chest is associated with a vertically positioned heart. Arrhythmias, particularly atrial fibrillation and multifocal atrial tachycardia, are common.

Echocardiographic imaging is often difficult because of the air in the distended lungs but usually reveals an increased cross-section of the right ventricular cavity, abnormal thickening of the RVwall, and pulmonary hypertension. Myocardial perfusion scintigraphy shows an abnormally high ratio of right-to-left ventricular uptake.

Right heart catheterization can be carried out at the bedside with a balloon-tipped, flow-directed, multilumen catheter fitted with thermocouples for measuring cardiac output by thermodilution (Chap. 228). The pulmonary artery wedge pressure is usually normal at rest in patients with uncomplicated cor pulmonale. Cardiac catheterization may be useful in assessing the severity of the pulmonary hypertension and its response to respiring oxygen.

TREATMENT

First, medical management of the acute and/or chronic lung disease must be optimal (Chaps. 258 and265). Acute respiratory infection, often the precipitant ofRVfailure, must be treated promptly and vigorously. Alveolar hypoxia at rest and during exertion and sleep should be corrected by improving alveolar ventilation through relieving the airflow obstruction and by judiciously increasing the inspired O_2concentration. Long-term O_2therapy is helpful in patients with severeCOLD and reduces pulmonary artery pressure and pulmonary vascular resistance. When the lung disease improves and pulmonary vasoconstriction secondary to the alveolar hypoxia and hypercapnia are corrected, tachypnea and the signs attributed to right heart failure are relieved. Bronchodilators and antibiotics lessen airflow obstruction, and diuretics relieve the edema. Loop diuretics must be used with care since they may cause a metabolic alkalosis and thereby blunt the respiratory drive. Digitalis should be used cautiously in the presence of overt RV failure, and small phlebotomies should be considered when the hematocrit exceeds 55 to 60%. Inhalation of nitric oxide and infusion of prostacyclin are undergoing evaluation as agents to reduce pulmonary hypertension.The prognosis in cor pulmonale depends on that of the underlying pulmonary disease.

RESTRICTIVE LUNG DISEASES (See alsoChap. 259)

Cor pulmonale in a variety of restrictive disorders of the lung is often associated with obliteration of the pulmonary vascular bed by lung destruction and fibrosis. Treatment of the underlying disorder and management ofRVfailure, as described above, are indicated.

DISORDERS OF VENTILATION

A variety of disorders of the neuromuscular apparatus, diaphragm, and chest wall cause pulmonary hypertension and cor pulmonale secondary to chronic hypoxia and/or compression of pulmonary vessels. Disorders of ventilatory control, including the sleep apnea syndrome, and upper airways obstruction may be responsible for chronic hypoxia, secondary pulmonary hypertension, cor pulmonale, and eventualRVfailure. Management consists of treating the underlying disorder, as discussed in Chaps. 263 and264; the inhalation of oxygen; and the management of RV failure with diuretics and digoxin.

CHRONIC MOUNTAIN SICKNESS (MONGE'S DISEASE)

Residents at high altitudes with chronic hypoxia and secondary polycythemia may develop pulmonary hypertension and cor pulmonale. Psychiatric symptoms -- confusion and loss of mental acuity -- are common features. Descent to a lower altitude and/or cautious phlebotomy result in lowering of pulmonary artery pressure and relief of symptoms.

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238. THE CARDIOMYOPATHIES AND MYOCARDITIDES - *Joshua Wynne*, *Eugene Braunwald*

The cardiomyopathies are diseases that involve the myocardium directly and are not the result of hypertension or congenital, valvular, coronary, arterial, or pericardial abnormalities.

*Diffuse myocardial fibrosis secondary to multiple myocardial scars produced by extensive coronary arterial narrowing and occlusion can impair left ventricular function and is frequently referred to as *ischemic cardiomyopathy*. This is a colloquial use of the term, however, and should be avoided; the term *cardiomyopathy* should be restricted to a condition *primarily* involving heart muscle. In so-called ischemic cardiomyopathy the *primary* involvement is of the coronary vessels.

When the cardiomyopathies are classified on an etiologic basis, two fundamental forms are recognized: (1) a primary type, consisting of heart muscle disease of unknown cause; and (2) a secondary type, consisting of myocardial disease of known cause or associated with a disease involving other organ systems (Table 238-1). (In the World Health Organization classification, *specific cardiomyopathy* is used to describe heart muscle diseases associated with certain systemic or cardiac disorders; examples include hypertensive and metabolic cardiomyopathy.) In many cases, however, it is not possible to arrive at a specific etiologic diagnosis, and thus it is often more desirable to classify the cardiomyopathies on the basis of differences in their pathophysiology and clinical presentation (Tables 238-2 and238-3).

DILATED CARDIOMYOPATHY

Left and/or right ventricular systolic pump function is impaired, leading to progressive cardiac enlargement, a process called *remodeling*, and often, but not invariably, producing symptoms of congestive heart failure. There is, however, no close correlation between the degree of contractile dysfunction and the severity of symptoms. Mural thrombi may be present, particularly in the left ventricular apex. Histologic examination reveals extensive areas of interstitial and perivascular fibrosis. Myocyte necrosis and cellular infiltration may be present but are not prominent.

Although no cause is apparent in many cases, dilated cardiomyopathy is probably the end result of myocardial damage produced by a variety of toxic, metabolic, or infectious agents. Dilated cardiomyopathy may be the late sequel of acute viral myocarditis, possibly mediated through an immunologic mechanism. Most commonly a disease of middle-aged men and more common in African Americans than in whites, it may occur in any patient population. The prevalence of this condition appears to be increasing. A reversible form of dilated cardiomyopathy may be found with alcohol abuse, pregnancy, selenium deficiency, hypophosphatemia, hypocalcemia, thyroid disease, cocaine use, and chronic uncontrolled tachycardia. Approximately 20% of patients have familial forms of the disease, with mutations of genes encoding myocardial structure proteins as well as transcription factors that control the expression of other myocyte genes. The disease is genetically heterogeneous; autosomal dominant, autosomal recessive, and X-linked transmission have been documented.

Right ventricular dysplasia is a unique cardiomyopathy marked by progressive replacement of the right ventricular wall with adipose tissue. Often associated with ventricular arrhythmias, the clinical course is variable, but sudden death is a constant threat. Catheter ablation of putative arrhythmia sites and insertion of an implantable cardioverter-defibrillator are often employed.

CLINICAL MANIFESTATIONS

Symptoms of left- and right-sided congestive failure (Chap. 232), manifested by exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and palpitations, develop gradually in most patients. Some patients have left ventricular dilatation for months or even years before becoming symptomatic. Others develop symptoms after recovery from a viral infection. Although vague chest pain may be present, typical angina pectoris is unusual and suggests the presence of concomitant ischemic heart disease. Systemic embolism, stroke, and syncope may occur.

PHYSICAL EXAMINATION

Variable degrees of cardiac enlargement and findings of congestive heart failure are noted. In patients with advanced disease, the pulse pressure is narrow and the jugular venous pressure is elevated. Third and fourth heart sounds are common, and mitral or tricuspid regurgitation may occur.

LABORATORY EXAMINATIONS

The chest roentgenogram demonstrates enlargement of the cardiac silhouette due to left ventricular enlargement, although generalized cardiomegaly is often seen. The lung fields may demonstrate evidence of pulmonary venous hypertension and interstitial or alveolar edema. The electrocardiogram often shows sinus tachycardia or atrial fibrillation, ventricular arrhythmias, left atrial abnormality, diffuse nonspecific ST-T wave abnormalities, and sometimes intraventricular conduction defects and low voltage. Echocardiography and radionuclide ventriculography show left ventricular dilatation, with normal or minimally thickened or thinned walls, and systolic dysfunction (reduced ejection fraction) (Fig. 238-CD1).

Cardiac catheterization and coronary angiography are usually performed to exclude ischemic heart disease, although hemodynamic monitoring may occasionally be helpful in the management of the acutely decompensated patient. The left ventricular end-diastolic, left atrial, and pulmonary capillary wedge pressures are usually elevated; when failure of the right side of the heart supervenes, the right ventricular end-diastolic, right atrial, and central venous pressures also rise. Angiography reveals a dilated, diffusely hypokinetic left ventricle, often with some degree of mitral regurgitation; the coronary arteries are normal, thereby excluding so-called ischemic cardiomyopathy. Transvenous endomyocardial biopsy is usually not necessary in idiopathic or familial dilated cardiomyopathy, in which it reveals nonspecific findings of myocyte hypertrophy and fibrosis. However, it may be helpful in the recognition of secondary cardiomyopathies such as myocardial infiltration with amyloid and of acute myocarditis.

TREATMENT

Most patients pursue an inexorably downhill course, and the majority, particularly those over 55 years of age, die within 3 years of the onset of symptoms (Fig. 238-CD2). African Americans are more likely to suffer progressive heart failure and death than Caucasians. Spontaneous improvement or stabilization occurs in about a quarter of patients. Death is due to either congestive heart failure or ventricular tachy- or bradyarrhythmia; sudden death is a constant threat. Systemic embolization is a concern, and patients with heart failure secondary to cardiomyopathy should be considered for chronic anticoagulation. Standard therapy of heart failure with salt restriction, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digitalis produces symptomatic improvement (Chap. 232). An angiotensin II receptor blocker may be substituted in ACE-intolerant patients. Most ambulatory patients profit as well from the addition of a b-adrenergic blocker. Some patients with dilated cardiomyopathy who have biopsy evidence of myocardial inflammation have been treated with immunosuppressive therapy, but long-term evidence of efficacy is lacking. Alcohol should be avoided because of its cardiac toxic effects. Antiarrhythmic agents are best avoided for fear of proarrhythmic and other side effects, unless they are needed to treat symptomatic or serious arrhythmias. Insertion of an implantable cardioverter-defibrillator is useful in patients with malignant arrhythmias. In patients with advanced disease who are refractory to medical therapy, cardiac transplantation should be considered (Chap. 233).

ALCOHOLIC CARDIOMYOPATHY

Individuals who consume large quantities of alcohol over many years may develop a clinical picture identical to idiopathic dilated cardiomyopathy; indeed, alcoholic cardiomyopathy is the major form of secondary dilated cardiomyopathy in the western world. Ceasing alcohol consumption before severe heart failure has developed may halt the progression or even reverse the course of this disease, unlike the idiopathic variety, which is marked by progressive deterioration. Alcoholic patients with advanced heart failure have a poor prognosis, particularly if they continue to drink; fewer than one-quarter survive 3 years. The key to the treatment of alcoholic cardiomyopathy is total and permanent abstinence.

A second presentation of alcoholic cardiotoxicity may be found in individuals without overt heart failure and consists of recurrent supraventricular or ventricular tachyarrhythmias. Termed the *holiday heart syndrome*, it typically appears after a drinking binge; atrial fibrillation is seen most frequently, followed by atrial flutter and ventricular premature depolarizations. Other patients develop left ventricular hypertrophy, perhaps related to concomitant systemic hypertension; they may present with symptoms of pulmonary congestion due to abnormal diastolic stiffness (diminished compliance) of the left ventricle (Chap. 231).

PERIPARTUM CARDIOMYOPATHY (See Chap. 7)

Cardiac dilatation and congestive heart failure of unexplained cause may develop during the last trimester of pregnancy or within 6 months after delivery; most women develop symptoms in the month before or immediately after delivery. The cause of this disorder is unknown, but in some patients endomyocardial biopsy has shown evidence of a myocarditis. Necropsy shows cardiac enlargement, often with mural thrombi, along with

histologic evidence of myocardial degeneration and fibrosis. The patient who develops peripartum cardiomyopathy typically is multiparous, African American, and over the age of 30, although the disease may be found in a wide spectrum of patients. The symptoms, signs, and treatment are similar to those in patients with idiopathic dilated cardiomyopathy. The mortality rate is quite variable but may be as high as 25 to 50%. The prognosis in these patients appears to be closely related to whether the heart size returns to normal after the first episode of congestive heart failure. If it does, subsequent pregnancies may sometimes be well tolerated; if the heart remains enlarged, however, further pregnancies frequently produce increasing myocardial damage, ultimately leading to refractory congestive heart failure and death. Those who recover should be encouraged to avoid further pregnancies, particularly if cardiomegaly persists.

NEUROMUSCULAR DISEASE (See also Chap. 381)

Cardiac involvement is common in many of the muscular dystrophies. In *Duchenne's progressive muscular dystrophy*, mutations in a gene that encodes a cardiac structural protein called *dystrophin* lead to myocyte death. Myocardial involvement is most frequently indicated by a distinctive and unique electrocardiographic pattern consisting of tall R waves in right precordial leads with an R/S ratio greater than 1.0, often associated with deep Q waves in the limb and lateral precordial leads. These electrocardiographic abnormalities appear to result from selective transmural necrosis of the posterobasal left ventricle and associated papillary muscle. A variety of supraventricular and ventricular arrhythmias are frequently found. Rapidly progressive congestive heart failure may develop despite extended periods of apparent circulatory stability during which the only detectable abnormalities are in the electrocardiogram. *Myotonic dystrophy* is characterized by a variety of electrocardiographic abnormalities, especially disorders of impulse formation and conduction, but other overt clinical evidence of heart disease is uncommon. Because of these abnormalities, syncope and sudden death are major hazards; in appropriate patients, insertion of a permanent pacemaker may be effective. In *limb-girdle dystrophy* and *fascioscapulohumeral dystrophy*, cardiac involvement is uncommon and seldom severe, although arrhythmias and conduction disturbances may be seen on occasion. Involvement of the heart is very common in *Friedreich's ataxia* (manifested by abnormal electrocardiographic or echocardiographic findings), with as many as half the patients developing cardiac symptoms. The electrocardiogram most commonly demonstrates ST-segment and T-wave abnormalities. The echocardiogram may demonstrate left ventricular hypertrophy, with either symmetric or asymmetric hypertrophy of the left ventricular septum compared with the free wall. Although morphologically similar to some cases of hypertrophic cardiomyopathy, cellular disarray is lacking.

DRUGS

A variety of pharmacologic agents may damage the myocardium acutely, producing a pattern of inflammation (myocarditis), or they may lead to chronic damage of the type seen with idiopathic dilated cardiomyopathy (Chap. 71). Certain drugs produce only electrocardiographic abnormalities, while others may precipitate fulminant congestive heart failure and death.

The anthracycline derivatives, particularly *doxorubicin* (Adriamycin), are powerful

antineoplastic agents that, when given in high doses (more than 550 mg/m^2 for doxorubicin), may produce fatal heart failure. The incidence of heart failure is related not only to the dose of the drug but also to the presence or absence of several risk factors (cardiac irradiation, age>70 years, underlying heart disease, hypertension, treatment with cyclophosphamide); at any dose, patients with these risk factors have an eight- to tenfold greater frequency of developing heart failure than do patients lacking them. Radionuclide ventriculography and echocardiography, usually combined with exercise stress, may document preclinical deterioration of left ventricular function and allow appropriate dose adjustments; by so monitoring left ventricular function, it is often possible to continue doxorubicin even in patients at high risk for developing heart failure. Efforts to modify the dose schedule by giving the drug more slowly, along with the selective use of potentially cardioprotective agents such as the iron-chelator dexrazoxone, have further reduced the risk of cardiotoxicity. Some patients with congestive heart failure, even those with severe depression of left ventricular function, have demonstrated recovery of cardiac function with aggressive management withACEinhibitors and diuretics. In others, late asymptomatic contractile dysfunction is common, even in those without initial cardiotoxicity. Children may demonstrate reduced myocardial hypertrophy and mass over time, presumably due to doxorubicin's inhibition of myocardial cell growth.

High-dose *cyclophosphamide* may produce congestive heart failure acutely or within 2 weeks of administration; a characteristic histopathologic feature is myocardial edema and hemorrhagic necrosis. Rarely, patients treated with *5-fluorouracil* will develop chest pain and electrocardiographic changes of myocardial ischemia or infarction. Electrocardiographic changes and arrhythmias may result from treatment with tricyclic antidepressants, the phenothiazines, emetine, lithium, and various aerosol propellants. *Cocaine abuse* is associated with a variety of life-threatening cardiac complications, including sudden death, myocarditis, dilated cardiomyopathy, and acute myocardial infarction (resulting from coronary spasm and/or thrombosis with or without underlying coronary artery stenosis). Nitrates and calcium channel blockers have been used to treat cocaine-induced cardiotoxicities; b-adrenergic blockers should be avoided.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy, typically of a nondilated chamber, without obvious cause such as hypertension or aortic stenosis (Fig. 238-CD3). It is found in about 1 in 500 of the general population. Two features of HCM have attracted the greatest attention: (1) heterogeneous left ventricular hypertrophy, often with preferential hypertrophy of the interventricular septum resulting in asymmetric septal hypertrophy; and (2) a dynamic left ventricular outflow tract pressure gradient, related to a narrowing of the subaortic area as a consequence of the midsystolic apposition of the anterior mitral valve leaflet against the hypertrophied septum, i.e., systolic anterior motion (SAM) of the mitral valve (Fig. 238-CD4). Initial studies of this disease emphasized the dynamic "obstructive" features, and it has been termed *idiopathic hypertrophic subaortic stenosis* and *hypertrophic obstructive cardiomyopathy*. It has become clear, however, that only about one-quarter of patients with HCM demonstrate an outflow tract pressure gradient. The ubiquitous pathophysiologic abnormality is not systolic but rather *diastolic* dysfunction (Chap. 231), characterized by increased stiffness of the hypertrophied muscle. This results in

elevated diastolic filling pressures and is present despite a hyperdynamic left ventricle.

The pattern of hypertrophy is distinctive in HCM and differs from that seen in secondary hypertrophy (as in hypertension). Most patients have striking regional variations in the extent of hypertrophy in different portions of the left ventricle, and the majority demonstrate a ventricular septum whose thickness is disproportionately increased when compared with the free wall. Other patients may demonstrate disproportionate involvement of the apex or left ventricular free wall; 10% or more of patients have concentric involvement of the ventricle. A bizarre and disorganized arrangement of cardiac muscle cells in the septum occurs, with disorganization of the myofibrillar architecture, along with a variable degree of myocardial fibrosis and thickening of the small intramural coronary arteries. In some children, systolic compression of an intramyocardial segment of a coronary artery may lead to ischemia and death.

GENETIC CONSIDERATIONS

About half of all patients with HCMhave a positive family history compatible with autosomal-dominant transmission, and more than 100 different mutations have been identified. About 40% of these are associated with mutations of the cardiac b-myosin heavy chain gene on chromosome 14, with certain mutations associated with more malignant prognoses. About 15% have a mutation of the cardiac troponin T gene on chromosome 1, 20% a mutation of myosin-binding protein C (chromosome 11), and about 5% a mutation of the a-tropomyosin gene. The remainder of familial cases are due to mutations of other genes such as the gene for troponin I. Echocardiographic studies have confirmed that about one-third of the first-degree relatives of patients with familial HCM have evidence of the disease, although in many of these patients the extent of hypertrophy is mild, no outflow tract pressure gradient is present, and symptoms are not prominent. Since the hypertrophic characteristics may not be apparent in childhood and often appear first in adolescence, a single normal echocardiogram in a child does not exclude the presence of the disease. Many sporadic cases of HCM probably represent spontaneous mutations.

HEMODYNAMICS

In contrast to the obstruction produced by a fixed narrowed orifice, such as valvular aortic stenosis, the pressure gradient inHCM, when present, is dynamic and may change between examinations and even from beat to beat. Obstruction appears to result from further narrowing of an already small left ventricular outflow tract bySAM of the mitral valve against the hypertrophied septum. While SAM is occasionally found in a variety of conditions besides HCM, it is *always* found when obstruction is present in HCM. Three basic mechanisms are involved in the production and intensification of the dynamic pressure gradient: (1) increased left ventricular contractility, (2) decreased ventricular volume (preload), and (3) decreased aortic impedance and pressure (afterload). Interventions that increase myocardial contractility, such as exercise, sympathomimetic amines, and digitalis glycosides, and those that reduce ventricular volume, such as the Valsalva maneuver, sudden standing, nitroglycerin, amyl nitrite, or tachycardia, may all cause an increase in the gradient and the murmur. Conversely, elevation of arterial pressure by phenylephrine, squatting, sustained handgrip, augmentation of venous return by passive leg raising, and expansion of the blood

volume all increase ventricular volume and ameliorate the gradient and murmur.

CLINICAL FEATURES

The clinical course ofHCM is highly variable. Many patients are asymptomatic or mildly symptomatic and may be relatives of patients with known disease. Unfortunately, the first clinical manifestation of the disease may be sudden death, frequently occurring in children and young adults, often during or after physical exertion. In symptomatic patients, the most common complaint is dyspnea, largely due to increased stiffness of the left ventricular walls, which impairs ventricular filling and leads to elevated left ventricular diastolic and left atrial pressures. Other symptoms include angina pectoris, fatigue, syncope, and near-syncope ("graying-out spells"). Symptoms are not closely related to the presence or severity of an outflow pressure gradient. Most patients with gradients demonstrate a double or triple apical precordial impulse, a rapidly rising carotid arterial pulse, and a fourth heart sound. The hallmark of obstructive HCM is a systolic murmur, which is typically harsh, diamond-shaped, and usually begins well after the first heart sound, since ejection is unimpeded early in systole (Fig. 238-CD5). The murmur is best heard at the lower left sternal border as well as at the apex, where it is often more holosystolic and blowing in quality, no doubt due to the mitral regurgitation that usually accompanies obstructive HCM.

LABORATORY EVALUATION

The *electrocardiogram* commonly shows left ventricular hypertrophy and widespread, deep, broad Q waves that suggest an old myocardial infarction. Many patients demonstrate arrhythmias, both atrial (supraventricular tachycardia or atrial fibrillation) and ventricular (ventricular tachycardia), during ambulatory (Holter) monitoring. *Chest roentgenography* may be normal, although a mild to moderate increase in the cardiac silhouette is common. The mainstay of the diagnosis ofHCM is the *echocardiogram* (Fig. 238-CD6), which demonstrates left ventricular hypertrophy, often with the septum 1.3 or more times the thickness of the high posterior left ventricular free wall. The septum may demonstrate an unusual "ground-glass" appearance, probably related to its abnormal cellular architecture and myocardial fibrosis.SAM of the mitral valve is found in patients with pressure gradients. The left ventricular cavity typically is small in HCM, with vigorous posterior wall motion but reduced septal excursion. A rare form of HCM, characterized by apical hypertrophy, is often associated with giant negative T waves on the electrocardiogram and a "spade-shaped" left ventricular cavity on angiography; it usually has a benign clinical course. *Radionuclide scintigraphy* with thallium 201 frequently reveals evidence of myocardial perfusion defects even in asymptomatic patients.

Although cardiac catheterization is not required to diagnose HCM, the two typical *hemodynamic* features are an elevated left ventricular diastolic pressure due to diminished left ventricular compliance and, when obstruction is present, a systolic pressure gradient between the body of the left ventricle and the subaortic region. When a gradient is not present, it can be induced in some patients by provocative maneuvers such as infusion of isoproterenol, inhalation of amyl nitrite, or the Valsalva maneuver.

TREATMENT

Since sudden death often occurs during or just after physical exertion, competitive sports and probably strenuous activity should be proscribed. Dehydration should be avoided, and diuretics should be used with caution.b-Adrenergic blockers are often used and ameliorate angina pectoris and syncope in one-third to one-half of patients. Resting intraventricular pressure gradients are usually unchanged, although these drugs may limit the increase in the gradient that occurs during exercise. It is not known whether b-adrenergic blockers offer any protection against sudden death. Amiodarone appears to be effective in reducing the frequency of supraventricular as well as life-threatening ventricular arrhythmias, and anecdotal data suggest that it may reduce the risk of sudden death. Verapamil and diltiazem may reduce the stiffness of the ventricle, reduce the elevated diastolic pressures, increase exercise tolerance, and, in some instances, reduce the severity of outflow tract pressure gradients, although adverse side effects occur in about one-quarter of patients. Nifedipine should be avoided. The combination of beta blockers and calcium antagonists should be used with caution. Disopyramide has been used in some patients to reduce left ventricular contractility and the outflow pressure gradient.

If atrial fibrillation occurs, a strenuous effort should be made to restore and then maintain sinus rhythm. Dual-chamber permanent pacing with a short PR interval has been reported to improve symptoms and reduce the outflow gradient in some patients with severe symptoms, presumably by altering the pattern of ventricular depolarization and contraction. Infarction of the interventricular septum induced by ethanol injections into the septal artery has also been reported to reduce obstruction. The insertion of an implantable cardioverter defibrillator should be considered in patients surviving cardiac arrest and those with high-risk ventricular tachyarrhythmias (Chap. 230). A surgical myotomy/myectomy of the hypertrophied septum may result in lasting symptomatic improvement in about three-quarters of severely symptomatic patients with large pressure gradients who are unresponsive to medical management. The effect of any of these therapies on the natural history is not clear. Digitalis, diuretics, nitrates, vasodilators, and b-adrenergic agonists are best avoided if possible, particularly in patients with known left ventricular outflow tract pressure gradients. Even social alcohol ingestion may produce sufficient vasodilatation to exacerbate an outflow pressure gradient.

First-degree relatives of patients with HCMshould be screened by echocardiography.

PROGNOSIS

The natural history ofHCM is variable, although many patients never exhibit any clinical manifestations. Others demonstrate an improvement of symptoms with time. Atrial fibrillation is common late in the course of the disease; its onset may lead to an increase in symptoms, due to loss of the atrial contribution to filling of the thickened ventricle. Infective endocarditis occurs in fewer than 10% of patients, and endocarditis prophylaxis is indicated, particularly in patients with resting obstruction and mitral regurgitation. Progression of HCM to left ventricular dilatation and dysfunction without an outflow pressure gradient has been reported but is unusual; in about 5 to 10% of patients, however, some degree of left ventricular systolic impairment, wall thinning, and chamber enlargement occurs over time. The major cause of mortality in HCM is sudden death,

which may occur in asymptomatic patients or interrupt an otherwise stable course in symptomatic ones. Predictors of sudden death include age less than 30 years, ventricular tachycardia on ambulatory monitoring, marked ventricular hypertrophy, syncope (especially in children), genetic mutations associated with an increased risk, and a family history of sudden death. There is no correlation between the risk of sudden death and the severity of symptoms or the presence or severity of an outflow tract pressure gradient.

RESTRICTIVE CARDIOMYOPATHY

The hallmark of the restrictive cardiomyopathies is abnormal diastolic function (Chap. 231); the ventricular walls are excessively rigid and impede ventricular filling. Myocardial fibrosis, hypertrophy, or infiltration due to a variety of causes (Fig. 238-CD7) is usually responsible. The infiltrative diseases, which represent important causes for secondary restrictive cardiomyopathy, may also show some impairment of systolic function. Myocardial involvement with *amyloid* is a common cause of secondary restrictive cardiomyopathy, although restriction is also seen in hemochromatosis, glycogen deposition, endomyocardial fibrosis, sarcoidosis, Fabry's disease, the eosinophilias, and scleroderma; in the transplanted heart and following mediastinal radiation; and in neoplastic infiltration and myocardial fibrosis of diverse causes. In many of these conditions, particularly those with substantial concomitant endocardial involvement, partial obliteration of the ventricular cavity by fibrous tissue and thrombus contributes to the abnormally increased resistance to ventricular filling. Thromboembolic complications ensue in about a third of patients.

The inability of the ventricle to fill limits cardiac output and raises filling pressure. Therefore, exercise intolerance and dyspnea are usually the most prominent symptoms. As a result of persistently elevated venous pressure, these patients commonly have dependent edema, ascites, and an enlarged, tender, and often pulsatile liver. The jugular venous pressure is elevated and does not fall normally, or it may rise with inspiration (Kussmaul's sign). The heart sounds may be distant, and third and fourth heart sounds are common. In contrast to constrictive pericarditis, which the restrictive cardiomyopathies resemble in many respects, the apex impulse is usually easily palpable, and mitral regurgitation is more common. The electrocardiogram often shows low-voltage, nonspecific ST-T-wave changes and various arrhythmias. Pericardial calcification on x-ray, which would suggest constrictive pericarditis, is absent. Echocardiography typically reveals symmetrically thickened left ventricular walls and normal or slightly reduced ventricular volumes and systolic function. Doppler recordings demonstrate accentuated early diastolic filling. Cardiac catheterization shows a decreased cardiac output, elevation of the right and left ventricular end-diastolic pressures, and a dip-and-plateau configuration of the diastolic portion of the ventricular pressure pulse resembling that seen in constrictive pericarditis.

Differentiation from constrictive pericarditis may be challenging (Chap. 239). This distinction is of importance because the latter condition is potentially curable by operation. Helpful in the differentiation of these two diseases are right ventricular transvenous endomyocardial biopsy (by revealing myocardial infiltration or fibrosis in restrictive cardiomyopathy) and computed tomography or magnetic resonance imaging (by demonstrating a thickened pericardium in constrictive pericarditis). Treatment is

usually disappointing, except for hemochromatosis (where desferoxamine has been helpful in reducing myocardial iron content). Chronic anticoagulation is often recommended to reduce the risk of embolization from the heart.

ENDOMYOCARDIAL FIBROSIS

This is a progressive disease of unknown cause that occurs most commonly in children and young adults residing in tropical and subtropical Africa, particularly Uganda and Nigeria. Endomyocardial fibrosis is a frequent cause of heart failure in Africa, accounting for up to one-quarter of deaths due to heart disease. The condition is characterized by fibrous endocardial lesions of the inflow portion of the right or left ventricle (or both) and often involves the atrioventricular valves, producing valvular regurgitation. The apex of the ventricles may be obliterated by a mass of thrombus and fibrous tissue. In some ways this disease resembles eosinophilic endomyocardial disease (see below), although they occur in quite different geographic areas and age groups and generally are felt to be different diseases.

The clinical picture depends on which ventricle and atrioventricular valve show predominant involvement; left-sided involvement results in symptoms of pulmonary congestion, while predominant right-sided disease presents features of a restrictive cardiomyopathy. Medical treatment is often disappointing, and surgical excision of the fibrotic endocardium and replacement of the involved atrioventricular valve have led to substantial symptomatic improvement in some patients.

EOSINOPHILIC ENDOMYOCARDIAL DISEASE

Also called *Loeffler's endocarditis* and *fibroplastic endocarditis*, this disease appears to be a subcategory of the hypereosinophilic syndrome in which the heart is predominantly involved, with cardiac damage the apparent result of the toxic effects of eosinophilic proteins. Typically, the endocardium of either or both ventricles thickens markedly, with involvement of the underlying myocardium. Large mural thrombi may develop in either ventricle, thereby compromising the size of the ventricular cavity and serving as a source of pulmonary and systemic emboli. Hepatosplenomegaly and localized eosinophilic infiltration of other organs are usually present. Management usually includes diuretics, afterload-reducing agents, and anticoagulation. The use of glucocorticoids and cytotoxic drugs (hydroxyurea in particular) appears to have improved survival substantially. Surgical treatment, as for endomyocardial fibrosis, may be helpful in selected patients.

DIFFERENTIAL DIAGNOSIS

Involvement of the heart is the most frequent cause of death in *primary amyloidosis* (Chap. 319), while clinically significant cardiac involvement is uncommon in the secondary form. Focal deposits of amyloid in elderly patients (*senile cardiac amyloidosis*) are common and usually clinically insignificant. Aspiration of abdominal fat or biopsy of the rectal mucosa, gingiva, liver, kidney, or myocardium permits the diagnosis to be made before death in over three-quarters of cases. The heart is firm, rubbery, and noncompliant, and four clinical presentations (alone or in combination) are seen: (1) diastolic dysfunction (restrictive cardiomyopathy), (2) systolic dysfunction, (3)

arrhythmias and conduction disturbances, and (4) orthostatic hypotension. The two-dimensional echocardiogram may be helpful in making the diagnosis of amyloidosis and may show a thickened myocardial wall with a distinctive "speckled" appearance. Chemotherapy, often with alkylating agents, appears to have improved survival in specific cases, but the overall prognosis is poor.

Hemochromatosis (Chap. 345) is often the result of multiple transfusions or a hemoglobinopathy; the familial (autosomal recessive) form should be suspected if cardiomyopathy occurs in the setting of diabetes mellitus, hepatic cirrhosis, and increased skin pigmentation. The diagnosis may be confirmed by endomyocardial biopsy. Phlebotomy may be of some benefit if employed early in the course of the disease. Continuous subcutaneous administration of deferoxamine may reduce body iron stores and result in clinical improvement.

Myocardial *sarcoidosis* (Chap. 318) is generally associated with other manifestations of systemic disease and may cause restrictive as well as congestive features, since cardiac infiltration by sarcoid granulomas results not only in increased stiffness of the myocardium but also in diminished systolic contractile function. A variety of arrhythmias, including high-grade atrioventricular block, have been noted. A common cardiac manifestation of systemic sarcoidosis is right heart overload due to pulmonary artery hypertension as a result of parenchymal pulmonary involvement. The *carcinoid syndrome* results in endocardial fibrosis and stenosis and/or regurgitation of the tricuspid and/or pulmonary valve (Chap. 236); morphologically similar lesions have been seen with the use of the anorexic agents fenfluramine and phentermine.

MYOCARDITIDES

Myocarditis, i.e., cardiac inflammation, is most commonly the result of an infectious process. Myocarditis may also result from a hypersensitivity to drugs or may be caused by radiation, chemicals, or physical agents. In an unknown number of cases, acute myocarditis progresses to chronic dilated cardiomyopathy. While almost every infectious agent is capable of producing myocarditis (Table 238-1), clinically significant acute myocarditis in the United States is caused most commonly by viruses, especially coxsackievirus B. The clinical manifestations range from an asymptomatic state, with the presence of myocarditis inferred only by the finding of transient electrocardiographic ST-T-wave abnormalities, to a fulminant condition with arrhythmias, heart failure, and death. In some patients, myocarditis simulates acute myocardial infarction, with chest pain, electrocardiographic changes, and elevated serum levels of myocardial enzymes.

The physical examination is often normal, although more severe cases may show a muffled first heart sound, along with a third heart sound and a murmur of mitral regurgitation. A pericardial friction rub may be audible in patients with associated pericarditis.

Though viral myocarditis is most often self-limited and without sequelae, severe involvement may recur, and it is likely that acute viral myocarditis occasionally progresses to a chronic form and to dilated cardiomyopathy. Patients with viral myocarditis often give a history of a preceding upper respiratory febrile illness or a flulike syndrome, and viral nasopharyngitis or tonsillitis may be evident clinically. The

isolation of virus from the stool, pharyngeal washings, or other body fluids and changes in specific antibody titers are helpful clinically. Endomyocardial biopsy, carried out early in the illness, may show round-cell infiltration and necrosis of adjacent myocytes.

Experimental studies suggest that exercise may be deleterious in patients with viral myocarditis, and strenuous activity should be proscribed until the electrocardiogram has returned to normal. Patients who develop congestive heart failure respond to the usual measures (ACEinhibitors, diuretics, and salt restriction), but they appear to be unusually sensitive to digitalis. Arrhythmias are common and are occasionally difficult to manage. Deaths attributed to heart failure, tachyarrhythmias, and heart block have been reported, and it seems prudent to monitor the electrocardiogram of patients with arrhythmias, especially during the acute illness.

HIV MYOCARDITIS (See alsoChap. 309)

Many HIV-infected patients have subclinical cardiac involvement, including pericardial effusion, right-sided chamber enlargement, and neoplastic involvement. Overt clinical involvement is seen in 10% of HIV patients, and the most common finding is left ventricular dysfunction that in some cases appears to be due to infiltration of the myocardium by the virus itself. In other patients, the heart is affected by any of the various opportunistic infections common in AIDS, such as toxoplasmosis, as well as by cardiac metastases in Kaposi's sarcoma. The clinical manifestations of cardiac involvement may be incorrectly attributed to concurrent noncardiac problems such as pneumonia. This is unfortunate, since the dilated cardiomyopathy of HIV infection may respond at least transiently to standard therapy with digitalis, diuretics, and ACE inhibitors.

BACTERIAL MYOCARDITIS

Bacterial involvement of the heart is uncommon, but when it does occur, it is usually as a complication of bacterial endocarditis (typically due to *Staphylococcus aureus* and enterococci). Myocardial abscess formation may involve the valve rings and interventricular septum. *Diphtheritic myocarditis* develops in over one-quarter of the patients with diphtheria, is one of the most serious complications, and is the most common cause of death (Chap. 141). Cardiac damage is due to the liberation of a toxin that inhibits protein synthesis and leads to a dilated, flabby, hypocontractile heart; the conducting system is frequently involved as well. Cardiomegaly and severe congestive heart failure typically appear after the first week of illness. Prompt therapy with antitoxin is crucial; antibiotic therapy is also indicated but is of less urgency.

CHAGAS' DISEASE

Chagas' disease, caused by the protozoan *Trypanosoma cruzi* and transmitted by an insect vector (Chap. 216), produces an extensive myocarditis that typically becomes evident years after the initial infection. It is one of the most common causes of heart disease encountered in Central and South America; in rural endemic areas 20 to 75% of the population may be affected. An increasing number of cases are found in the United States as patients migrate from endemic areas. Although only about 1% of infected individuals have an acute illness, which may include acute myocarditis, upwards of

one-third develop chronic myocardial damage many years later. The chronic form is characterized by dilatation of several cardiac chambers, fibrosis and thinning of the ventricular wall, aneurysm formation (especially at the left ventricular apex), and mural thrombi. Chronic progressive heart failure is the rule and is associated with poor survival. The electrocardiogram is abnormal in most patients with cardiac involvement and typically shows right bundle branch block and left anterior hemiblock, which may progress to complete atrioventricular block. The *echocardiogram* may reveal a unique pattern of hypokinesis of the posterior left ventricular wall and relatively preserved septal motion. Ventricular arrhythmias are common and are seen especially during and after exertion; oral amiodarone appears to be particularly effective in treating ventricular tachyarrhythmias. The cause of death is either intractable congestive heart failure or an arrhythmia, with a minority of patients dying from embolic phenomena.

TREATMENT

Therapy is directed toward amelioration of the congestive heart failure and arrhythmias; progressive conduction system disease and heart block may require implantation of a pacemaker. Anticoagulation (if feasible) may reduce the risk of thromboembolism. Medical therapy is often unsatisfactory or unavailable (especially in poor rural areas), however, and a more promising tactic in endemic areas has been the institution of public health measures, particularly the use of insecticides to eliminate the vector.

GIANT CELL MYOCARDITIS

This rare myocarditis of unknown cause is characterized by the presence of multinucleated giant cells in the myocardium. It usually causes rapidly fatal congestive heart failure and arrhythmia in young to middle-aged adults. At necropsy, the distinctive features include cardiac enlargement, ventricular thrombi, grossly visible serpiginous areas of myocardial necrosis in both ventricles, and microscopic evidence of giant cells within an extensive inflammatory infiltrate. The cause of giant cell myocarditis remains obscure, although it occurs in association with thymoma, systemic lupus erythematosus, and thyrotoxicosis. While treatment with immunosuppressive therapy may help in some patients, cardiac transplantation is the treatment of choice.

LYME CARDITIS(See also Chap. 176)

Lyme disease is caused by a tick-borne spirochete and is most common in the Northeast, upper Midwest, and Pacific Coastal regions of the United States during the summer months. About 10% of patients develop symptomatic cardiac involvement during the acute phase of the disease. Atrioventricular nodal conduction abnormalities are the most common manifestations of involvement, and may lead to syncope. Concomitant myopericarditis is not uncommon, and mild asymptomatic left ventricular dysfunction may occur. Intravenous ceftriaxone or penicillin is used in all but the mildest forms of Lyme carditis, in which case oral amoxicillin or doxycycline is employed. Hospitalization with electrocardiographic monitoring is indicated in patients with second- or third-degree atrioventricular block. A temporary pacemaker may be needed for symptomatic heart block; the utility of glucocorticoids in reversing heart block is uncertain, but they are usually employed. Long-term cardiac manifestations of Lyme disease are uncommon.

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239. PERICARDIAL DISEASE - *Eugene Braunwald*

NORMAL FUNCTIONS OF THE PERICARDIUM

The visceral pericardium is a serous membrane that is separated by a small quantity (15 to 50 mL) of fluid, an ultrafiltrate of plasma, from a fibrous sac, the parietal pericardium. The pericardium normally prevents sudden dilatation of the cardiac chambers during exercise and with hypervolemia. As the result of the development of a negative intrapericardial pressure during ejection, the pericardial sac facilitates atrial filling during ventricular systole. The pericardium also restricts the anatomic position of the heart, minimizes friction between the heart and surrounding structures, prevents displacement of the heart and kinking of the great vessels, and probably retards the spread of infections from the lungs and pleural cavities to the heart. Notwithstanding the foregoing, total absence of the pericardium does not produce obvious clinical disease. In partial left pericardial defects the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium, may be classified both clinically and etiologically (Table 239-1). Pain, a pericardial friction rub, electrocardiographic changes, and pericardial effusion with cardiac tamponade and paradoxic pulse are cardinal manifestations of many forms of acute pericarditis and will be considered prior to a discussion of the most common forms of the disorder.

Chest pain is an important but not invariable symptom in various forms of acute pericarditis (Chap. 13); it is usually present in the acute infectious types and in many of the forms presumed to be related to hypersensitivity or autoimmunity. Pain is often absent in a slowly developing tuberculous, postirradiation, neoplastic, or uremic pericarditis. The pain of pericarditis is often severe. It is characteristically retrosternal and left precordial, referred to the back and the left trapezius ridge. Often the pain is pleuritic consequent to accompanying pleural inflammation, i.e., sharp and aggravated by inspiration, coughing, and changes in body position, but sometimes it is a steady, constricting pain that radiates into either arm or both arms and resembles that of myocardial ischemia; therefore, confusion with myocardial infarction is common. Characteristically, however, pericardial pain may be relieved by sitting up and leaning forward and is intensified by lying supine. The differentiation of acute myocardial infarction from acute pericarditis becomes perplexing when, with acute pericarditis, the serum creatine kinase level rises, presumably because of concomitant involvement of the epicardium. However, these enzyme elevations, if they occur, are quite modest, given the extensive electrocardiographic ST-segment elevation in pericarditis.

The *pericardial friction rub* is the most important physical sign of acute pericarditis; it may have up to three components per cardiac cycle and is high-pitched, scratching, and grating, as described in Chap. 225; it can sometimes be elicited only when firm pressure with the diaphragm of the stethoscope is applied to the chest wall at the left lower sternal border. It is heard most frequently during expiration with the patient in the sitting

position. The rub is often inconstant and the loud to-and-fro leathery sound may disappear within a few hours, possibly to reappear the following day.

The *electrocardiogram* (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation (seeFig. 226-18, p. 1270). There is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_2 to V_6, with reciprocal depressions only in aVR and sometimes V_1. Usually there are no significant changes in QRS complexes, except for some reduction in voltage in patients with large pericardial effusions. After several days, the ST segments return to normal, and only then do the T waves become inverted. In contrast, in acute myocardial infarction, reciprocal depression of ST segments is usually more prominent; QRS changes occur, particularly the development of Q waves, as well as notching and loss of R-wave amplitude; and T-wave inversions usually occur within hours *before* the ST segments have become isoelectric. Sequential ECGs are useful in distinguishing acute pericarditis from acute myocardial infarction. In the latter, elevated ST segments return to normal within hours. Early repolarization is a normal variant and may also cause widespread ST-segment elevation, most prominent in left precordial leads. However, in this condition the T waves are usually tall and the ST/T ratio is under 0.25, but this ratio is higher in acute pericarditis. Depression of the PR segment (below the TP segment) is also common and reflects atrial involvement. With large pericardial effusions, the QRS voltage is reduced; atrial premature beats and atrial fibrillation are sometimes noted.

PERICARDIAL EFFUSION

In acute pericarditis, pericardial effusion is usually associated with pain and/or the above-mentionedECGchanges characteristic of pericarditis and an enlargement of the cardiac silhouette. Pericardial effusion is especially important clinically when it develops within a relatively short time, since it may lead to cardiac tamponade (see below). Differentiation from cardiac enlargement may be difficult on physical examination, but heart sounds tend to become faint with pericardial effusion; the friction rub may disappear, and the apex impulse may vanish, but sometimes it remains palpable, albeit medial to the left border of cardiac dullness. The base of the left lung may be compressed by pericardial fluid, producing Ewart's sign, a patch of dullness beneath the angle of the left scapula. The chest roentgenogram may show a "water bottle" configuration of the cardiac silhouette but may also be normal or almost so. Lucent pericardial fat lines may be seen deep within the cardiopericardial silhouette. Fluoroscopic examination may show the ventricular pulsations to be diminished. Pericardial effusion is common after cardiac surgery and myocardial infarction.

Diagnosis *Echocardiography* is the most effective diagnostic laboratory technique available, since it is sensitive, specific, simple, noninvasive, may be performed at the bedside, and can identify accompanying cardiac tamponade (see below). The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium in patients with small effusions and as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall in those with larger effusions. In the latter the heart may swing freely within the pericardial sac; when severe, the extent of this motion alternates and may be associated with electrical

alternans. Echocardiography allows localization and estimation of the quantity of pericardial fluid. The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI); these techniques may be superior to echocardiography in detecting loculated pericardial effusions and pericardial thickening.

Pericardiocentesis When pericardial fluid is removed for diagnostic and/or therapeutic purposes, a needle attached to a properly groundedECG lead is inserted into the pericardial space, usually through a subxiphoid approach, and, if possible, using echocardiographic control. Intrapericardial pressure should be measured before fluid is withdrawn. Pericardial effusion nearly always has the physical characteristics of an exudate. Bloody fluid is commonly due to tuberculosis or tumor but may also be found in the effusion of rheumatic fever, post-cardiac injury, and post-myocardial infarction (especially following the administration of anticoagulant), and in uremic pericarditis. Transudative pericardial effusions may occur in heart failure.

CARDIAC TAMPONADE

The accumulation of fluid in the pericardium in an amount sufficient to cause serious obstruction to the inflow of blood to the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The three most common causes of tamponade are neoplastic disease, idiopathic pericarditis, and uremia. Tamponade may also result from bleeding into the pericardial space either following cardiac operations and trauma (including cardiac perforation during diagnostic procedures) or from tuberculosis and hemopericardium. The latter may occur when a patient with any form of acute pericarditis is treated with anticoagulants.

The three principal features of tamponade are elevation of intracardiac pressures, limitation of ventricular filling, and reduction of cardiac output. The quantity of fluid necessary to produce this critical state may be as small as 200 mL when the fluid develops rapidly or more than 2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume. The volume of fluid required to produce tamponade also varies directly with the thickness of the ventricular myocardium and inversely with the thickness of the parietal pericardium.

Table 239-2 lists the features that distinguish cardiac tamponade from constrictive pericarditis. The classic findings of falling arterial pressure, rising venous pressure, and faint heart sounds usually occur only with severe, acute tamponade, as occurs with cardiac trauma or rupture. Tamponade may also develop more slowly, and under these circumstances the clinical manifestations may resemble those of heart failure, including dyspnea, orthopnea, hepatic engorgement, and jugular venous hypertension. A high index of suspicion for cardiac tamponade is required, since, in many instances, no obvious cause for pericardial disease is apparent. Tamponade should be considered in any patient with hypotension and elevation of jugular venous pressure with a prominent *x* descent; in contrast to constrictive pericarditis, in which the *y* descent is prominent (Chap. 225), in cardiac tamponade it is diminutive or absent. A positive Kussmaul sign (see below) is rare in cardiac tamponade, as is a pericardial knock. Their presence suggests that an organizing process and epicardial constriction are present in addition to effusion. A widening of the area of flatness to percussion across the anterior aspect

of the chest wall, a paradoxical pulse (see below), hypotension, relatively clear lung fields, diminished pulsations of the cardiac silhouette on fluoroscopy, enlargement of the cardiac silhouette (especially in subacute or chronic tamponade), reduction in amplitude of the QRS complexes, and *electrical alternans* of the P, QRS, and T waves should raise the suspicion of cardiac tamponade.

Paradoxical Pulse This important clue to the presence of cardiac tamponade consists of *a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure.* When severe, it may be detected by palpating weakness or disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required (Fig. 239-CD1).

Since both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle in cardiac tamponade compresses and reduces left ventricular volume; leftward bulging of the interventricular septum further reduces the left ventricular cavity as the right ventricle enlarges during inspiration (Fig. 239-CD2). Thus in cardiac tamponade the normal inspiratory augmentation of right ventricular volume causes an exaggerated reciprocal reduction in left ventricular volume. Also, respiratory distress increases the fluctuations in intrathoracic pressure, which exaggerates the mechanism just described. Right ventricular infarction (Chap. 243) may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, an absent *y* descent in the jugular venous pulse, and occasionally pulsus paradoxus. The differences between these two conditions are shown inTable 239-2.

Paradoxical pulse occurs not only in cardiac tamponade but also in approximately one-third of patients with constrictive pericarditis. Paradoxical pulse is not pathognomonic of pericardial disease because it may be observed in some cases of hypovolemic shock, acute and chronic obstructive airways disease, and pulmonary embolus.

Low-pressure tamponade refers to mild tamponade in which the intrapericardial pressure is increased from its slightly subatmospheric levels to +5 to +10 mmHg; in some instances hypovolemia coexists. As a consequence, the central venous pressure is normal or only slightly elevated, while arterial pressure is unaffected and there is no paradoxical pulse. The patients are asymptomatic or complain of mild weakness and dyspnea. The diagnosis is aided by echocardiography, and both hemodynamic and clinical manifestations improve following pericardiocentesis.

Diagnosis Since immediate treatment of cardiac tamponade may be lifesaving, prompt measures to establish the diagnosis by echocardiography should be undertaken (Fig 239-1). When pericardial effusion causes tamponade, during inspiration right ventricular diameter increases while left ventricular diameter and mitral valve opening decrease. Often the right ventricular cavity is reduced in diameter, and there is late diastolic inward motion (collapse) of the right ventricular free wall and of the right atrium. Doppler ultrasound shows exaggerated pulmonic (and tricuspid) flow during inspiration, with reciprocal changes in aortic (and mitral) flow (Fig 239-2).

If measured, the pericardial pressure is elevated and equal to the right atrial pressure. There is "equalization" of pressures, i.e., the pulmonary artery wedge is equal, or close,

to right atrial, right ventricular, and pulmonary artery diastolic pressures. The "square root" sign in the ventricular pressure pulses and the prominent *y* descent in atrial and jugular venous pressure are characteristic of constrictive pericarditis (see below) and are rarely present in tamponade.

TREATMENT

Patients with acute pericarditis should be observed frequently for the development of an effusion; if a large effusion is present, the patient should be hospitalized and watched closely for signs of tamponade. In the presence of an effusion, arterial and venous pressures and heart rate should be monitored or followed carefully and serial echocardiograms obtained. If manifestations of tamponade appear, pericardiocentesis must be carried out at once, since relief of the intrapericardial pressure may be lifesaving. It is helpful, though not essential, to carry this out in the catheterization laboratory with hemodynamic and fluoroscopic monitoring. A small catheter advanced over the needle inserted into the pericardial cavity may be left in place to allow draining of the pericardial space if fluid reaccumulates. When a *diagnostic* pericardiocentesis of a large effusion is carried out, an attempt should be made to remove as much fluid as possible. Surgical drainage through a limited thoracotomy may be required in recurrent tamponade and/or when it is necessary to obtain tissue for diagnosis.

VIRAL OR IDIOPATHIC FORM OF ACUTE PERICARDITIS

In some cases of this common disorder, an A or B coxsackievirus or the virus of influenza, echovirus, mumps, herpes simplex, chickenpox, adenovirus, or Epstein-Barr has been isolated from pericardial fluid and/or appropriate elevations in viral antibody titers have been noted. In many instances, acute pericarditis occurs in association with illnesses of known viral origin and, presumably, are caused by the same agent. Commonly, there is an antecedent infection of the respiratory tract, but in many patients such an association is not evident and viral isolation and serologic studies are negative. Most frequently, a viral causation cannot be established; the term *acute idiopathic pericarditis* is then appropriate. Acute pericarditis is a common complication in patients infected with AIDS (Chap. 309). It may be caused by HIV itself; by opportunistic infections, such as cytomegalovirus and tuberculosis; or by associated neoplasms, such as lymphoma or Kaposi's sarcoma.

Acute pericarditis occurs at all ages but is more frequent in young adults. Regardless of the specific cause, the clinical manifestations are similar. Acute pericarditis is often associated with pleural effusions and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10 to 12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from myocardial infarction, in which pain precedes fever. The constitutional symptoms are usually mild to moderate, but occasionally the initial symptoms are stormy, the temperature rising to 40°C. A pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks, but one or more recurrences occur in about one-fourth of patients. Although accumulation of some pericardial fluid is common, tamponade is unusual, and constrictive pericarditis is a possible complication. The ST-segment alterations in theECGusually disappear after 1 or more weeks, but the abnormal T waves may persist for several years and be a source of confusion in

persons without a clear history of pericarditis. Pleuritis and pneumonitis frequently accompany pericarditis. Granulocytosis followed by lymphocytosis is common.

TREATMENT

There is no specific therapy, but bed rest and anti-inflammatory treatment with aspirin, if necessary up to 900 mg qid, may be given. If this is ineffective, one of the nonsteroidal anti-inflammatory agents, such as indomethacin (25 to 75 mg qid) or a glucocorticoid (e.g., prednisone, 40 to 80 mg daily) usually suppresses the clinical manifestations of the acute illness and may be useful in patients in whom the purulent and tuberculous forms of pericarditis have been excluded. Anticoagulants should be avoided. After the patient has been asymptomatic and afebrile for about a week, the dose of the anti-inflammatory agent is gradually tapered. When recurrences are multiple, frequent, disabling, and continue beyond 2 years, pericardiectomy may be effective in terminating the illness.

POST-CARDIAC INJURY SYNDROME

Acute pericarditis may appear under a variety of circumstances that have one common feature: previous injury to the myocardium, with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiotomy syndrome); after cardiac trauma (Chap. 240), e.g., a stab wound, contusions after a nonpenetrating blow to the chest; or after perforation of the heart with a catheter. Rarely, it follows myocardial infarction.

The clinical picture of the post-cardiac injury syndrome mimics acute viral or acute idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1 to 4 weeks following the cardiac injury but sometimes appears only after an interval of months. Recurrences of pericarditis are common and may occur up to 2 years or more after the injury. Fever with temperature up to 40°C, pericarditis, pleuritis, and pneumonitis are the outstanding features, and the bout of illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguineous, and may be accompanied by arthralgias, but rarely causes tamponade. Leukocytosis, an increased sedimentation rate, and electrocardiographic changes typical of acute pericarditis also may occur.

The mechanisms responsible for this syndrome have not been identified, but they are probably the result of a hypersensitivity reaction in which the antigen originates from injured myocardial tissue and/or pericardium; the suggested designation of *post-cardiac injury syndrome* for this group of disorders implies that they may have a common pathogenetic mechanism. Circulating autoantibodies to myocardium occur frequently, but their precise role has not been defined. Viral infection may also play an etiologic role, since antiviral antibodies are often elevated in patients who develop this syndrome following cardiac surgery.

Often no treatment is necessary aside from aspirin and analgesics. The management of pericardial effusion and tamponade has already been discussed. When the illness is followed by a series of disabling recurrences, therapy with a nonsteroidal anti-inflammatory agent or a glucocorticoid is usually effective.

Differential Diagnosis Since there is no specific test for *acute idiopathic pericarditis*, the diagnosis is one of exclusion. Consequently, all other disorders that may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for acute myocardial infarction and vice versa. When it is associated with *acute myocardial infarction*, acute fibrinous pericarditis may be confused with acute viral or idiopathic pericarditis; this complication of infarction, described in Chap. 243, is characterized by fever, pain, and a friction rub in the first 4 days following the development of the infarct (to be distinguished from the pericarditis in Dressler's syndrome, which is a form of post-cardiac injury pericarditis and which occurs a week or two following myocardial infarction).ECGabnormalities (such as the appearance of Q waves, brief ST-segment elevations with reciprocal changes, and earlier T-wave changes in myocardial infarction) and the extent of the elevations of myocardial enzymes are helpful in differentiating pericarditis from acute myocardial infarction.

Pericarditis secondary to post-cardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few weeks of a myocardial infarction or a chest blow, it may be justified to conclude that the two are probably related. If the infarct has been silent or the chest blow forgotten, the relationship to the pericarditis may not be recognized.

It is important to distinguish *pericarditis due to collagen vascular disease* from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE;Chap. 311) or drug-induced (procainamide or hydralazine) lupus. In these conditions, pain is often present; sometimes in SLE the pericarditis appears as an asymptomatic effusion, and rarely, tamponade develops. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis may be made on discovery of lupus erythematosus cells or a rise in the titer of antinuclear antibodies. Acute pericarditis may complicate the viral, pyogenic, mycobacterial, and fungal infections that occur in AIDS. Acute pericarditis is an occasional complication of *rheumatoid arthritis*, *scleroderma*, and *polyarteritis nodosa*, and other evidence of these diseases is usually obvious. Asymptomatic pericardial effusion is also frequent in these disorders. It is important to question every patient with acute pericarditis about the ingestion of procainamide, hydralazine, isoniazid, cromolyn, and minoxidil, since these drugs can cause this syndrome.

The pericarditis of *acute rheumatic fever* is generally associated with evidence of severe pancarditis and with cardiac murmurs (Chap. 235). *Pyogenic (purulent) pericarditis* is usually secondary to cardiothoracic operations, immunosuppressive therapy, rupture of the esophagus into the pericardial sac, or rupture of a ring abscess in a patient with infective endocarditis and with septicemia complicating aseptic pericarditis. It is accompanied by fever, chills, septicemia, and evidence of infection elsewhere. *Tuberculous pericarditis* (Chap. 169) may present as an acute pericarditis associated with fever, weight loss, and other clinical manifestations of active systemic tuberculosis; the diagnosis may be aided by a positive tuberculin test and evidence of pulmonary or mediastinal tuberculosis. Tubercle bacilli can be cultured from the pericardial space only infrequently, and a biopsy of the pericardium with bacteriologic and histologic examination may be required. Alternatively, tuberculous pericarditis may present as a

chronic asymptomatic effusion, as subacute effusive-constrictive pericarditis, or as frank chronic constrictive pericarditis (see below).

Uremic pericarditis (Chap. 270) occurs in up to one-third of patients with chronic uremia and is seen most frequently in patients undergoing chronic hemodialysis. It may be fibrinous and is generally associated with an effusion that may be sanguineous. A friction rub is common, but pain is usually absent. Treatment with an anti-inflammatory agent and intensification of hemodialysis is usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When uremic pericarditis is recurrent, persistent, or very troubling, pericardiectomy may be necessary. Pericarditis due to *neoplastic diseases* results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium; pain, atrial arrhythmias, and tamponade are complications that occur occasionally. *Mediastinal irradiation* for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis after eradication of the tumor. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, trichinosis).

CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms per se, and their presence may be detected by finding an enlarged cardiac silhouette on chest roentgenogram.

Tuberculosis This is a common cause of chronic pericardial effusion, although less so in the United States than in other parts of the world (Chap. 169). The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this condition in a middle-aged or elderly person with fever and enlargement of the cardiac silhouette of undetermined origin, with or without elevation of venous pressure. Weight loss, fever, and fatigability are sometimes observed. Inasmuch as treatment is quite effective, overlooking a tuberculous pericardial effusion may have serious consequences. A chest roentgenogram for pulmonary tuberculosis should be obtained, and a search for tuberculosis in other organs carried out; tuberculin skin tests should be performed and repeated after several weeks. If the etiology of chronic pericardial effusion remains obscure, a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is then still lacking but the specimen shows caseation necrosis, antituberculous chemotherapy is indicated. If the biopsy specimen shows a thickened pericardium, pericardiectomy should be carried out in order to prevent the development of constriction.

Other Causes of Chronic Pericardial Effusion *Myxedema* may be responsible for a pericardial effusion that is sometimes massive but rarely, if ever, causes cardiac tamponade. The cardiac silhouette is markedly enlarged, and an echocardiogram is necessary to distinguish cardiomegaly from pericardial effusion. The diagnosis of myxedema is frequently overlooked. It is important, therefore, to carry out appropriate tests for thyroid function (Chap. 330) as well as echocardiography in patients with an enlarged cardiac outline of undetermined origin. *Cholesterol pericardial disease* is

sometimes associated with myxedema. It is characterized by large pericardial effusions with a high cholesterol content, which may induce an inflammatory response and constrictive pericarditis.

Neoplasms,SLE, rheumatoid arthritis, mycotic infections, radiation therapy, pyogenic infections, severe chronic anemia, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically looked for in such patients.

Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. In infections the organism can often be identified by smear or culture. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, uremia, or slow leakage from an aortic aneurysm.

CHRONIC CONSTRICTIVE PERICARDITIS

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar, encasing the heart and interfering with filling of the ventricles. In some reports, a high percentage of cases has been of tuberculous origin. In North America, tuberculosis is now an infrequent cause. Chronic constrictive pericarditis may also follow purulent infection, trauma, cardiac operation of any type, mediastinal irradiation, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), acute viral or idiopathic pericarditis, rheumatoid arthritis,SLE, and chronic renal failure with uremia treated by chronic dialysis. In many patients the cause of the pericardial disease is undetermined, and in them an asymptomatic or forgotten bout of viral pericarditis, acute or idiopathic, may have been the inciting event. The heart may also be constricted and compressed by malignant tumors or organized blood clot in the pericardial cavity.

The basic physiologic abnormality in symptomatic patients with chronic constrictive pericarditis, as in those with cardiac tamponade, is the inability of the ventricles to fill because of the limitations imposed by the rigid, thickened pericardium or the tense pericardial fluid. In constrictive pericarditis, ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, while in cardiac tamponade, ventricular filling is impeded throughout diastole. In chronic constrictive pericarditis, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonic veins, and systemic veins are all elevated to similar levels, i.e., within 5 mmHg. The fibrotic process may extend into the myocardium and cause myocardial scarring, and venous congestion may then be due to the combined effects of the myocardial and pericardial lesions. Despite these hemodynamic changes, myocardial function may be normal or only slightly impaired.

In constrictive pericarditis, the central venous and right and left atrial pressure pulses display an M-shaped contour, with prominent *x* and *y* descents; the *y* descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis and is interrupted by a rapid rise in pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These

characteristic changes are transmitted to the jugular veins, where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic "square root" signs during diastole (Fig. 239-3). These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis but may also be observed in cardiomyopathies characterized by restriction of ventricular filling (Chap. 238).

CLINICAL AND LABORATORY FINDINGS (Table 239-2)

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common. The patient often appears to be chronically ill with decreased skeletal muscle mass and a protuberant abdomen. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. Acute left ventricular failure (acute pulmonary edema) is very uncommon. The cervical veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (Kussmaul's sign). The latter is frequent in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy. The pulse pressure is normal or reduced. In about one-third of the cases a paradoxical pulse can be detected. Congestive hepatomegaly is pronounced and may impair hepatic function; ascites is common and is usually more prominent than dependent edema. In about half of patients the heart is normal in size; if it is enlarged, the enlargement is rarely extreme. The apical pulse is reduced in intensity, retracts in systole, and moves outward in diastole. The heart sounds may be distant; an early third heart sound, i.e., a pericardial knock, occurring 0.09 to 0.12 s after aortic valve closure that coincides with a sudden deceleration in ventricular filling, is often conspicuous, and murmurs are usually absent. Because of the high sustained venous pressure, congestive splenomegaly may make the spleen palpable. In the absence of infective endocarditis or tricuspid valve disease, splenomegaly in a patient with congestive heart failure should arouse suspicion of constrictive pericarditis. Protein-losing gastroenteropathy, due to impaired lymphatic drainage from the small intestine, and marked proteinuria or hypoalbuminemia may complicate chronic constrictive pericarditis.

The *ECG* frequently displays low voltage of the QRS complex and diffuse flattening or inversion of the T waves. P mitrale may be present in patients with sinus rhythm; atrial fibrillation is present in about one-third of patients. The *chest roentgenogram* shows a normal or slightly enlarged heart, sometimes with pericardial calcification.

Inasmuch as the usual physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with intractable ascites may lead to a mistaken diagnosis of cirrhosis of the liver. This error can be avoided if the neck veins are inspected carefully in patients with ascites and hepatomegaly. *Given a clinical picture resembling hepatic cirrhosis, but with the added feature of distended neck veins, careful search for calcification of the pericardium by chest roentgenography and CT or MRI should be carried out and may disclose this curable or remediable form of heart disease.*

The echocardiogram typically shows pericardial thickening, atrial enlargement, dilatation of the inferior vena cava and hepatic veins, and a sharp halt in ventricular filling in early

diastole, with normal ventricular systolic function; there is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography. There is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve during inspiration, with the opposite occurring during expiration. Diastolic flow velocity in the vena cavae into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration (Fig. 239-4). However, echocardiography cannot definitively exclude the diagnosis.MRI andCTscanning (Fig. 239-CD3), especially the latter (Fig. 239-5), are more accurate than echocardiography in establishing or excluding the presence of a thickened pericardium. Pericardial thickening and even pericardial calcification, however, are not synonymous with constrictive pericarditis since they may occur without seriously impairing ventricular filling.

DIFFERENTIAL DIAGNOSIS

Like cor pulmonale (Chap. 237), chronic constrictive pericarditis may be associated with severe systemic venous hypertension but little pulmonary congestion; the heart usually is not enlarged, and a paradoxical pulse may be present. However, in cor pulmonale advanced parenchymal pulmonary disease is usually obvious and venous pressure *falls* during inspiration, i.e., Kussmaul's sign is negative. *Tricuspid stenosis* (Chap. 236) may also simulate chronic constrictive pericarditis; congestive hepatomegaly, splenomegaly, ascites, and venous distention may be equally prominent, and the manifestations of left-sided heart failure may be inconspicuous. However, in tricuspid stenosis, a characteristic murmur as well as mitral stenosis are usually present. In tricuspid stenosis, a paradoxical pulse and a steep, deep *y* descent in the jugular venous pulse do not occur, serving to differentiate it from chronic constrictive pericarditis.

Because constrictive pericarditis can be corrected surgically, it is important, though often difficult, to distinguish chronic constrictive pericarditis from restrictive cardiomyopathy (Chap. 238), which has a similar physiologic abnormality, i.e., restriction of ventricular filling. In many of these patients the ventricular wall is thickened on echocardiographic examination (Table 239-2). The features favoring the diagnosis of restrictive cardiomyopathy over chronic constrictive pericarditis include a well-defined apex beat, cardiac enlargement, and pronounced orthopnea with attacks of acute left ventricular failure, left ventricular hypertrophy, gallop sounds (in place of a pericardial knock), bundle branch block, and in some cases abnormal Q waves on theECG. The echocardiogram in chronic constrictive pericarditis characteristically shows pericardial thickening, i.e., a distinct echo posterior to the left ventricular wall, and paradoxical septal motion. The left ventricular wall moves sharply outward in early diastole and then remains flat. Marked respiratory variations in atrioventricular flow velocities on Doppler echocardiography are characteristic of constrictive pericarditis but not restrictive cardiomyopathy (Fig. 239-4). The definitive diagnosis of restrictive cardiomyopathy, when it is due to an infiltrative disease such as amyloidosis, can often be established by endomyocardial biopsy.CTscanning andMRI are very useful in distinguishing between restrictive cardiomyopathy and chronic constrictive pericarditis. In the former, the ventricular walls are hypertrophied, while in the latter the pericardium is thickened and sometimes calcified.

When a patient has progressive, disabling, and unresponsive congestive failure and

displays any of the features of constrictive heart disease, the most careful and detailed clinical and laboratory studies must be carried out in order to detect or exclude constrictive pericarditis, since the latter is usually curable.

Occult Constrictive Disease Patients with this condition may have unexplained fatigue, dyspnea, and chest pain. No overt manifestations of pericardial disease are present, but following the rapid intravenous infusion of 1 L of saline solution, diastolic equilibration of intracardiac atrial and ventricular pressures found in overt constrictive pericarditis occur. Although symptomatic improvement may follow pericardiectomy, this procedure should not be carried out in asymptomatic persons.

TREATMENT

Pericardial resection is the only definitive treatment of constrictive pericarditis, but dietary sodium restriction and diuretics are useful during preoperative preparation. The benefits derived from cardiac decortication are often striking, and the improvement, though slight at first, usually is progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the calcific process, by the severity of myocardial atrophy, by the extent of secondary impairment of hepatic and/or renal function, and by the patient's general condition. Operative mortality is in the range of 3 to 10%; the patients with the most severe and/or advanced disease are at highest risk. Therefore, surgical treatment should be carried out relatively early in the course.

Many cases of constrictive pericarditis are of tuberculous origin. Antituberculous therapy during the phase of effusion may prevent the development of constriction, and such therapy should be carried out before and after operation if a tuberculous origin can be diagnosed, is suspected, or cannot be excluded in a patient with chronic constrictive pericarditis (Chap. 169).

Subacute Effusive-Constrictive Pericarditis This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. It shares a number of features both with chronic pericardial effusion (p. 1366) producing cardiac compression and with pericardial constriction. It may be caused by tuberculosis, multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, uremia, and scleroderma. The heart is generally enlarged, and a paradoxical pulse and a prominent *x* descent (without a prominent *y* descent) are present in the atrial and jugular venous pressure pulses. Following pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction, with a "square root" sign in the ventricular pressure pulse and a prominent *y* descent in the atrial and jugular venous pressure pulses. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. In many patients the condition progresses to the chronic constrictive form of the disease. Wide excision of both the visceral and parietal pericardium is usually effective.

OTHER DISORDERS OF THE PERICARDIUM

Pericardial cysts appear as rounded or lobulated deformities of the cardiac silhouette,

most commonly at the right cardiophrenic angle. They do not cause symptoms, and their major clinical significance lies in the possibility of confusion with a tumor, ventricular aneurysm, or massive cardiomegaly. *Tumors* involving the pericardium are most commonly secondary to malignant neoplasms originating in or invading the mediastinum, including carcinoma of the bronchus and breast, lymphoma, and melanoma. The most common *primary* malignant tumor is the mesothelioma. The usual clinical picture of malignant pericardial tumor is an insidiously developing, often bloody, pericardial effusion. Surgical exploration is required to establish a definitive diagnosis and to carry out definitive or, more commonly, palliative treatment.

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240. CARDIAC TUMORS, CARDIAC MANIFESTATIONS OF SYSTEMIC DISEASES, AND TRAUMATIC CARDIAC INJURY - *Wilson S. Colucci*, *Daniel T. Price*

TUMORS OF THE HEART

PRIMARY TUMORS

Primary tumors of the heart are rare. Approximately three-quarters are histologically benign, and the remainder, which in almost all cases are sarcomas, are malignant (Table 240-1). Because all cardiac tumors have the potential for causing life-threatening complications, and many are now curable by surgery, it is important that the diagnosis be made whenever possible.

Clinical Presentation Cardiac tumors may present with a wide array of cardiac and noncardiac manifestations. The location and the size of the tumor are the major determinants of the specific signs and symptoms, many of which are present in more common forms of heart disease, such as chest pain, syncope, heart failure, murmurs, arrhythmias, conduction disturbances, and pericardial effusion with or without tamponade.

Myxoma Myxomas are the most common type of primary cardiac tumor in all age groups, accounting for one-third to one-half of all cases at postmortem and for about three-quarters of the tumors treated surgically. They occur at all ages, most commonly in the third through sixth decades. There is a female predilection. Although most myxomas are sporadic, some are familial with autosomal dominant transmission or are part of a syndrome that involves a complex of abnormalities including lentigines or pigmented nevi, primary nodular adrenal cortical disease with or without Cushing's syndrome, myxomatous mammary fibroadenomas, testicular tumors, and/or pituitary adenomas with gigantism or acromegaly. Certain constellations of findings have been referred to as the *NAME* syndrome (nevi, atrial myxoma, myxoid neurofibroma, and ephelides) or the *LAMB* syndrome (lentigines, atrial myxoma, and blue nevi). Approximately 7% of cardiac myxomas are familial or part of the syndrome myxoma with the complex of abnormalities described above.

Pathologically, myxomas are gelatinous structures consisting of myxoma cells imbedded in a stroma rich in glycosaminoglycans. Most are pedunculated on a fibrovascular stalk and average 4 to 8 cm in diameter. The majority are solitary and located in the atria, particularly the left, where they arise from the interatrial septum in the vicinity of the fossa ovalis. In contrast to sporadic tumors, familial or syndrome myxoma tumors tend to occur in younger individuals, be multiple or ventricular in location, and have more postoperative recurrences, probably reflecting their multicentric nature.

Myxomas commonly present with obstructive, embolic, or constitutional signs and symptoms. The most common clinical presentation mimics that of mitral valve disease, either stenosis due to tumor prolapse into the mitral orifice or regurgitation due to tumor-induced valvular trauma. Ventricular myxomas may cause outflow obstruction similar to that caused by subaortic or subpulmonic stenosis. The symptoms and signs of myxoma may be of sudden onset or positional in nature, reflecting changes in tumor

position due to gravity. An ausculatory finding, termed a "tumor plop," is a characteristic low-pitched sound that may be audible during early or middiastole and is thought to result from the tumor abruptly stopping as it strikes the ventricular wall. Myxomas may also present with peripheral or pulmonary emboli, or constitutional signs and symptoms including fever, weight loss, cachexia, malaise, arthralgia, rash, clubbing, Raynaud's phenomenon, hypergammaglobulinemia, anemia, polycythemia, leukocytosis, elevated erythrocyte sedimentation rate, thrombocytopenia, or thrombocytosis. Not surprisingly, myxomas are frequently misdiagnosed as endocarditis, collagen vascular disease, or noncardiac tumor.

Two-dimensional transthoracic or transesophageal echocardiography is useful in the diagnosis of cardiac myxoma and allows determination of the site of tumor attachment and tumor size, which are important considerations in the planning of surgical excision (Fig. 240-1). Computed tomography and particularly magnetic resonance imaging may provide important information regarding size, shape, composition, and surface characteristics of the tumor. Because myxomas may be familial, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or evidence of syndrome myxoma. Although cardiac catheterization and angiography have previously been performed routinely before surgery, catheterization of the chamber from which the tumor arisees is attended by the risk of tumor emboli. Catheterization is no longer considered mandatory when adequate noninvasive information is available and other cardiac diseases (e.g., coronary artery disease) are not considered likely.

TREATMENT

Surgical excision utilizing cardiopulmonary bypass is indicated and is generally curative. Myxomas recur in approximately 12 to 22% of familial cases and in about 1 to 2% of sporadic cases. Tumor recurrence is most likely due to multifocal lesions in the former and inadequate resection in the latter.

Other Benign Tumors Cardiac *lipomas*, although relatively common, are usually incidental findings at postmortem examination. However, they may grow as large as 15 cm and may present with symptoms due to mechanical interference with cardiac function, arrhythmias, or conduction disturbances, or as an abnormality of the cardiac silhouette on chest x-ray. *Papillary fibroelastomas*, similarly, are relatively common findings on cardiac valves or the adjacent endothelium at postmortem, but seldom result in clinical symptoms. Occasionally, these growths may cause mechanical interference with valve function. *Rhabdomyomas* and *fibromas*, the most frequent tumors in infants and children, most commonly occur in the ventricles and therefore produce signs and symptoms by mechanical obstruction that may mimic valvular stenosis, congestive heart failure, restrictive or hypertrophic cardiomyopathy, and pericardial constriction. Rhabdomyomas are probably hamartomatous growths; are multiple in 90% of cases; and may be associated with tuberous sclerosis, adenoma sebaceum, and benign kidney tumors in approximately 30% of patients. Calcification of a cardiac tumor strongly suggests that it is a fibroma, although myxomas and sarcomas also may be calcified. *Hemangiomas* and *mesotheliomas* are generally small tumors, most often intramyocardial in location, and may cause atrioventricular conduction disturbances and even sudden death as a result of their propensity for location in the region of the AV

node. Other benign tumors arising from the heart include *teratoma*, *chemodectoma*, *neurilemoma*, *granular cell myoblastoma*, and *bronchogenic cysts*.

Sarcoma Almost all primary cardiac malignancies are sarcomas, which may be of several histologic types. In general, these tumors are characterized by a rapidly downhill course leading to the patient's death in weeks to months from the time of presentation as a result of hemodynamic compromise, local invasion, or distant metastases. Sarcomas commonly involve the right side of the heart, and because of their rapid growth, invasion of the pericardial space and obstruction of the cardiac chambers or venae cavae are common. Sarcomas can also occur on the left side of the heart and may be mistaken for myxomas.

TREATMENT

At the time of presentation these tumors have often spread too extensively for surgical excision. Although scattered reports exist of palliation with surgery, radiotherapy, and/or chemotherapy, the overall experience with cardiac sarcomas is poor. The one exception appears to be cardiac lymphosarcomas, which may respond to a combination of chemo- and radiotherapy.

TUMORS METASTATIC TO THE HEART

Tumors metastatic to the heart are many times more common than primary tumors; and as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy, the frequency of cardiac metastases will also increase. Although cardiac metastases occur in 1 to 20% of all tumor types, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, in leukemia and lymphoma. In absolute numbers, the most common primary originating sites of cardiac metastases are carcinoma of the breast and lung, reflecting the high incidence of these cancers. Cardiac metastases almost always occur in the setting of widespread primary disease, and most often either primary or metastatic disease exists elsewhere in the thoracic cavity. Nevertheless, a cardiac metastasis may occasionally be the initial presentation of a tumor elsewhere in the body.

Cardiac metastases reach the heart from the blood stream, the lymphatics, or by direct invasion. They generally are small, firm nodules. Diffuse infiltration may also occur, especially with sarcomas or hematologic neoplasms. The pericardium is most often involved, followed by myocardial involvement of any chamber, and, rarely, by involvement of the endocardium or cardiac valves.

Cardiac metastases result in clinical manifestations only about 10% of the time and rarely are the cause of death. In most instances the metastases are not the cause of the presenting clinical features but occur in the setting of a previously recognized malignant neoplasm. Although cardiac metastases may present with a large number of nonspecific signs and symptoms, the most common are dyspnea, signs of acute pericarditis, cardiac tamponade, a rapid increase in the cardiac silhouette on chest x-ray, new onset of ectopic tachyarrhythmia or AV block, and congestive heart failure. As with primary cardiac tumors, the clinical presentation is more closely related to the location and size of the tumor rather than histologic type. Many of these signs and symptoms also occur

with myocarditis, pericarditis, or cardiomyopathy resulting from radiotherapy or chemotherapy.

Electrocardiographic findings are nonspecific. On chest roentgenography the cardiac silhouette is most often normal but may reveal a pericardial effusion or bizarre contour. Echocardiography is useful for the diagnosis of pericardial effusion and the visualization of larger metastases. Computed tomography, magnetic resonance imaging, and radionuclide imaging with gallium or thallium may provide useful anatomic information. Angiography may delineate discrete lesions, and pericardiocentesis can allow a specific cytologic diagnosis.

TREATMENT

Because most patients with cardiac metastases have widespread disease, therapy generally consists of treatment of the primary tumor. Symptomatic malignant effusions are treated by removal of fluid by pericardiocentesis, with or without concomitant instillation of a sclerosing agent (e.g., tetracycline), or placement of a pericardial window for drainage to the pleural space to palliate symptoms and delay or prevent reaccumulation of the effusion.

CARDIAC EFFECTS OF CANCER THERAPY®*SEE CHAP. 238.*

CARDIOVASCULAR MANIFESTATIONS OF SYSTEMIC DISEASES

DIABETES MELLITUS (See alsoChap. 333)

There is an increased incidence of large vessel atherosclerosis and myocardial infarction in patients with both insulin- and non-insulin-dependent diabetes mellitus. Coronary artery disease is the most common cause of death in adults with diabetes mellitus. Diabetes mellitus is an independent risk factor for coronary artery disease (Chap. 241), and the incidence of coronary artery disease is related to the duration of diabetes. In patients with diabetes mellitus, myocardial infarctions are not only more frequent but also tend to be larger in size and more likely to result in complications such as heart failure, shock, and death. Patients with diabetes mellitus are more likely to have an abnormal or absent pain response to myocardial ischemia, probably as a result of generalized autonomic nervous system dysfunction. Ambulatory electrocardiographic monitoring has shown that up to 90% of episodes of ischemia are silent in diabetic patients with coronary artery disease; the presentation of ischemia may be exertional or episodic dyspnea, flash pulmonary edema, arrhythmias, heart block, or syncope. Since coronary artery disease is more common in in patients with diabetes mellitus and often is not associated with typical anginal symptoms, the threshold for the diagnosis should be low, particularly when the duration of disease is long and concomitant risk factors for coronary artery disease (e.g., hypertension, smoking, hyperlipidemia) are present.

Patients with diabetes mellitus may also have myocardial dysfunction characteristic of a restrictive cardiomyopathy in the absence of large-vessel (epicardial) coronary artery disease, with abnormal relaxation of the myocardium, and evidenced clinically by elevated left ventricular filling pressures. Histologically, these patients have interstitial fibrosis with increased amounts of collagen, glycoprotein, triglycerides, and cholesterol

in the myocardial interstitium; and in some cases intimal thickening, hyaline deposition, and inflammatory changes have been observed in small intramural arteries. Patients with diabetes mellitus have an increased risk of developing clinical heart failure, even after correction for the presence of coronary artery disease, hypertension, and obesity, and it is likely that diabetic cardiomyopathy contributes to excessive cardiovascular morbidity and mortality in these patients. There is some evidence that insulin therapy results in an amelioration of the myocardial dysfunction.

MALNUTRITION AND VITAMIN DEFICIENCY MALNUTRITION (See alsoChap. 74)

In patients whose intake of protein, calories, or both is severely deficient, the heart may become thin, pale, and flabby with myofibrillar atrophy and interstitial edema. The systolic pressure and cardiac output are low, and the pulse pressure is narrow. Generalized edema is common and is due to a combination of factors, including reduced serum oncotic pressure and myocardial dysfunction. Such profound states of malnutrition, termed *marasmus* in the case of caloric deficiency and *kwashiorkor* in the case of relative protein deficiency, are most common in underdeveloped countries. However, significant nutritional heart disease may also occur in developed nations, particularly in patients with chronic diseases such as AIDS, in patients with anorexia nervosa, and in patients with severe cardiac failure in whom gastrointestinal hypoperfusion and venous congestion may lead to anorexia and malabsorption. Open-heart surgery poses increased risk in malnourished patients, and they may benefit from preoperative hyperalimentation.

Thiamine Deficiency (Beriberi) (See also Chap. 75) In many cases, malnutrition is accompanied by thiamine deficiency, although this hypovitaminosis may also occur in the presence of an adequate protein and caloric intake, particularly in the Far East, where polished rice deficient in thiamine may be a major dietary component. In western nations, the widespread use of thiamine-enriched flour limits the presence of deficiency primarily to alcoholics and food faddists. The measurement of the thiamine-pyrophosphate effect (TPPE) can biochemically quantitate thiamine stores. An elevated TPPE, indicative of thiamine deficiency, has been found in 20 to 90% of patients with chronic heart failure. The deficiency appears to result from both reduced dietary intake and a diuretic-induced increase in the urinary excretion of thiamine. The acute administration of thiamine to these patients increases the left ventricular ejection fraction and the excretion of salt and water.

Clinically, there is usually evidence of generalized malnutrition, peripheral neuropathy, glossitis, and anemia. The characteristic cardiovascular syndrome is heart failure with increased cardiac output, tachycardia, and often elevated filling pressures in the left and right sides of the heart. The major cause of the high-output state is vasomotor depression, the precise mechanism of which is not understood but which leads to a reduced systemic vascular resistance. The cardiac examination reveals a wide pulse pressure, tachycardia, a third heart sound, and, frequently, an apical systolic murmur. The electrocardiogram may show decreased voltage, a prolonged QT interval, and T-wave abnormalities. The chest x-ray generally shows a large heart with signs of congestive heart failure. The response to thiamine is often dramatic, with an increase in systemic vascular resistance, decrease in cardiac output, clearing of pulmonary congestion, and a reduction in heart size often occurring in 12 to 48 h. Although the

response to digitalis and diuretics may be poor before thiamine therapy, these agents may be important *after* thiamine is given, since the left ventricle may not be capable of dealing with the increased workload presented by the return of vascular tone.

Vitamin B_6, B_{12}, and Folate Deficiency (See also Chap. 241) These vitamin cofactors in the metabolism of homocysteine probably contribute to the majority of cases of hyperhomocysteinemia in the general population. Hyperhomocysteinemia is associated with increased risk of atherosclerosis. Supplementation of these vitamins has reduced the incidence of hyperhomocysteinemia in the United States. The clinical benefit of normalizing elevated homocysteine levels, however, remains unproven.

OBESITY (See also Chap. 77)

Severe obesity, particularly when it occurs in an upper-body distribution, is associated with an increase in cardiovascular morbidity and mortality. Although obesity itself is not considered a disease, there is clearly an increased prevalence of hypertension, glucose intolerance, and atherosclerotic coronary artery disease in obese patients. In addition, these patients have a distinct abnormality of the cardiovascular system characterized by increases in total and central blood volumes, cardiac output, and left ventricular filling pressure. The elevated cardiac output appears to be required to support the metabolic needs of the excessive adipose tissue. Left ventricular filling pressure is often at the upper limits of normal and rises excessively with exercise. As a result of chronic volume overload, eccentric cardiac hypertrophy with cardiac dilatation and abnormal ventricular function may develop. Pathologically, there are left and, in some cases, right ventricular hypertrophy and generalized cardiac dilatation, which is not due simply to fatty infiltration of the myocardium. Although these patients may develop pulmonary congestion, peripheral edema, and exercise intolerance, the recognition of these findings may be difficult in massively obese patients.

Weight reduction is the most effective therapy and results in reduction in blood volume and in the return of cardiac output toward normal. However, rapid weight reduction may be dangerous, as cardiac arrhythmias and sudden death due to electrolyte imbalance have been described. Digitalis, sodium restriction, and diuretics may also be useful. This form of heart disease should be distinguished from the Pickwickian syndrome (Chap. 263), which may share several of the cardiovascular features of heart disease secondary to severe obesity but, in addition, frequently has components of central apnea, hypoxemia, pulmonary hypertension, and cor pulmonale.

THYROID DISEASE (See also Chap. 330)

Thyroid hormone exerts a major influence on the cardiovascular system by a number of direct and indirect mechanisms, and not surprisingly, cardiovascular effects are prominent in both hypo- and hyperthyroidism. Thyroid hormone causes increases in total-body metabolism and oxygen consumption that indirectly place an increased workload on the heart. In addition, although the exact mechanism has not been defined, thyroid hormone exerts direct inotropic, chronotropic, and dromotropic effects that are similar to those seen with adrenergic stimulation (e.g., tachycardia, increased cardiac output). Thyroid hormone increases the synthesis of myosin and of Na^+,K^+-ATPase, as well as the density of myocardial beta-adrenergic receptors.

Hyperthyroidism Cardiovascular presentations of hyperthyroidism include palpitations, systolic hypertension, fatigue, or, in patients with underlying heart disease, angina or heart failure. Sinus tachycardia is found in about 40% of patients and atrial fibrillation in about 15%. Other findings include a hyperdynamic precordium, a widened pulse pressure, an increase in the intensity of the first heart sound and the pulmonic component of the second heart sound, and a third heart sound. An increased incidence of mitral valve prolapse has been associated with hyperthyroidism, and in some cases there may be a midsystolic murmur heard best at the left sternal border with or without a systolic ejection click. A *Means-Lerman scratch* is a systolic scratchy sound, heard at the left second intercostal space during expiration; it is thought to result from the rubbing of the hyperdynamic pericardium against the pleura. Elderly patients with hyperthyroidism, so-called apathetic hyperthyroidism, may present with only the cardiovascular manifestations of thyrotoxicosis, such as atrial fibrillation, which may be resistant to therapy until the hyperthyroidism is controlled. Angina pectoris and congestive heart failure are unusual unless there is coexistent underlying heart disease, and in many cases symptoms resolve with treatment of the hyperthyroidism.

Hypothyroidism Cardiac manifestations of hypothyroidism include a reduction in cardiac output, stroke volume, heart rate, blood pressure, and pulse pressure. In about one-third of patients there is a pericardial effusion which only rarely results in tamponade. Increased capillary permeability results in pleural and pericardial effusions. Other clinical signs include cardiomegaly, bradycardia, weak arterial pulses, and distant heart sounds. Although the signs and symptoms of myxedema may suggest the diagnosis of congestive heart failure, in the absence of other cardiac disease, myocardial failure is uncommon. The electrocardiogram generally shows sinus bradycardia and low voltage and may show prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T wave abnormalities. Chest x-ray may show cardiomegaly, often with a "water bottle" configuration, pleural effusions, and, in some cases, evidence of congestive heart failure. Pathologically, the heart is pale, dilated, and flabby, often with myofibrillar swelling, loss of striations, and interstitial fibrosis.

Patients with hypothyroidism frequently have elevations of cholesterol and triglycerides and severe atherosclerotic coronary artery disease. Before treatment with thyroid hormone, patients with hypothyroidism frequently do not have angina pectoris, presumably because of the low metabolic demands made by their condition. However, angina and myocardial infarction may be precipitated during initiation of thyroid hormone replacement, especially in elderly patients with underlying heart disease. Therefore, replacement should be done with care, starting with low doses that are increased gradually.

MALIGNANT CARCINOID (See alsoChap. 93)

These tumors elaborate a variety of vasoactive amines (e.g., serotonin), kinins, indoles, and other substances believed to be responsible for the diarrhea, flushing, and labile blood pressure in these patients. The cardiac lesions due to gastrointestinal carcinoids are almost exclusively in the right side of the heart and occur only when there are hepatic metastases, suggesting that the substance responsible for the cardiac lesions is

inactivated by passage through the liver and lungs. Similar lesions occur in the left side of the heart when there exists a right-to-left shunt or the tumor is located in the lungs. These lesions are fibrous plaques on the endothelium of the cardiac chambers, valves, and great vessels. These plaques, which result in distortion of the cardiac valves, consist of smooth-muscle cells embedded in a stroma of acid mucopolysaccharide and collagen and presumably result from healing of endothelial injury. The clinical syndrome is most often that of tricuspid regurgitation, pulmonic stenosis, or both. In some cases a high-output state may occur, presumably as a result of a decrease in systemic vascular resistance due to a vasoactive substance released by the tumor. Progression of the cardiac lesions does not appear to be affected by treatment with serotonin antagonists, and in some severely symptomatic patients valve replacement is indicated. Coronary artery spasm, presumably due to a circulating vasoactive substance, may occur in patients with carcinoid syndrome.

PHEOCHROMOCYTOMA (See alsoChap. 332)

In addition to causing labile or sustained hypertension, the high circulating levels of catecholamines may also cause direct myocardial injury. Focal myocardial necrosis and inflammatory cell infiltration are present in about 50% of patients who die with pheochromocytoma and may contribute to clinically significant left ventricular failure and pulmonary edema. Left ventricular function and congestive heart failure may resolve after removal of the tumor. In addition, hypertension results in left ventricular hypertrophy.

RHEUMATOID ARTHRITIS AND THE COLLAGEN VASCULAR DISEASES

Rheumatoid Arthritis (See also Chap. 312) There may be inflammation of any or all parts of the heart in patients with rheumatoid arthritis. Pericarditis is the most common cause of clinically apparent disease and may be found by echocardiography in 10 to 50% of all patients with rheumatoid arthritis, particularly those with subcutaneous nodules. However, only a small fraction of these patients have clinical evidence of pericarditis, which usually follows a benign course but occasionally may progress to cardiac tamponade or constrictive pericarditis. The pericardial fluid is generally an exudate, with decreased concentrations of complement and glucose and elevated cholesterol. Coronary arteritis with intimal inflammation and edema is present in about 20% of cases but only rarely results in angina pectoris or myocardial infarction. The cardiac valves, most often the mitral and aortic, may be involved by inflammation and granuloma formation that in some cases may cause clinically significant regurgitation due to valve deformity. Myocarditis rarely results in cardiac dysfunction.

Treatment is directed at the underlying rheumatoid arthritis and may include glucocorticoids. Pericardiectomy is usually required in cases of tamponade or persistent effusion.

Seronegative Arthropathies The seronegative arthropathies (Chaps. 315 and324), ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, and the arthritides associated with ulcerative colitis and regional enteritis may be accompanied by a pancarditis and proximal aortitis; the latter may result in aortic regurgitation and may extend into the anterior mitral valve ring and/or AV node. Conduction disturbances are

common, occurring in up to one-third of patients; they are more common in patients with aortic valve disease and appear to be associated with the presence of the HLA-B27 antigen. Both aortic regurgitation and AV block are more common in patients with peripheral joint involvement and long-standing disease; treatment with aortic valve replacement and permanent pacemaker placement may be required. Up to one-fifth of patients with peripheral joint involvement and disease for more than 30 years have significant aortic regurgitation. Occasionally, aortic regurgitation precedes the onset of arthritis, and, therefore, the diagnosis of a seronegative arthritis should be considered in young males with isolated aortic regurgitation.

Systemic Lupus Erythematosus (SLE) (See also Chap. 311) Pericarditis is common, occurring in about two-thirds of patients, and generally pursues a benign course, although rarely tamponade or constriction may result. The characteristic *endocardial lesions* of SLE, described by Libman and Sacks, consist of wartlike lesions most often located at the angles of the AV valves or on the ventricular surface of the mitral valve. Hemodynamically important valvular regurgitation is rare. Patients with the antiphospholipid syndrome have a higher incidence of cardiovascular abnormalities, including valvular disease (particularly regurgitant lesions), a variety of thrombotic disorders (venous and arterial thrombosis, thrombocytopenia, premature stroke), myocardial infarction, pulmonary hypertension, and cardiomyopathy. Myocarditis generally parallels the activity of the disease, and although common histologically, seldom results in clinical heart failure unless associated with hypertension. Although arteritis of large coronary arteries may rarely result in myocardial ischemia, there is also an increased frequency of coronary atherosclerosis that may be related to hypertension or glucocorticoid therapy.

TRAUMATIC HEART DISEASE

Cardiac damage may be due to either penetrating or nonpenetrating injuries. The most frequent cause of a *nonpenetrating injury* is the impact of the chest against the steering wheel of an automobile. The absence of external signs of thoracic trauma does not exclude serious injury of the heart. Although the commonest injury is myocardial contusion, any structure of the heart may be affected by the trauma.

Myocardial contusions are often not immediately recognized in trauma patients due to focus on more obvious injuries. Myocardial contusion may cause arrhythmias, bundle branch block, or electrocardiographic abnormalities resembling those of infarction or pericarditis, and so it is important to bear trauma in mind as a cause of otherwise unexplained electrocardiographic changes. Serum creatine kinase (CK) MB isoenzyme levels are increased in about 20% of patients, but false-positive elevations of MB may occur in the presence of massive injuries associated with large increases in total CK. Cardiac troponin levels may have a greater diagnostic value than CK-MB. Echocardiography can detect abnormal wall motion and the presence of pericardial effusion, in addition to aiding in diagnosis of other forms of cardiac trauma. Myocardial contusion may produce positive radionuclide scans and regional impairment of ventricular function, as occurs in myocardial infarction (Chap. 243). Pericardial effusion may occur weeks or even months after the accident. In these cases, the pericardial effusion is a manifestation of the postcardiac injury syndrome, which resembles the postpericardiotomy syndrome (Chap. 239).

Rupture of the heart valves or the supporting structures leads to acute valvular incompetence. The presence of a loud heart murmur followed by the development of rapidly progressive heart failure after trauma heralds this diagnosis, which can be made by either transthoracic or transesophageal echocardiography.

The most serious consequence of nonpenetrating injury is myocardial rupture, leading to tamponade or intracardiac shunting. Although it is generally immediately fatal, up to 40 percent of patients with cardiac rupture have been reported to survive long enough to reach a specialized trauma center. Hemopericardium may also follow tearing of a pericardial vessel or coronary artery.

Rupture of the aorta is a common consequence of nonpenetrating chest trauma. Indeed, rupture of the aorta at the isthmus or just above the aortic valve is the most common vascular deceleration injury. The clinical presentation is similar to that in aortic dissection (Chap. 247). The arterial pressure and pulse amplitude may be increased in the upper extremities and decreased in the lower extremities, and on chest roentgenogram there may be widening of the mediastinum. Occasionally, aortic rupture is limited by the aortic adventitia and results in a silent false aneurysm that may be discovered months or years after the injury.

Penetrating injuries of the heart, produced by bullets or stab wounds, usually result in immediate or very rapid death because of hemopericardium or massive hemorrhage. However, up to half of such patients may survive if they are resuscitated and/or survive long enough to reach a specialized trauma center. Perforation complicating the placement of an intravenous intracardiac catheter or pacemaker lead is another common cause of penetrating injuries to the heart and great vessels.

When great vessel rupture is due to a penetrating injury, there is usually a hemothorax and, less often, a hemopericardium. Hematoma formation may compress major vessels, and arteriovenous fistulae may form, sometimes resulting in high-output congestive heart failure.

Patients who suffer penetrating injuries of the heart should be carefully examined several weeks after the event to rule out a ventricular septal defect or mitral regurgitation that may have gone undetected at the time of emergency surgery. Sometimes the patient survives the acute incident and presents with a cardiac murmur and congestive heart failure. A left-to-right shunt due to traumatic ventricular septal defect, aortopulmonary artery fistula, or coronary arteriovenous fistula may be suspected and confirmed by cardiac catheterization and angiocardiography.

TREATMENT

The treatment of an uncomplicated myocardial contusion, with or without myocardial infarction, is similar to that for a myocardial infarction, except that anticoagulation is contraindicated, and should include monitoring for the development of complications such as arrhythmia and cardiac rupture (Chap. 243). Acute myocardial failure resulting from the rupture of a valve usually requires operative correction. Immediate thoractomy should be carried out for most cases of penetrating injury or if there is evidence of

cardiac tamponade and/or shock regardless of the type of trauma. Pericardiocentesis may be helpful in patients with tamponade, but usually only as holding maneuver on the way to the operating room. Pericardial hemorrhage often leads to constriction, which must be treated by decortication.

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SECTION 4 -VASCULAR DISEASE

241. THE PATHOGENESIS OF ATHEROSCLEROSIS - *Peter Libby*

Atherosclerosis is the leading cause of death and disability in the developed world. Despite our familiarity with this disease, some of its fundamental characteristics remain poorly recognized and understood. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and yields distinct clinical manifestations depending on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction (Chap. 243) and angina pectoris (Chap. 244). Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia (Chap. 361). In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize limb viability (Chap. 248). Involvement of the splanchnic circulation can cause mesenteric ischemia. Atherosclerosis can affect the kidneys either directly (e.g., renal artery stenosis) or as a frequent site of atheroembolic disease (Chap. 278).

Even within a given arterial bed, atherosclerosis tends to occur focally, typically in certain predisposed regions. In the coronary circulation, for example, the proximal left anterior descending coronary artery exhibits a particular predilection for developing atherosclerotic occlusive disease. Likewise, atherosclerosis preferentially affects the proximal portions of the renal arteries and, in the extracranial circulation to the brain, the carotid bifurcation. Indeed, atherosclerotic lesions often form at branching points of arteries, regions of disturbed blood flow. Not all manifestations of atherosclerosis result from stenotic, occlusive disease. Ectasia and development of aneurysmal disease, for example, frequently occur in the aorta (Chap. 247). The mechanisms that underlie this discontinuous anatomic distribution of atherosclerosis remain uncertain.

Atherosclerosis manifests itself focally not only in space, as just described, but in time as well. Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth linear fashion, but rather discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. The clinical expressions of atherosclerosis may be chronic, as in the development of stable, effort-induced angina pectoris or of predictable and reproducible intermittent claudication. Alternatively, a much more dramatic acute clinical event, such as myocardial infarction, a cerebrovascular accident, or sudden cardiac death, may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated post mortem.

INITIATION OF ATHEROSCLEROSIS

Lipoprotein Accumulation and Modification

Fatty Streak Formation An integrated view of experimental results in animals and study of human atherosclerosis suggests that the "fatty streak" represents the initial lesion of atherosclerosis (Fig. 241-1). The formation of these early lesions of atherosclerosis

most often seems to arise from focal increases in the content of lipoproteins within regions of the intima (Fig. 241-1*B*;Fig. 241-CD1). This accumulation of lipoprotein particles may not result simply from an increased permeability, or "leakiness," of the overlying endothelium. Rather, these lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the lipid-rich particles within the arterial wall. Lipoproteins that accumulate in the extracellular space of the intima of arteries often associate with proteoglycan molecules of the arterial extracellular matrix. At sites of lesion formation, the balance of different matrix constituents may vary in important ways. Of the three major classes of proteoglycans, for example, a relative excess of heparan sulfate molecules in relation to keratan sulfate or chondritin sulfate may promote the retention of lipoprotein particles by binding them and slowing their egress from nascent lesions.

Lipoprotein particles in the extracellular space of the intima, particularly those bound to matrix macromolecules, may undergo chemical modifications. Accumulating evidence supports a pathogenic role for such modifications of lipoproteins in atherogenesis. Two types of such alterations in lipoproteins bear particular interest in the context of understanding how risk factors actually promote atherogenesis: oxidation and nonenzymatic glycation.

Lipoprotein Oxidation Lipoproteins sequestered from plasma antioxidants in the extracellular space of the intima may be particularly susceptible to oxidative modification. Oxidatively modified low-density lipoprotein (LDL), rather than being a defined homogenous entity, actually comprises a variable and incompletely defined mixture. Both the lipid and protein moieties of these particles can participate in oxidative modification. Modifications of the lipids may include formation of hydroperoxides, lysophospholipids, oxysterols, and aldehydic breakdown products of fatty acids. Recently recognized phospholipid oxidation products include palmitoyl-oxovaleroyl-glycero-phosphoryl choline (POVPC), palmitoyl-glutarolyl-glycero-phosphoryl choline (PGPC), and epoxyisoprostane E_2-glycero-phosphocholine (PEIPC). Modifications of the apoprotein moieties may include breaks in the peptide backbone as well as derivatization of certain amino acid residues. The side chain amino group of lysine may condense with components of the oxidized lipids (4-hydroxynonenol, or malondialdehyde). A more recently recognized modification may result from local hypochlorous acid production by inflammatory cells within the plaque, giving rise to chlorinated species such as chlorotyrosyl moieties. Ongoing work is characterizing specific chemical constituents of oxidized lipoproteins responsible for various biologic effects. Examples include oxovaleryl-phosphoryl choline. Considerable evidence supports the presence of such chemical entities in atherosclerotic lesions.

Nonenzymatic Glycation In diabetic patients with sustained hyperglycemia, nonenzymatic glycation of apolipoproteins and other arterial proteins likely occurs that may likewise alter their function and propensity to accelerate atherogenesis. A good deal of experimental work suggests that both oxidatively modified and glycated lipoproteins or their constituents can contribute to many of the subsequent cellular events of lesion development.

Leukocyte Recruitment After the accumulation of extracellular lipid, recruitment of

leukocytes occurs as a second step in formation of the fatty streak (Fig. 241-1*C*). The white blood cell types typically found in the evolving atheroma include primarily cells of the mononuclear lineage: monocytes and lymphocytes (Figs. 241-CD1 and241-CD2). A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell likely participate in the recruitment of leukocytes to the nascent fatty streak. Adhesion molecules of particular interest include vascular cell adhesion molecule (VCAM) 1 and intercellular adhesion molecule (ICAM) 1 (members of the immunoglobulin gene superfamily) and P-selectin (a member of a distinct family of leukocyte receptors known as selectins). Lysophosphatidylcholine, a constituent of oxidatively modifiedLDL, can augment expression of VCAM-1. This example illustrates how the accumulation of lipoproteins in the arterial intima may link mechanistically with leukocyte recruitment and subsequent events in lesion formation.

Laminar shear forces, such as those encountered in most regions of normal arteries, can also suppress the expression of leukocyte adhesion molecules such asVCAM-1. Sites of predilection for forming atherosclerotic lesions (e.g., branch points) often have disturbed laminar flow. Ordered laminar shear of normal blood flow augments the production of nitric oxide by endothelial cells. This molecule, in addition to its vasodilator properties, can act at the low levels constitutively produced by arterial endothelium as a local anti-inflammatory autacoid, for example, limiting local VCAM-1 expression. These examples indicate how hemodynamic forces may influence the cellular events that underlie atherosclerotic lesion initiation and illustrate a potential explanation for the focal distribution of atherosclerotic lesions at certain sites predetermined by altered flow patterns.

Once adherent to the surface of the arterial endothelial cell via interaction with a receptor such asVCAM-1, the monocytes and lymphocytes penetrate the endothelial layer and take up residence in the intima (Fig. 241-1*D*). In addition to products of modified lipoproteins, cytokines (a class of protein mediators of inflammation) can regulate the expression of adhesion molecules involved in leukocyte recruitment. For example, the cytokines interleukin (IL) 1 or tumor necrosis factor (TNF) a induce or augment the expression of VCAM-1 andICAM-1 on endothelial cells. Because modified lipoproteins can induce cytokine release from vascular wall cells, this pathway may provide an additional link between accumulation and modification of lipoproteins and leukocyte recruitment. The directed migration of leukocytes into the arterial wall may also result from the actions of modified lipoprotein (Fig. 241-CD3). For example, oxidizedLDL may promote the chemotaxis of leukocytes. Also, oxidatively modified lipoproteins can elicit the production by vascular wall cells of chemoattractant cytokines such as monocyte chemoattractant protein 1.

Foam-cell Formation Once resident within the intima, the mononuclear phagocytes differentiate into macrophages and transform into lipid-laden foam cells. Transformation of mononuclear phagocytes into foam cells requires the uptake of lipoprotein particles by receptor-mediated endocytosis. One might suppose that the well-known recognized receptor forLDLmediates this lipid uptake. Patients or animals lacking effective LDL receptors due to genetic alterations (e.g., familial hypercholesterolemia), however, have abundant arterial lesions and extraarterial xanthomata rich in macrophage-derived foam-cells. Also, the exogenous cholesterol suppresses expression of the LDL receptor, such that under hypercholesterolemic conditions the level of this cell-surface receptor

for LDL decreases. Candidates for alternative receptors that can mediate lipid-loading of foam cells include a growing number of macrophage "scavenger" receptors, which preferentially endocytose modified lipoproteins, and other receptors for oxidized LDL orb-VLDL (very low density lipoprotein), a type of lipoprotein commonly encountered in certain hypercholesterolemic states (Chap. 344). By imbibing lipids from the extracellular space, the mononuclear phagocytes bearing such scavenger receptors may remove lipoproteins from the developing lesion. Some lipid-loaded macrophages may leave the artery wall, functioning to clear lipid from the artery. Lipid accumulation, and hence propensity to form atheroma, ensues if the amount of lipid entering the artery wall exceeds that exported by mononuclear phagocytes or other pathways. Macrophages may thus play a vital role in the dynamic economy of lipid accumulation in the arterial wall during atherogenesis. Some lipid-laden foam cells within the expanding intimal lesion perish. Some of the death of foam cells may result from a program of cell death known as *apoptosis*. This death of mononuclear phagocytes results in formation of the lipid-rich center of more complicated atherosclerotic plaques, often called the *necrotic core* of the lesion.

Macrophages taking up modified lipoproteins, much like intrinsic vascular wall cells, may elaborate cytokines and growth factors that can further signal some of the cellular events in lesion complication. A number of growth factors or cytokines elaborated by mononuclear phagocytes can stimulate smooth-muscle cell proliferation and production of extracellular matrix, which accumulates in atherosclerotic plaques.IL-1 andTNF-aare examples of cytokines that can induce local production of growth factors such as forms of platelet-derived growth factor, fibroblast growth factor, and others that may play a role in plaque evolution and complication. Other cytokines, notably interferon (IFN) g derived from activated T cells within lesions, can inhibit smooth-muscle proliferation and synthesis of interstitial forms of collagen. These examples illustrate how atherogenesis likely depends on a complex balance between mediators that can promote lesion formation and other pathways that can mitigate the atherogenic process.

Factors That Modulate Inhibition of Atheroma Elaboration of small molecules by activated mononuclear phagocytes and vascular wall cells in the evolving lesion may also modulate atherogenesis. Notably, reactive oxygen species can modulate growth of smooth-muscle cells, activate inflammatory gene expression via the nuclear factor kappa B (NFkB) transcriptional control system, and annihilate NO radicals, decreasing the effect of this endogenous vasodilator. However, the macrophage in the lesion may be activated to express the inducible form of the enzyme that can synthesize NO, known as inducible NO synthase. This high-capacity form of the enzyme can produce relatively large, potentially cytotoxic amounts of NO radicals. While at low concentrations of×NO produced by the constitutive NO synthase in endothelial cells, this radical may produce beneficial effects; when overproduced by activated phagocytes, it may prove deleterious.

Export by phagocytes may constitute one response to local lipid overload in the evolving lesion. Another mechanism, reverse cholesterol transport mediated by high-density lipoproteins (HDL), may provide an independent pathway for lipid removal from atheroma. Multiple observational studies have established a tight inverse relationship between the level of HDL cholesterol and the risk for coronary events. Increased HDL may explain why premenopausal women have less atherosclerosis than age-matched

men. In various in vitro models, HDL can mediate net cholesterol removal from lipid-laden macrophages. This process likely involves a family of scavenger receptors (the "B" family), highly expressed by steroidogenic tissues and by cells within atheroma as well. Such "reverse cholesterol transport" may also pertain during human atherogenesis and help to explain HDL's protective effect on lesion formation.

Although clear evidence supports lipoprotein disorders as predisposing factors for atheroma formation, other etiologies may contribute to or modulate atherogenesis (Table 242-1). For example, hypertension constitutes an independent risk factor for coronary events. Male gender and the postmenopausal state also augment the risk of developing coronary artery disease. Premenopausal women have increasedHDLlevels compared to age-matched men. However, a favorable lipoprotein pattern only partially accounts for the protection against atherosclerosis conferred by the premenopausal state. Thus, as yet poorly understood direct effects of estrogens on the arterial wall may account for some of this benefit. Studies in progress are investigating possible mechanisms of estrogen's possible "vasculoprotective" effect and the role of estrogen replacement therapy as an antiatherogenic strategy in postmenopausal women.

Diabetes mellitus accelerates atherogenesis. In addition to the well-known microvascular complications of diabetes (Chap. 333), macrovascular disease such as atherosclerosis causes a great deal of excess mortality in the diabetic populations. Diabetes-associated dyslipidemias strongly promote atherogenesis. In particular, the constellation of insulin resistance, high triglycerides, and low HDL, often in association with central adiposity and hypertension frequent in type 2 diabetic patients, seems to accelerate atherogenesis potently. As noted above, hyperglycemia may promote the nonenzymatic glycation ofLDL. LDL modified in this manner, like oxidatively modified LDL, may signal many of the initial events in atherogenesis. Other lipoproteins such as triglyceride-rich particles or lipoprotein (a) [Lp(a)] may also prove particularly atherogenic.

Lp(a)(often pronounced "lipoprotein little a" to distinguish it from apolipoprotein AI and others found in HDL) provides a potential link between hemostasis and blood lipids. The Lp(a) particle consists of an apoprotein (a) molecule bound by a sulfhydryl link to the apolipoprotein B moiety of aLDLparticle. Apoprotein (a) has homology with plasminogen and may inhibit fibrinolysis by competing with plasminogen. Other risk factors for atherosclerosis related to blood clotting include elevated levels of fibrinogen or of the inhibitor of fibrinolysis, plasminogen-activator inhibitor (PAI) 1. Another nonlipid risk factor for coronary events, elevated levels of *homocysteine*, may act by promoting thrombosis, although the pathophysiology of this association is uncertain at present.

The relationship between *tobacco use* and atherosclerosis also remains poorly understood (Chap. 390). The rapid reduction in risk for cardiac events after cessation of cigarette smoking implies that tobacco may promote thrombosis or some other determinant of plaque stability as well as evolution of the atherosclerotic lesion itself. For example, tobacco smokers have elevated fibrinogen levels, a variable associated with increased atherosclerosis and acute cardiovascular events.

In other situations, antecedent inflammatory states may predispose towards atherosclerosis. For example, *Kawasaki disease* in childhood may promote

development of vascular lesions in the arteries of adults (Chap. 317). Infectious agents continue to be proposed as instigators or potentiators of atherogenesis. Both viral and microbial pathogens have been invoked in this context (e.g., Herpesviridiae, including cytomegalovirus, or *Chlamydia*). In some patients, immune or autoimmune reactions may contribute to atherogenesis. In the particular example of the accelerated form of coronary arteriopathy that plagues heart transplant recipients, immunologic factors may contribute importantly to the pathogenesis. The roles of the immune response and of infectious diseases in usual atherosclerosis remain speculative.

Known genetic defects in lipoprotein metabolism account for only a fraction of the familial risk for coronary artery disease. Thus, other as yet undefined genetic factors must contribute to coronary risk. Mechanisms of disease susceptibility involving the arterial wall might account for some of the genetic predisposition to atherosclerosis unexplained by lipoprotein disorders. Application of molecular genetic techniques should help identify new polymorphisms linked to coronary risk and may eventually shed light on new pathophysiologic mechanisms. For example, some data suggest a link between certain alleles of the genes encoding angiotensin-converting enzyme or PAI-1 with increased risk of myocardial infarction. Large studies currently in progress should clarify these and other potential markers of genetic susceptibility to atherosclerosis.

ATHEROMA EVOLUTION AND COMPLICATION

Involvement of Arterial Smooth-Muscle Cells Although the fatty streak commonly precedes the development of a more advanced atherosclerotic plaque, not all fatty streaks progress to yield atheroma. Fatty streaks occur in populations not prone to develop late lesions (e.g., indigenous Africans). These findings raise several questions. Why do some fatty streaks progress to fibrous lesions but not others? By what mechanisms do fatty streaks evolve into more complex lesions? While accumulation of lipid-laden macrophages is the hallmark of the fatty streaks, accumulation of fibrous tissue typifies the more advanced atherosclerotic lesion. The smooth-muscle cell synthesizes the bulk of the extracellular matrix of the complex atherosclerotic lesion. Hence, arrival of smooth-muscle cells and their elaboration of extracellular matrix probably provides a critical transition, yielding a fibrofatty lesion in place of a simple accumulation of macrophage-derived foam cells.

Recent research has provided insight into the mechanisms that may trigger migration and proliferation of smooth-muscle cells into and within the evolving intimal lesion and signal the accumulation of extracellular matrix. Cytokines and growth factors elicited by modified lipoproteins or other agents from both vascular wall cells and infiltrating leukocytes can modulate functions of the smooth-muscle cell. For example, platelet-derived growth factors (PDGF) elaborated by activated endothelial cells can stimulate the migration of smooth-muscle cells (Fig. 241-CD2). In this manner, smooth-muscle cells resident in the tunica media may migrate into the intima. Various growth factors produced locally can stimulate the proliferation of both resident smooth-muscle cells in the intima and those that have migrated from the media. Transforming growth factor (TGF) b, among other mediators, potently stimulates interstitial collagen production by smooth-muscle cells. These mediators may arise not only from neighboring vascular cells or leukocytes (a "paracrine" pathway) but in some instances from the same cell that responds to the factor (an "autocrine" pathway).

Together, these alterations in smooth-muscle cells, signaled by these mediators acting at short distances, can hasten transformation of the fatty streak into a more fibrous smooth-muscle cell and extracellular matrix-rich lesion.

In addition to locally produced mediators, atherogenic risk factor signals related to blood coagulation and thrombosis likely contribute to atheroma evolution and complication. Current evidence suggests that fatty streak formation begins without frank denuding endothelial injury or desquamation. In advanced fatty streaks, however, microscopic breaches in endothelial integrity may occur. Microthrombi rich in platelets can form at such sites of limited endothelial denudation, due to exposure of the highly thrombogenic extracellular matrix of underlying basement membrane. Activated platelets release numerous factors that can promote the fibrotic response. In addition toPDGF andTGF-b, low-molecular-weight mediators such as serotonin can also alter smooth-muscle function. Most of these microthrombi probably resolve without clinical manifestation by a process of local fibrinolysis, resorption, and endothelial repair.

As atherosclerotic lesions advance, abundant plexi of microvessels develop in connection with the artery's vasa vasorum. These newly developing microvascular networks may contribute to lesion complication in several ways. These blood vessels provide an abundant surface area for leukocyte trafficking and may serve as the portal of entry and exit of white blood cells from the established atheroma. The plaques' microvessels may also furnish foci for intraplaque hemorrhage. Like the neovessels in the diabetic retina, microvessels of the plaque may be friable and prone to rupture and produce focal hemorrhage. Such a vascular leak leads to thrombosis in situ and thrombin generation from prothrombin. In addition to its role in blood coagulation, thrombin can modulate many aspects of vascular cell function including stimulation of proliferation and cytokine release from smooth-muscle cells and production of growth factors such asPDGFfrom endothelial cells. Atherosclerotic plaques often contain fibrin and hemosiderin, indicating episodes of intraplaque hemorrhage as an element in plaque complication.

As they advance, atherosclerotic plaques also accumulate calcium. Proteins specialized in binding of calcium usually associated with bone also occur in atherosclerotic lesions. For example, osteocalcin, osteopontin, and bone morphogenetic proteins localize in atherosclerotic plaques. In fact, complication of the atherosclerotic plaque recapitulates many aspects of bone formation.

Traditionally, atherosclerosis research has focused much attention on proliferation of smooth-muscle cells, yet these cells actually replicate rather slowly in complicated atherosclerotic lesions. Estimates of the rate of smooth-muscle cell division at a given time point in such lesions show replicative rate below 1%. Such observations do not exclude bursts of proliferative activity at certain junctures in the history of an atheroma, perhaps in association with local thrombin generation due to microvascular hemorrhage or formation of a microthrombus at a site of localized endothelial denudation, as discussed above. On the other hand, cell death has been recognized as a component of atherogenesis since the time of Virchow in the mid-nineteenth century. Indeed, complex atheroma often have a primarily fibrous character lacking the hypercellular appearance of less advanced lesions and actually exhibiting a paucity of smooth-muscle cells. This relative lack of smooth-muscle cells in advanced atheroma may result from the ultimate

predominance of cytostatic mediators such asTGF-borIFN-g, which can inhibit smooth-muscle cell proliferation. Also, smooth-muscle cells as well as macrophages in advanced atherosclerotic lesions can undergo programmed cell death, or apoptosis. Some of the same cytokines that activate atherogenic functions of vascular wall cells can also trigger the program of apoptosis in these cells.

Thus, during the evolution of the atherosclerotic plaque, a complex balance between entry and egress of lipoproteins and leukocytes, cell proliferation and cell death, extracellular matrix production and remodeling, as well as calcification and neovascularization contribute to lesion formation. Multiple and often competing signals trigger these various cellular events. Increasingly, we appreciate links between atherogenic risk factors and the altered behavior of intrinsic vascular wall cells and infiltrating leukocytes that underlie the complex pathogenesis of these lesions.

CLINICAL SYNDROMES OF ATHEROSCLEROSIS

Atherosclerotic lesions occur ubiquitously in western societies. Most atheroma produce no symptoms, and many never cause clinical manifestations. Numerous patients with diffuse atherosclerosis may succumb to unrelated illnesses without ever having experienced a clinically significant manifestation of atherosclerosis. What accounts for this variability in the clinical expression of atherosclerotic disease?

Arterial remodeling during atheroma formation (Fig. 241-2*A*) represents a frequently overlooked but clinically important feature of lesion evolution. During the initial phases of atheroma development, the plaque usually grows outward, in an abluminal direction. Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as *compensatory enlargement*, a type of vascular remodeling. The growing atheroma does not encroach upon the arterial lumen until the burden of atherosclerotic plaque exceeds approximately 40% of the area encompassed by the internal elastic lamina. Thus, during much of its life history, an atheroma will not cause stenosis that can limit blood flow.

Flow-limiting stenoses commonly form later in the history of the plaque. Many such plaques manifest themselves by stable syndromes such as demand-induced angina pectoris or intermittent claudication in the extremities. In the coronary and other circulations, even occlusion due to atheroma does not invariably lead to infarction. The hypoxic stimulus of repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium, mitigating the consequences of an acute occlusion of an epicardial coronary artery. On the other hand, we now appreciate that many lesions that cause acute or unstable atherosclerotic syndromes, particularly in the coronary circulation, may arise from atherosclerotic plaques that do not produce a flow-limiting stenosis. Such lesions may produce only minimal luminal irregularities on traditional angiograms and often do not meet the traditional criteria for "significance" by arteriography. Instability of such nonocclusive stenoses may explain the frequency of myocardial infarction as an initial manifestation of coronary artery disease (in about a third of cases) in patients who report no prior history of angina pectoris, a syndrome usually caused by flow-limiting stenoses.

Pathologic studies afford considerable insight into the microanatomic substrate

underlying "instability" of plaques that are not critically stenotic. A superficial erosion of the endothelium or a frank plaque rupture or fissure usually produces the thrombus that causes episodes of unstable angina pectoris or the occlusive and relatively persistent thrombus that causes acute myocardial infarction (Fig. 241-2*C*). In the case of carotid atheroma, a deeper ulceration that provides a nidus for formation of platelet thrombi may underlie the unstable syndromes that cause transient ischemic attacks.

Rupture of the plaque's fibrous cap (Fig. 241-2*C*) permits contact of coagulation factors in the blood with highly thrombogenic tissue factor expressed by macrophage foam cells in the plaque's lipid-rich core. If the ensuing thrombus is nonocclusive or transient, the episode of plaque disruption may not cause symptoms or may result in ischemic symptoms such as rest angina. Occlusive thrombi that endure will often cause acute myocardial infarction, particularly in the absence of a well-developed collateral circulation supplying the affected territory. Repetitive episodes of plaque disruption and healing provide one likely mechanism of transition of the fatty streak to a more complex fibrous lesion (Fig. 241-2*D*). The healing process in arteries, as in skin wounds, involves the laying down of new extracellular matrix and fibrosis.

Not all atheroma exhibit the same propensity to rupture. Studies of the pathology of culprit lesions that have caused acute myocardial infarction reveal several characteristic features. Plaques that have proven vulnerable tend to have thin fibrous caps, relatively large lipid cores, and a high content of macrophages (Fig. 241-CD4). Morphometric studies of such culprit lesions show that macrophages and T lymphocytes predominate at the site of plaque rupture. On the other hand, sites of plaque rupture contain relatively few smooth-muscle cells. The cells that concentrate at sites of plaque rupture bear markers of inflammatory activation. The presence of the transplantation, or histocompatibility, antigen HLA-DR provides one convenient gauge of the degree of inflammation in cells in atheroma. Resting cells in normal arteries seldom express this transplantation antigen. However, macrophages and smooth-muscle cells at sites of human coronary artery plaque disruption do bear this inducible cell-surface marker. Therefore, the presence of HLA-DR-positive macrophages and T cells indicates an ongoing inflammatory response at sites of plaque rupture.

Inflammatory mediators may actually regulate processes that govern the integrity of the plaque's fibrous cap and hence its propensity to rupture. For example, the T cell-derived cytokineIFN-g, found in atherosclerotic plaques and required to induce the HLA-DR present at sites of rupture, can inhibit growth and collagen synthesis of smooth-muscle cells. Cytokines derived from activated macrophages such asTNF-aor IL-1 in addition to T cell-derived IFN-g can elicit the expression of genes that encode the proteinases that can degrade the extracellular matrix of the plaque's fibrous cap. Thus, inflammatory mediators can impair collagen synthesis required for maintenance and repair of the fibrous cap and trigger degradation of extracellular matrix macromolecules, processes that should weaken the plaque's fibrous cap and enhance its vulnerability to rupture. In contrast to vulnerable plaques, those with a dense extracellular matrix and relatively thick fibrous cap without substantial tissue factor-rich lipid cores seem generally resistant to rupture and unlikely to provoke thrombosis.

In conclusion, we now appreciate that features of the biology of the atheromatous plaque in addition to its degree of luminal encroachment influence the clinical

manifestations of this disease. This enhanced understanding of plaque biology provides insight into the diverse ways in which atherosclerosis can present clinically, and why the disease may remain silent or stable for prolonged periods and be punctuated by acute complications at certain times. Increased understanding of atherogenesis provides new insight into the ways in which current therapies may improve outcomes and also suggests new targets for future intervention.

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242. PREVENTION AND TREATMENT OF ATHEROSCLEROSIS - *Peter Libby*

Atherosclerosis remains the major cause of death and premature disability in developed societies. Moreover, current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis, will become the leading global cause of total disease burden, defined as the years subtracted from healthy life by disability or premature death. Substantial success has been achieved in recent years in reducing morbidity and mortality due to acute coronary events. However, the opportunity for treating the underlying disease process, atherosclerosis, and preventing its acute complications presents an enormous challenge and opportunity at the same time.

THE CONCEPT OF ATHEROSCLEROTIC RISK FACTORS

During the first half of the twentieth century, animal experiments and clinical observation linked certain variables, such as hypercholesterolemia, to the risk of atherosclerotic events. The systematic study of risk factors in humans, however, began approximately mid-century. The prospective, community-based Framingham Heart Study provided rigorous support for the concept that hypercholesterolemia, hypertension, and other factors correlated with cardiovascular risk. Similar observational studies performed in the United States and abroad provided independent support for the concept of "risk factors" for cardiovascular disease. Numerous studies, including the Seven Countries Study performed by Keys and colleagues, suggested a link between dietary habits and cardiovascular risk based upon population studies.

From a practical viewpoint, it is useful to group the cardiovascular risk factors that have emerged from such studies into two categories: (1) those modifiable by lifestyle and/or pharmacotherapy, and (2) those that are essentially unmodifiable (Table 242-1). The weight of evidence supporting various risk factor differs. For example, hypercholesterolemia and hypertension indubitably predict coronary risk, but other so-called nontraditional risk factors, such as levels of homocysteine, lipoprotein (a) [Lp(a)], or infection, remain controversial. It is worth distinguishing further between factors that actually participate in the pathogenesis of atherosclerosis and those that may merely serve as markers of risk without themselves playing a primary role in pathogenesis. The sections below will consider some of these risk factors and approaches to their modification.

LIPID DISORDERS (See also Chap. 344)

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank as the most firmly established and best understood risk factors for atherosclerosis. Descriptions of the lipoprotein classes, and a detailed explication of lipoprotein metabolism are given inChap. 344. The mechanisms by which lipoproteins may influence atherogenesis are considered inChap. 241. Therefore this section will focus on preventive aspects of treatment of lipid disorders.

Current national guidelines recommend cholesterol screening in all adults. The screen should include a fasting lipid profile [total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol]. Dietary measures, including specific consultation by practitioners with training in nutrition,

should be offered to all patients with hyperlipidemia as defined by the National Cholesterol Education Project Adult Treatment Panel II (Table 242-2). A "normal" total cholesterol level should not falsely reassure individuals with additional risk factors for coronary heart disease or when the HDL level is below 1 mmol/L (40 mg/dL). Many patients with established atherosclerosis fall into this category. Such individuals should receive particular encouragement to adopt life-style measures such as diet and exercise aimed at increasing their HDL levels.

The addition of drug therapy to dietary and other nonpharmacologic measures to reduce the risk of atherosclerotic events in asymptomatic patients without manifest vascular disease remains unsettled. In asymptomatic patients with heterozygous familial hypercholesterolemia,LDLlowering by pharmacologic measures reduces atherosclerosis in both men and women. The West of Scotland Study established that lipid lowering with the HMG-CoA inhibitor pravastatin can effectively reduce cardiac events and total mortality in a cohort of patients with hypercholesterolemia but without prior myocardial infarction (Table 242-3). The recent AFCAPS/TexCAPS Study showed that treatment with lovastatin similarly reduced coronary events in patients without previous myocardial infarction but with "average" total and LDL cholesterol levels and somewhat decreasedHDLlevels.

Although the role of drug therapy in primary prevention of the manifestations of atherosclerosis remains incompletely defined, abundant evidence establishes the benefit of drug therapy in patients with hypercholesterolemia and established coronary artery disease (Table 242-3). A number of well-designed and -executed large-scale clinical trials have now shown that treatment with statins reduces recurrent myocardial infarction, reduces strokes, and lessens the need for revascularization or hospitalization for unstable angina pectoris. These studies have enrolled patients in numerous countries on at least three continents and encompass individuals with clearly elevated levels of cholesterol and those with "average" total andLDLcholesterol levels.

Lipid-lowering therapies do not appear to exert their beneficial effect on cardiovascular events by causing a marked "regression" of obstructive coronary lesions. Angiographically monitored studies of lipid lowering have shown at best a modest reduction in coronary artery stenoses over the duration of study. Yet these same studies consistently show substantial decreases in coronary events. These results suggest that the mechanism of benefit of lipid lowering does not require a substantial reduction in the fixed stenoses. Rather, the benefit may derive from "stabilization" of atherosclerotic lesions without decreased stenosis. Such stabilization of atherosclerotic lesions and the attendant decrease in coronary events may result from the egress of lipids or by favorably influencing aspects of the biology of atherogenesis discussed inChap. 241. In addition, as sizeable lesions may protrude abluminally rather than into the lumen, shrinkage of such plaques might not be apparent on angiograms.

The benefit ofLDLlowering by HMG-CoA reductase inhibitor (statin) therapy on cardiovascular events seems to require 6 to 24 months of treatment. Improvement of vasomotor responses to endothelial-dependent vasodilators occurs much more rapidly, requiring 6 months or less. Thus, HMG-CoA reductase inhibitors may act by two or more mechanisms on the arteries of hypercholesterolemic individuals. The relatively rapid improvement in endothelial-dependent vasomotion may reflect enhanced

production or reduced destruction of the endogenous vasodilator nitric oxide at the level of the arterial endothelium. Reduction in the thrombotic complications of atherosclerosis, such as myocardial infarction or unstable angina, probably requires more prolonged treatment to effect removal of lipid from deeper within the atheroma, yielding improvements in the biology underlying plaque destabilization described in Chap. 241.

Our current understanding of the mechanism by which elevated LDL levels promote atherogenesis relates to oxidative modification of these particles within the artery wall, promoting formation of macrophage-derived foam cells and providing a stimulus for inflammation (Chap. 241). These concepts have given rise to considerable interest in the possibility that antioxidants, either dietary or pharmacologic, might reduce atherogenesis. Considerable experimental evidence supports this notion. In addition, many observational studies show a correlation of antioxidant consumption and reduced cardiovascular risk. Rigorous, controlled clinical trial evidence, however, has not yet proven the effectiveness of antioxidant therapy, whether dietary or with supplements of vitamins or drugs, for prevention or treatment of atherosclerosis. Indeed, controlled trials withb-carotene have demonstrated no reduction in cardiovascular events. For these reasons, as its efficacy remains speculative, it is premature to consider antioxidant administration as a replacement for established therapies. Furthermore, general use of such treatments, particularly in lower risk individuals, should await the results of rigorous prospective studies designed to define the doses, appropriate patient groups, and evaluate the possibility of adverse or unwanted effects of antioxidants.

HYPERTENSION (See also Chap. 246)

The preponderance of epidemiologic data supports a relationship between hypertension and atherosclerotic risk. Clinical trial evidence available since the 1970s established that pharmacologic treatment of hypertension can reduce the risk of stroke and heart failure. However, clinical trial evidence demonstrating reduced risk of coronary events due to antihypertensive therapy has lagged. At present, the combined weight of the evidence supports a reduction in coronary risk by antihypertensive therapy. Some of the difficulty in demonstrating this benefit may derive from the potentially adverse effects of certain classes of antihypertensive drugs on the lipid profile, notably, thiazide diuretics and beta-blocking agents. Indeed, studies of patients with previous myocardial infarction or reduced left ventricular function have shown that treatment with angiotensin-converting enzyme (ACE) inhibitors can reduce the risk of coronary events, an unanticipated outcome. Therefore "lipid-neutral" antihypertensive agents such as ACE inhibitors or α_1-adrenergic blocking agents merit consideration in patients with other risk factors for coronary artery disease or with established atherosclerosis.

DIABETES MELLITUS AND INSULIN RESISTANCE (See also Chap. 333)

Most patients with diabetes mellitus die of atherosclerosis and its complications. Secular trends towards aging of the population and increased girth will make type 2 (noninsulin-dependent) diabetes mellitus an increasing public health problem in the coming years. The criteria for diagnosis of diabetes have recently undergone revision. Currently, a fasting plasma glucose level of 6.9 mmol/L (125 mg/dL) establishes the diagnosis of diabetes. In the intermediate range, plasma glucose levels between 6.1 and 6.9 mmol/L (110 and 125 mg/dL) indicate impaired fasting glucose. Thus, fasting

glucose>6.1 mmol/L (110 mg/dL) indicates abnormal glucose tolerance. These definitions based on fasting plasma glucose alone obviate the need for performing glucose tolerance tests.

A major feature of elevated cardiovascular risk in patients with type 2 diabetes probably relates to the abnormal lipoprotein profile associated with insulin resistance known as *diabetic dyslipidemia*. While diabetic patients may often haveLDLcholesterol levels near average, the LDL particles tend to be smaller and denser and thus more atherogenic (Chap. 344). Other features of diabetic dyslipidemia include lowHDL and elevated triglycerides. Establishing that strict glycemic control reduces the risk of macrovascular complications of diabetes has proven much more elusive than the established beneficial effects on microvascular complications such as retinopathy or renal disease. In the absence of clear-cut evidence that tight glycemic control reduces coronary risk in diabetic patients, attention to other aspects of risk in this patient population assumes even greater importance. In this regard, recent clinical trials have demonstrated unequivocal benefit of HMG-CoA reductase inhibitor therapy in diabetic patients, including those with "average" LDL cholesterol levels. Having diabetes places patients in the same risk category as those with established atherosclerotic disease. Therefore, recent guidelines promulgated by the American Diabetes Association recommend an aggressive approach to lipid lowering in the diabetic population, as supported by recent clinical trials. These guidelines establish a target LDL cholesterol level of 2.6 mmol/L (100 mg/dL) for the patient with diabetes.

MALE GENDER/POSTMENOPAUSAL STATE

Decades of observational studies have verified excess coronary risk in males compared with premenopausal females. After menopause, however, coronary risk accelerates in women. At least part of the apparent protection against coronary heart disease in premenopausal women derives from their relatively higherHDLlevels compared with those of men. After menopause, HDL values fall in concert with increased coronary risk. Estrogen therapy lowersLDLcholesterol and raises HDL cholesterol, changes that should decrease coronary risk. A multitude of observational studies has suggested that estrogen-replacement therapy (ERT) reduces coronary risk. Substantial experimental data support the biologic plausibility of a beneficial effect of estrogen in reducing atherosclerotic events, but a number of potential confounding factors render clinical trials necessary to establish the cardiovascular benefits of ERT. In men, high-dose estrogen treatment caused excess mortality, probably due to increased thromboembolic complications.

The recently reported Heart and Estrogen/Progestin Replacement Study (HERS) has highlighted the need for clinical trial evidence to substantiate the observational and experimental data regarding estrogen's beneficial effects on the vasculature and lipid profile. In this trial, postmenopausal female survivors of acute myocardial infarction were randomized to an estrogen/progestin combination or to placebo. This study showed no overall reduction in recurrent coronary events in the active treatment arm. Indeed, early in the 5-year course of this trial, there was a trend toward an actual increase in vascular events in the treated women. As in the previous Coronary Drug Project trial, the excess events may have resulted from an increase in thromboembolism. HERS does not definitively exclude a potential benefit of other combinations of estrogens with

progestins or a benefit of estrogens alone in patients lacking a uterus. A more prolonged follow-up might have disclosed an accrual of benefit in the treatment group, as the excess events appeared in the first years of the trial in the treated group. Moreover, drugs of the selective estrogen receptor modulator class might dissociate the increased risk of breast and/or uterine cancer from cardiovascular benefit. This possibility will likewise require randomized clinical trial evidence evaluating coronary events to validate widespread application. The current quandary surroundingERT as a means of reducing cardiovascular risk highlights the need for redoubled attention to known modifiable risk factors in women. In the recent clinical trials with HMG-CoA reductase inhibitors, women, when included, have derived benefits at least commensurate with those seen in men. Data from HERS itself showed that application of lipid-lowering therapy to female survivors of myocardial infarction lagged far behind guidelines. Choices regarding ERT in postmenopausal women remain complex. Physicians should work together with women to provide information and help weigh the risks and benefits of ERT, taking personal preferences into account.

DYSREGULATED COAGULATION OR FIBRINOLYSIS

Thrombosis ultimately causes the gravest complications of atherosclerosis. The propensity to form thrombi and/or to lyse clots once they form could clearly influence the manifestations of atherosclerosis. Thrombosis provoked by atheroma rupture and subsequent healing may promote plaque growth, as described inChap. 241. Certain individual characteristics can influence thrombosis or fibrinolysis and have received attention as potential coronary risk factors. For example, fibrinogen levels correlate with coronary risk and provide information regarding coronary risk independent of the lipoprotein profile. Elevated fibrinogen levels might promote a thrombotic diathesis. Alternatively, fibrinogen, an acute-phase reactant, may serve as a marker of inflammation rather than directly participating in the pathogenesis of coronary events.

The stability of an arterial thrombus depends on the balance between fibrinolytic factors, such as plasmin, and inhibitors of the fibrinolytic system, such as plasminogen activator inhibitor (PAI) 1. Certain genotypes of the PAI-1 gene appear to correlate with increased coronary risk. Yet, overall, the levels of tissue plasminogen activator and PAI-1 in plasma have not proven to add information beyond the lipid profile to assessment of cardiovascular risk. Likewise, the role ofLp(a)(Chap. 344) as a modulator of fibrinolysis remains controversial. Apo Lp(a) has high homology to plasminogen but lacks the enzymatic activity of this fibrinolytic molecule. Thus, Lp(a) might antagonize fibrinolysis, serving as a type of "dominant negative" competitor of plasminogen. However, in vivo evidence for this mechanism, and, indeed, the independent contribution of Lp(a), is clouded by difficulties in standardizing the assays and the highly polymorphic nature of this protein in humans.

HOMOCYSTEINE

A large body of literature suggests a relationship between hyperhomocysteinemia and coronary events. Several mutations in the enzymes involved in homocysteine accumulation correlate with thrombosis and, in some studies, coronary risk. Although thrombosis and atherosclerosis seem intimately linked, direct evidence of an atherogenic effect of hyperhomocysteinemia in humans remains weak. The role of

hyperhomocysteinemia in atherosclerotic complications, however, has important practical implications. The plasma level of homocysteine can vary with diet. Nutritional supplementation with folic acid can lower homocysteine levels in many individuals. A substantial portion of the elderly population in the United States has only a marginal sufficiency of folate intake. A fortification of the American diet with folic acid, aimed at reduction of neural tube defects, is lowering homocysteine levels in the population at large. Recommending a diet rich in folate or consumption of multivitamin supplements containing folic acid should be considered in individuals with atherosclerosis out of proportion to traditional or established risk factors and with elevated levels of homocysteine. The possibility that folate treatment might mask pernicious anemia should be considered when advising such supplementation. No clinical trial evidence currently establishes a reduction in coronary events in patients with hyperhomocysteinemia treated with folate.

INFECTION/INFLAMMATION

Recent years have witnessed a resurgence of interest in the possibility that infections may cause or contribute to atherosclerosis. A spate of recent publications has furnished evidence in support for a role of *Chlamydia pneumoniae*, cytomegalovirus, or other infectious agents in atherosclerosis and restenosis following coronary intervention. Some microorganisms exist in human atherosclerotic plaques. However, seroepidemiologic evidence for an association between infection with various agents and atherosclerosis remains inconclusive. Several ongoing large trials of antibiotic treatment in survivors of myocardial infarction may provide support for an etiologic or contributory role of microbial infection in recurrent coronary events. Even if positive, however, such clinical trials would neither inculpate any particular microorganisms nor even prove that a benefit derived from the antimicrobial action of the agent employed.

Although direct infection may not cause atherosclerosis, the infectious agents and the host defenses against these invaders might potentiate atherogenesis, acting as inflammatory stimuli. Just as inflammation may mediate some of the altered arterial biology in response to hyperlipoproteinemia, so might infectious agents incite an inflammatory response that could promote atherosclerosis and its complications. Thus, microbial pathogens might act in concert with traditional risk factors to accelerate atherogenesis or cause complication or aggravation of existing atheroma.

In this regard, evidence is accumulating that markers of inflammation correlate with coronary risk. For example, elevated plasma levels of C-reactive protein (CRP) can prospectively predict risk of myocardial infarction and correlate with outcome of patients with acute coronary syndromes. As in the case of fibrinogen, elevated levels of the acute-phase reactant CRP may merely reflect ongoing inflammation rather than a direct etiologic role for CRP in coronary artery disease. It remains uncertain whether elevations in acute-phase reactants such as fibrinogen or CRP serve as a marker for the overall atherosclerotic burden, and hence of coronary events. Alternatively, the elevation in acute-phase reactants could reflect extravascular inflammation that could potentiate atherosclerosis or its complications. In all likelihood, both factors contribute to elevation of inflammatory markers in patients at risk for coronary events. These observations raise the possibility that anti-inflammatory therapies might reduce atherosclerotic events. Indeed, lipid-lowering therapy may reduce coronary events in

part by reducing the inflammatory aspects of the pathogenesis of atherosclerosis.

LIFE-STYLE MODIFICATION

The prevention of atherosclerosis presents a long-term challenge to all health care professionals and for public health policy. Both individual practitioners and organizations providing health care should strive to help patients optimize their risk factor profile long before atherosclerotic disease might become manifest. The care plan for all patients seen by internists should include measures to assess and minimize cardiovascular risk. Physicians must counsel patients regarding the health risks of tobacco use and provide guidance regarding smoking cessation. Likewise, physicians should advise all patients about prudent dietary and exercise habits for maintaining ideal body weight. The recent National Institutes of Health Consensus Panel on Physical Activity and Cardiovascular Health established a goal of accumulating at least 30 min of moderate-intensity physical activity on a daily basis. Obesity, particularly the male pattern of centripetal or visceral fat accumulation, can promote an atherogenic dyslipidemia characterized by elevated triglycerides, a low HDL level, and glucose intolerance. Physicians should encourage their patients to take responsibility for behavior related to modifiable risk factors for development of premature atherosclerotic disease. Conscientious counseling and patient education may forestall the need for pharmacologic measures intended to reduce coronary risk.

ISSUES IN RISK ASSESSMENT

A growing panel of markers of coronary risk presents a perplexing array to the practitioner. Such markers include size fractionation of LDL particles, measurement of concentrations of homocysteine, Lp(a), fibrinogen, CRP, and PAI-1, among others. In general, such specialized tests add little to the information available from a careful history and physical examination and measurement of a plasma lipoprotein profile and fasting blood sugar. Evaluation of such specialized markers might be considered in individuals without evident risk factors other than premature vascular disease or a worrisome family history. A similar confusion surrounds the use of specialized radiographic estimations of coronary artery calcification. Information is accumulating that the amount of calcium determined by such techniques as electron beam computed tomography correlates with coronary risk. However, the utility of using such estimates of coronary artery calcium content as a guide to therapy remains unproven, particularly in asymptomatic individuals. Inappropriate use of such imaging modalities might promote excessive invasive diagnostic and therapeutic procedures. Widespread application of such modalities for screening should await proof that clinical benefit derives from their application.

THE CONCEPT OF GLOBAL RISK

Adoption of hygienic life-style changes to ameliorate coronary risk entails little expense or possibility of adverse effects. In contrast, pharmacotherapy can prove costly. Although lipid-lowering drugs such as the HMG-CoA reductase inhibitors have proven exceedingly well tolerated in clinical trials, the use of these or other lipid-lowering agents could produce adverse reactions in some individuals. The decision to initiate drug treatment for reduction of risk of atherosclerotic events requires careful consideration,

particularly in the setting of "primary prevention" or in patients without known atherosclerotic disease. In this regard, it is prudent to consider not only theLDLcholesterol but also the individual patient's global cardiovascular risk. For example, an individual with an average LDL but a lowHDL, hypertension, and a family history of premature coronary artery disease might warrant initiation of drug therapy more than an individual with the same LDL level in the absence of the other risk factors. Rather than considering plasma lipoprotein values in insolation, current European guidelines reserve drug treatment for individuals with a calculated absolute coronary heart disease risk of greater than 20% over 10 years. The calculation of coronary risk includes taking gender, smoking history, and systolic blood pressure into account, in addition to plasma cholesterol levels. This policy illustrates how estimations of global risk may be applied to optimize decisions regarding initiation of drug therapy to prevent atherosclerotic events (Fig. 242-1).

THE CHALLENGE OF IMPLEMENTATION: CHANGING PHYSICIAN AND PATIENT BEHAVIOR

Enormous strides have been made in the prevention and treatment of atherosclerosis. Despite declining age-adjusted rates of coronary death, cardiovascular mortality is on the rise due to the aging of the population overall. There is a powerful global trend toward increased atherosclerotic disease. Enormous challenges remain regarding translation of the current evidence base into practice. The obstacles to implementation of current evidence-based prevention and treatment of atherosclerosis include economics, education, physician awareness, and patient adherence to recommended regimens. Future goals in the field of treatment of atherosclerosis should include application of the current knowledge regarding risk factor management and, when appropriate, drug therapy.

(Bibliography omitted in Palm version)

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243. ACUTE MYOCARDIAL INFARCTION - *Elliott M. Antman*, *Eugene Braunwald*

Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients in industrialized countries. In the United States, approximately 1.1 million AMIs occur each year. The mortality rate with AMI is approximately 30%, with more than half of these deaths occurring before the stricken individual reaches the hospital. Although the mortality rate after admission for AMI has declined by about 30% over the last two decades, approximately 1 of every 25 patients who survives the initial hospitalization dies in the first year after AMI. Survival is markedly reduced in elderly patients (over age 75), whose mortality rate is 20% at 1 month and 30% at 1 year after AMI.

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE

AMIgenerally occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis. Slowly developing, high-grade coronary artery stenoses usually do not precipitate AMI because of the development of a rich collateral network over time. Instead, AMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, infarction occurs when an atherosclerotic plaque fissures, ruptures, or ulcerates and when conditions (local or systemic) favor thrombogenesis, so that a mural thrombus forms at the site of rupture and leads to coronary artery occlusion (Fig. 243-CD1). Histologic studies indicate that the coronary plaques prone to rupture are those with a rich lipid core and a thin fibrous cap (Chap. 241). After an initial platelet monolayer forms at the site of the ruptured plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, there is production and release of thromboxane A_2 (a potent local vasoconstrictor), further platelet activation, and potential resistance to thrombolysis.

In addition to the generation of thromboxane A_2, activation of platelets by agonists promotes a conformational change in the glycoprotein IIb/IIIa receptor (Chap. 116). Once converted to its functional state, this receptor develops a high affinity for amino acid sequences on soluble adhesive proteins (i.e., integrins) such as von Willebrand factor (vWF) and fibrinogen. Since vWF and fibrinogen are multivalent molecules, they can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the ruptured plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin (Chap. 117). Fluid-phase and clot-bound thrombin participate in an autoamplification reaction that leads to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands.

In rare cases,AMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic -- particularly inflammatory -- diseases. The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not

the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) native factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk of developingAMIinclude those with multiple coronary risk factors (Chap. 241) and those with unstable angina or Prinzmetal's variant angina (Chap. 244). Less common underlying medical conditions predisposing patients to AMI include hypercoagulability, collagen vascular disease, cocaine abuse, and intracardiac thrombi or masses that can produce coronary emboli.

CLINICAL PRESENTATION

In up to one-half of cases, a precipitating factor appears to be present beforeAMI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness (Fig. 243-CD2). Although AMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening. The increased frequency early in the day may be due to a combination of an increase in sympathetic tone and an increased tendency to thrombosis between 6:00 A.M. and 12 noon.

Pain is the most common presenting complaint in patients withAMI. In some instances, it may be severe enough to be described asthe worst pain the patient has ever felt. The pain is deep and visceral; adjectives commonly used to describe it are *heavy*, *squeezing*, and *crushing*, although occasionally it is described as stabbing or burning (Chap. 13). It is similar in character to the discomfort of angina pectoris but usually is more severe and lasts longer. Typically the pain involves the central portion of the chest and/or the epigastrium, and on occasion it radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and patients' denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of AMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest. When the pain begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

Although pain is the most common presenting complaint, it is by no means always present. The proportion of painlessAMIs is greater in patients with diabetes mellitus, and it increases with age. In the elderly, AMI may present as sudden-onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained drop in arterial pressure. The pain of AMI can simulate pain from acute pericarditis (Chap. 239), pulmonary embolism (Chap. 261), acute aortic dissection (Chap. 247), costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis.

PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggestsAMI. Although many patients have a normal pulse rate and blood pressure within the first hour of AMI, about one-fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and up to one-half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction that may be present include, in order of decreasing incidence, fourth (S_4) and third (S_3) heart sounds, decreased intensity of heart sounds, and, in more severe cases, paradoxical splitting of the second heart sound (Chap. 225). A transient apical systolic murmur due to dysfunction of the mitral valve apparatus may be midsystolic or late systolic in timing. A pericardial friction rub is heard in many patients with transmuralAMI at some time in the course of the disease, if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Jugular venous distention with clear lung fields should raise suspicion of right ventricular infarction. Temperature elevations up to 38°C may be observed during the first week after AMI; however, a temperature exceeding 38°C should prompt a search for other causes. The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by approximately 10 to 15 mmHg from the preinfarction state.

LABORATORY FINDINGS

Myocardial infarction (MI) progresses through the following temporal stages: (1) acute (first few hours to 7 days), (2) healing (7 to 28 days),and (3) healed (29 days and beyond). When evaluating the results of diagnostic tests forAMI, the temporal phase of the infarction process must be considered. The laboratory tests of value in confirming the diagnosis may be divided into 4 groups: (1) electrocardiogram (ECG), (2) serum cardiac markers, (3) cardiac imaging, and (4) nonspecific indexes of tissue necrosis and inflammation.

ELECTROCARDIOGRAM

The electrocardiographic manifestations ofAMI are described in Chap. 226. During the initial stage of the acute phase of MI, total occlusion of the infarct artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation evolve Q waves on theECG and are ultimately diagnosed as having sustained a Q-wave MI. A small proportion may sustain only a non-Q-wave MI. When the obstructing thrombus is not totally occlusive, obstruction is transient, or if a rich collateral network is present, no ST-segment elevation is seen. Such patients are initially considered to be

experiencing either unstable anigna or a non-ST-segment elevation MI (NSTEMI). Among patients presenting without ST-segment elevation, if a serum cardiac marker is detected and no Q wave develops, the diagnosis of non-Q-wave MI is ultimately made. A minority of patients who present initially without ST-segment elevation may develop a Q-wave MI. Previously it was believed that transmural MI is present if the ECG demonstrates Q waves or loss of R waves, and nontransmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, electrocardiographic-pathologic correlations are far from perfect; and therefore a more rational nomenclature for designating electrocardiographic infarction is now commonly in use, with the terms Q-wave and non-Q-wave MI replacing the terms transmural and nontransmural MI, respectively.

The presentations that comprise the spectrum ranging from unstable angina through non-Q-waveMI to Q-wave MI are called the *acute coronary syndromes* (Fig. 243-1). This classification scheme provides a conceptual framework for interpreting the diagnostic and prognostic information gleaned from serum cardiac marker measurements as well as for planning antithrombotic therapy.

SERUM CARDIAC MARKERS

Certain proteins, called *serum cardiac markers*, are released into the blood in large quantities from necrotic heart muscle afterAMI. The rate of liberation of specific proteins differs depending on their intracellular location and molecular weight, and the local blood and lymphatic flow. The temporal pattern of protein release is of diagnostic importance, but contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical andECGfindings) before the results of blood tests have returned from the central laboratory. Rapid whole-blood bedside assays for serum cardiac markers are now available and may facilitate management decisions, particularly in patients with nondiagnostic ECGs.

Creatine phosphokinase (CK) rises within 4 to 8 h and generally returns to normal by 48 to 72 h. An important drawback of total CK measurement is its lack of specificity forAMI, as CK may be elevated with skeletal muscle trauma. A two- to threefold elevation of total CK may follow an intramuscular injection, for example. This ambiguity may lead to the erroneous diagnosis of AMI in a patient who has been given an intramuscular injection of a narcotic for chest pain of noncardiac origin. Other potential sources of total CK elevation are (1) skeletal muscular diseases, including muscular dystrophy, myopathies, and polymyositis; (2) electrical cardioversion; (3) hypothyroidism; (4) stroke; (5) surgery; and (6) skeletal muscle damage secondary to trauma, convulsions, and prolonged immobilization.

The MB isoenzyme ofCK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and therefore is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CKMB mass:CK activity $^{3}2.5$ suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CKMB elevation. This ratio is less useful when levels of total CK are high owing to skeletal muscle injury or when the total CK level is within the normal range but CKMB is elevated.

Rather than attempting to make the diagnosis ofAMI on the basis of a single measurement ofCK and CKMB, clinicians should evaluate a series of measurements obtained over the first 24 h. Skeletal muscle release of CKMB typically produces a "plateau" pattern, whereas AMI produces a CKMB elevation that peaks approximately 20 h after the onset of coronary occlusion. When released into the circulation, the myocardial form of CKMB (CKMB2) is acted on by the enzyme carboxypeptidase, which cleaves a lysine residue from the carboxyl terminus to produce an isoform (CKMB1) with a different electrophoretic mobility. A CKMB2:CKMB1 ratio of>1.5 is highly sensitive for the diagnosis of AMI, particularly 4 to 6 h after the onset of coronary occlusion.

Cardiac-specific troponin T (cTnT) and *cardiac-specific troponin I (cTnI)* have amino acid sequences different from those of the skeletal muscle forms of these proteins. These differences have permitted the development of quantitative assays for cTnT and cTnI with highly specific monoclonal antibodies. Since cTnT and cTnI are not normally detectable in the blood of healthy individuals but may increase afterAMI to levels over 20 times higher than the cutoff value (usually set only slightly above the noise level of the assay), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI. The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit forCK and CKMB measurements. Levels of cTnI may remain elevated for 7 to 10 days after AMI, and cTnT levels may remain elevated for up to 10 to 14 days. Thus, measurement of cTnT or cTnI has replaced measurement of lactate dehydrogenase (LDH) and its isoenzymes in patients with suspected MI who come to medical attention more than 24 to 48 h after the onset of symptoms.

Myoglobin is released into the blood within only a few hours of the onset ofAMI. Although myoglobin is one of the first serum cardiac markers that rises above the normal range after AMI, it lacks cardiac specificity, and it is rapidly excreted in the urine, so that blood levels return to the normal range within 24 h of the onset of infarction.

Many hospitals are usingcTnT orcTnIrather thanCKMB as the routine serum cardiac marker for diagnosis ofAMI, although any of these analytes remains clinically acceptable. It is not cost-effective to measure both a cardiac-specific troponin and CKMB at all time points in every patient. However, in view of the prolonged elevation of cardiac-specific troponins (>1 week), episodes of recurrent ischemic discomfort and suspected recurrentMI are more readily diagnosed with a serum cardiac marker that remains elevated in the blood more briefly, such as CKMB or myoglobin.

While it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours ofAMIcauses earlier and higher peaking (at about 8 to 12 h after reperfusion) of serum cardiac markers.

Characteristic rises occur in serum cardiac markers in virtually all patients with clinically provenMI.CK and CKMB levels generally do not rise in unstable angina. However, approximately one-third of patients who are considered to have unstable angina on the

basis of a lack of CK or CKMB elevation have elevations of cTnT or cTnI, probably indicating the presence of microinfarction. The finding of an elevated cardiac-specific troponin level, even in the presence of normal CK and CKMB values, is indicative of an adverse prognosis, and such patients should be considered to have sustained MI and managed as described below.

For the purposes of confirming the diagnosis of MI, serum cardiac markers should be measured on admission, 6 to 9 h after admission, and 12 to 24 h after admission if the diagnosis remains uncertain.

The *nonspecific reaction* to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain, persists for 3 to 7 days, and often reaches levels of 12,000 to 15,000 leukocytes per microliter. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

CARDIAC IMAGING

Two-dimensional echocardiography (Chap. 227) is the most frequently employed imaging modality in patients with AMI. Abnormalities of wall motion are almost universally present (Fig. 243-CD3). Even when no ST-segment elevation is seen, echocardiographically detectable wall motion abnormalities may be observed. Although AMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool. In the emergency department setting, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy [e.g., thrombolysis or a percutaneous coronary intervention (PCI)]. Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an angiotensin-converting enzyme inhibitor (see "Angiotensin-Converting Enzyme Inhibitors," below). Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of AMI (see below).

Several radionuclide imaging techniques are available for evaluating patients with suspected AMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and they lack sensitivity and specificity in many clinical circumstances. Myocardial perfusion imaging with ^{201}Tl or ^{99m}Tc-sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium (Chap. 244) reveal a defect ("cold spot") in most patients during the first few hours after development of a transmural infarct. However, although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and thus is not specific for the diagnosis of *acute* MI. Radionuclide ventriculography, carried out with ^{99m}Tc-labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with AMI. While of value in assessing the hemodynamic consequences of infarction and in aiding in the diagnosis of RV infarction when the RV ejection fraction is depressed, this

technique is also quite nonspecific, as many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

MANAGEMENT (FIG. 243-CD4)

PREHOSPITAL CARE

The prognosis in AMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical problems ("pump failure"). Most out-of-hospital deaths from AMI are due to the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms, and, of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected AMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative maneuvers, including defibrillation; and (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias, providing advanced cardiac life support, and (4) expeditious implementation of reperfusion therapy. The biggest delay usually occurs not during transportation to the hospital but rather between the onset of pain and the patient's decision to call for help. This delay can best be reduced by education of the public by health care professionals concerning the significance of chest pain and the importance of seeking early medical attention. Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment.

INITIAL MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the emergency department, the goals for the management of patients with suspected AMI include control of cardiac pain, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with AMI. Many aspects of the treatment of AMI are initiated in the emergency department and then continued during the in-hospital phase of management.

Aspirin is now considered an essential element in the management of patients with suspected AMI and is effective across the entire spectrum of acute coronary syndromes (Fig. 243-2 and 243-3). Rapid inhibition of cyclooxygenase in platelets followed by a reduction of thromboxane A_2 levels is achieved by buccal absorption of a chewed 160 to 325 mg tablet in the emergency department. This measure should be followed by daily oral administration of aspirin in a dose of 160 to 325 mg.

Since patients with AMI may develop hypoxemia secondary to ventilation-perfusion abnormalities from LV failure and intrinsic pulmonary disease, it has been a common practice to routinely administer *supplemental oxygen*. In patients whose arterial oxygen saturation is normal as estimated by pulse oximetry or measured by an arterial blood gas specimen, supplemental oxygen is of limited if any clinical benefit and therefore is not cost effective. However, when hypoxemia is present, oxygen should be administered by nasal prongs or face mask (2 to 4 L/min) for the first 6 to 12 h after

infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

CONTROL OF PAIN

Morphine is a very effective analgesic for the pain associated withAMI. However, it may reduce sympathetically mediated arteriolar and venous constriction, and the resulting venous pooling may reduce cardiac output and arterial pressure. This complication does not contraindicate the use of morphine. Hypotension associated with venous pooling usually responds promptly to elevation of the legs, but in some patients volume expansion with intravenous saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with posteroinferior infarction. These side effects usually respond to atropine (0.5 mg intravenously). Morphine is routinely administered by repetitive (every 5 min) intravenous injection of small doses (2 to 4 mg) rather than by the subcutaneous administration of a larger quantity, because absorption may be unpredictable by the latter route.

Before morphine is administered, sublingual *nitroglycerin* can be given safely to most patients withAMI. Up to three 0.4-mg doses should be administered at about 5-min intervals. In addition to diminishing or abolishing chest discomfort, nitroglycerin, once considered contraindicated in the setting of AMI, may be capable of both decreasing myocardial oxygen demand (by lowering preload) and increasing myocardial oxygen supply (by dilating infarct-related coronary vessels or collateral vessels). In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest pain, particularly if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of intravenous nitroglycerin should be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<100 mmHg) or in whom there is clinical suspicion of right ventricular infarction (inferior infarction on electrocardiogram, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken the phosphodiasterase 5 inhibitor sildenafil for erectile dysfunction within the preceding 24 h since it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can usually be reversed promptly by the rapid administration of intravenous atropine.

Intravenous *beta blockers* are also useful in the control of the pain ofAMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial oxygen demand and hence ischemia. More important, there is evidence that intravenous beta blockers reduce in-hospital mortality, particularly in high-risk patients (see "b-Adrenoceptor Blockers," below). A commonly employed regimen is metoprolol, 5 mg every 2 to 5 min for a total of three doses, provided the patient has a heart rate>60 beats per minute (bpm), systolic pressure>100 mmHg, a PR interval<0.24 s, and rales that are no higher than 10 cm up from the diaphragm. Fifteen minutes after the last intravenous dose, an oral regimen is initiated of 50 mg every 6 h for 48 h followed by 100 mg every 12 h.

Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

MANAGEMENT STRATEGIES (Figs. 243-2 and243-3)

The primary tool for screening patients and making triage decisions is the initial 12-leadECG. When ST-segment elevation in at least two contiguous leads of at least 2 mm in V1-V3 and 1 mm in other leads is present, a patient should be considered a candidate for *reperfusion therapy* (Fig. 243-2;Fig. 243-CD5). If no contraindications are present (see "Contraindications and Complications," under "Thombolysis," below), thrombolytic therapy should ideally be initiated within 30 min. The process of selecting patients for thrombolysis versus primaryPCI(angioplasty, or stenting) (Chap. 245) is discussed below. In the absence of ST-segment elevation, thrombolysis is not helpful, and evidence exists suggesting that it may be harmful. Pharmacotherapy for patients presenting without ST-segment elevation (Fig. 243-3) typically includes measures to control cardiac pain (as discussed above), aspirin, antithrombin therapy (preferably with low-molecular-weight heparin), and infusion of nitroglycerin as needed to control recurrent ischemia. For high-risk patients an intravenous infusion of a glycoprotein IIb/IIIa inhibitor should be considered. Further management recommendations for patients without ST-segment elevation are outlined inFig. 243-3.

LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the site of occlusion. While the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium may be improved by timely restoration of coronary perfusion, reduction of myocardial oxygen demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients withAMI may achieve *spontaneous* reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue. Reperfusion either pharmacologically (by thrombolysis) or mechanically (by angioplasty and/or stenting) accelerates the process of opening the occluded infarct-related artery in those patients in whom spontaneous thrombolysis ultimately would have occurred and also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct-related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial oxygen supply and demand through pain control, treatment of congestive heart failure, and minimization of tachycardia and hypertension extends the "window" of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in the setting ofAMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition,

they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

THROMBOLYSIS

The thrombolytic agents tissue plasminogen activator (tPA), streptokinase, anisoylated plasminogen streptokinase activator complex (APSAC) and reteplase (rPA) have been approved by the Food and Drug Administration for intravenous use in the setting ofAMI. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with tPA. The principal goal of thrombolysis is prompt restoration of coronary arterial patency.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the TIMI grading system: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. Early reports frequently lumped TIMI grades 2 and 3 under the general category of *patency*, but it is now recognized that grade 3 flow is the goal of reperfusion therapy, because full perfusion of the infarct-related coronary artery yields far better results in terms of infarct size, maintenance ofLVfunction, and reduction of both short- and long-term mortality rates. Relatively new methods of angiographic assessment of the efficacy of thrombolysis include counting the number of frames required on the cine film for dye to flow from the origin of the infarct-related artery to a landmark in the distal vascular bed (TIMI frame count) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (TIMI Myocardial Perfusion Grade).

Thrombolytic therapy can reduce the relative risk of in-hospital death by up to 50% when administered within the first hour of the onset of symptoms ofAMI, and much of this benefit is maintained for at least 10 years. Appropriately used thrombolytic therapy appears to reduce infarct size, limitLVdysfunction, and reduce the incidence of serious complications such as septal rupture, cardiogenic shock, and malignant ventricular arrhythmias. Since myocardium can be salvaged only before it has been irreversibly injured, the timing of reperfusion therapy, by thrombolysis or a catheter-based approach, is of extreme importance in achieving maximum benefit. While the upper time limit depends on specific factors in individual patients, it is clear that "every minute counts" and that patients treated within 1 to 3 h of the onset of symptoms generally benefit most. Although reduction of the mortality rate is more modest, the therapy remains of benefit for many patients seen 3 to 6 h after the onset of infarction, and some benefit appears to be possible up to 12 h, especially if chest discomfort is still present and ST segments remain elevated inECGleads that do not yet demonstrate new Q waves. In addition to the possibility of early treatment, clinical factors that favor proceeding with thrombolytic therapy include anterior wall injury, hemodynamically complicated infarction, and widespread ECG evidence of myocardial jeopardy. Although

patients (younger than 65 years) achieve a greater relative reduction in the mortality rate than elderly patients, the higher *absolute* mortality rate (15 to 25%) in elderly patients results in similar absolute reductions in the mortality rates for both age groups.

Intriguing data are accumulating to indicate that improved ventricular function and reduced mortality may also be achieved by *late coronary reperfusion*. The benefits of late reperfusion cannot be attributed to a reduction of infarct size but appear to result from improvement of tissue healing in the infarct zone with prevention of infarct expansion, enhancement of collateral flow, improvement of myocardial contractile performance, and reduction in the tendency to electrical instability. In addition, *hibernating myocardium* (i.e., poorly contractile myocardium in a zone that is supplied by a stenotic infarct-related coronary artery with slow antegrade perfusion,Chap. 244) may show improved contraction after angioplasty to increase coronary blood flow.

tPAis more effective than streptokinase at restoring full perfusion -- i.e., TIMI grade 3 coronary flow -- and has a small edge in improving survival as well. The current recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg intravenously over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) intravenously over 1 h. Reteplase is administered in a double bolus regimen consisting of a 10-MU bolus given over 2 to 3 min followed by a second 10-MU bolus 30 min later.

Promising new pharmacologic regimens for reperfusion combine an intravenous glycoprotein IIb/IIIa inhibitor with a reduced dose of a thrombolytic agent. Such combination reperfusion regimens appear to facilitate the rate and extent of thrombolysis by inhibiting platelet aggregation, weakening the clot structure, and allowing penetration of the thrombolytic agent deeper into the clot.

Contraindications and Complications Clear contraindications to the use of thrombolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure>180 mmHg and/or a diastolic pressure>110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with an increase in hemorrhagic complications, the benefit of thrombolytic therapy in the elderly appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial.

Relative contraindications to thrombolytic therapy, which require careful assessment of the risk:benefit ratio, include current use of anticoagulants (international normalized ratio³2), a recent (<2 weeks) invasive or surgical procedure or prolonged (>10 min) cardiopulmonary resuscitation, known bleeding diasthesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

Allergic reactions to streptokinase occur in approximately 2% of patients who receive it. While a minor degree of hypotension occurs in 4 to 10% of patients given this agent,

marked hypotension occurs, although rarely, in association with severe allergic reactions.

Hemorrhage is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving thrombolytic agents. Hemorrhagic stroke is the most serious complication and occurs in approximately 0.5 to 0.9% of patients being treated with these agents. This rate increases with advancing age, with patients older than 70 years experiencing roughly twice the rate of intracranial hemorrhage as those younger than 65 years. Large-scale intervention trials have suggested that the rate of intracranial hemorrhage withtPA orrPA is slightly higher than that with streptokinase.

Routine angiography after thrombolysis with the intent of performing aPCI on underlying coronary artery stenoses in the culprit vessel is not recommended. Higher rates of abrupt closure of the infarct-related coronary artery with a need for urgent coronary artery bypass surgery as well as a trend toward an increase in mortality rate have been noted with this approach. Instead, after thrombolytic therapy, cardiac catheterization and coronary angiography should be carried out if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation beyond 90 min) in which case a *rescue PCI* should be considered, or (2) coronary artery reocclusion (reelevation of ST segments and/or recurrent chest pain) or the development of recurrent ischemia (such as recurrent angina in the early hospital course or a positive exercise stress test before discharge), in which case an *elective PCI* should be considered. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to angioplasty but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

Primary Percutaneous Coronary Intervention (See alsoChap. 245) PCI, usually angioplasty and/or stenting without preceding thrombolysis, is also effective in restoring perfusion inAMI when carried out on an emergency basis in the first few hours ofMI. It has the advantage of being applicable to patients who have contraindications to thrombolytic therapy but otherwise are considered appropriate candidates for reperfusion. It appears to be more effective than thrombolysis in opening occluded coronary arteries and, *when performed by experienced operators in dedicated medical centers*, is associated with better short-term and long-term clinical outcomes. It remains to be determined whether the advantages of primary PCI reported from organized research efforts can be replicated in routine clinical practice. However, PCI is expensive in terms of personnel and facilities, and its applicability is seriously limited by its availability, around the clock, in only a minority of hospitals.

HOSPITAL PHASE MANAGEMENT

CORONARY CARE UNITS

These units are routinely equipped with a system that permits continuous monitoring of the cardiac rhythm of each patient and hemodynamic monitoring in selected patients. Defibrillators, respirators, noninvasive transthoracic pacemakers, and facilities for introducing pacing catheters and flow-directed balloon-tipped catheters are also usually

available. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias; adjust the dosage of antiarrhythmic, vasoactive, and anticoagulant drugs; and perform cardiac resuscitation, including electroshock, when necessary.

Patients should be admitted to a coronary care unit early in their illness when it is expected that they will derive benefit from the sophisticated and expensive care provided. The availability of electrocardiographic monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to "intermediate care units."

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. IfAMI has been ruled out (ideally within 8 to 12 h) and symptoms are controlled with oral therapy, patients may be transferred out of the coronary care unit. Also, patients who have a confirmed AMI but who are considered to be at low risk (no prior infarction and no persistent chest discomfort, congestive heart failure, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit in 24 to 36 h.

Activity Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients withAMIshould be kept at bed rest for the first 12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 h. This practice is both psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, by the second or third day patients typically are ambulating in their room with increasing duration and frequency, and they may shower or stand at the sink to bathe. By day 3 or 4 after infarction, patients should be increasing their ambulation progressively to a goal of 600 ft at least three times a day.

Diet Because of the risk of emesis and aspiration soon afterMI, patients should receive either nothing or only clear liquids by mouth for the first 4 to 12 h. The typical coronary care unit diet should provide£30% of total calories as fat and have a cholesterol content of £300 mg/d. Complex carbohydrates should make up 50 to 55% of total calories. Portions should not be unusually large, and the menu should be enriched with foods that are high in potassium, magnesium, and fiber but low in sodium. Diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

Bowels Bed rest and the effect of the narcotics used for the relief of pain often lead to constipation. A bedside commode rather than a bedpan, a diet rich in bulk, and the routine use of a stool softener such as dioctyl sodium sulfosuccinate (200 mg/d) are recommended. If the patient remains constipated despite these measures, a laxative can be prescribed. Contrary to prior belief, it is safe to perform a gentle rectal examination on patients withAMI.

Sedation Many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquillity. Diazepam (5 mg), oxazepam (15 to 30 mg), or

lorazepam (0.5 to 2 mg), given three or four times daily, is usually effective. An additional dose of any of the above medications may be given at night to ensure adequate sleep. Attention to this problem is especially important during the first few days in the coronary care unit, where the atmosphere of 24-h vigilance may interfere with the patient's sleep. However, sedation is no substitute for reassuring, quiet surroundings. Many drugs used in the coronary care unit, such as atropine, H_2blockers, and narcotics, can produce delirium, particularly in the elderly. This effect should not be confused with agitation, and it is wise to conduct a thorough review of the patient's medications before arbitrarily prescribing additional doses of anxiolytics.

PHARMACOTHERAPY

ANTITHROMBOTIC AGENTS

The use of antiplatelet and antithrombin therapy during the initial phase ofAMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and antithrombin agents is to establish and maintain patency of the infarct-related artery. A secondary goal is to reduce the patient's tendency to thrombosis and thus the likelihood of mural thrombus formation or deep venous thrombosis, either of which could result in pulmonary embolization. The degree to which antiplatelet and antithrombin therapy achieves these goals partly determines how effectively it reduces the risk of mortality from AMI.

As noted previously (see "Initial Management in the Emergency Department," above), aspirin is the standard antiplatelet agent for patients withAMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in AMI is found in the comprehensive overview by the Antiplatelet Trialists' Collaboration. Data from nearly 20,000 patients with AMI enrolled in nine randomized trials were pooled and revealed a reduction in the mortality rate from 11.7% in control patients to 9.3% in patients receiving antiplatelet agents. This difference corresponds to the prevention of 24 deaths for every 1000 patients treated. Similarly, 2 strokes and 12 recurrent infarctions are prevented for every 1000 patients treated with antiplatelet therapy.

The glycoprotein IIb/IIIa receptor is the focus of intense investigation by basic and clinical scientists (Fig. 243-CD6) (Chap. 116). Because platelet-rich thrombi are more resistant to thrombolytic agents than platelet-poor thrombi and because platelet aggregates appear to play a role in reocclusion after initially successful thrombolysis, glycoprotein IIb/IIIa inhibition may facilitate thrombolysis and reduce the rate of reocclusion of reperfused vessels. Compounds have been developed that block the glycoprotein IIb/IIIa receptor. These drugs appear useful for preventing thrombotic complications in patients withAMIundergoingPCI and reduce the rate of the composite endpoint of death and recurrent AMI in the medical management of patients without ST-segment elevation at presentation.

The standard antithrombin agent used in clinical practice is unfractionated heparin (UFH). Despite numerous clinical trials, the precise role of heparin in patients treated with thrombolytic agents remains uncertain. The available data fail to show any convincing benefit of UFH with respect to either coronary arterial patency or mortality

rate when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase. Although not conclusively proven, it appears that the immediate administration of intravenous UFH, in addition to a regimen of aspirin andtPA, helps to facilitate thrombolysis and to establish and maintain patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. Most clinicians who use tPA also administer a bolus and infusion of UFH, which should be administered as a bolus of 60 U/kg followed by a maintenance infusion of 12 U/kg per hour. The activated partial thromboplastin time during maintenance therapy should be 1.5 to 2 times the control value.

An alternative toUFH for anticoagulation of patients withAMI that is being used with increased frequency are the low-molecular-weight heparin preparations (LMWHs), which are formed by enzymatic or chemical depolymerization to produce saccharide chains of varying length but with a mean molecular weight of about 5000 Da. The LMWHs have several advantages over UFH including an increased anti-factor Xa:IIa ratio, decreased sensitivity to platelet factor IV, a more stable reliable anticoagulant effect, and enhanced bioavailability, thereby permitting administration via the subcutaneous route. Because of the stable anticoagulant effect when LMWHs are used, routine monitoring of hematologic tests such as the activated partial thromboplastin time (aPTT) is not required. Although the LMWHs share many pharmacologic similarities, they also vary in a number of important features; and therefore these agents should be considered individually rather than as members of an interchangeable class of compounds. Of the LMWHs, nadroparin and dalteparin have been found to be similar to UFH in therapeutic effectiveness, while enoxaparin (1 mg/kg subcutaneously every 12 h) appears to be superior to UFH for reducing the mortality rate and cardiac ischemic events in patients with AMI who do not present with ST-segment elevation. Direct comparisons among the LMWHs have not been carried out.

Patients with an anterior location of the infarction, severeLVdysfunction, congestive heart failure, a history of embolism, two-dimensional echocardiographic evidence of mural thorombus, or atrial fibrillation are at increased risk of systemic or pulmonary thromboembolism. Such individuals should receive full therapeutic levels of antithrombin therapy (UFH orLMWHs) while hospitalized, followed by at least 3 months of warfarin therapy.

BETA-ADRENOCEPTOR BLOCKERS

The benefits of beta blockers in patients withAMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an index infarction. Acute intravenous beta blockade improves the myocardial oxygen supply-demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. An overview of the data from 27,000 patients enrolled in nine randomized trials in the prethrombolytic era indicates that intravenous followed by oral beta blockade is associated with a 15% relative reduction in mortality, nonfatal reinfarction, and nonfatal cardiac arrest. In patients who undergo thrombolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with beta blockers, but recurrent ischemia and reinfarction are reduced.

Beta blocker therapy afterAMI thus is useful for most patients except those in whom it is specifically contraindicated (patients with heart failure or severely compromisedLVfunction, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of <1% per year) markedly diminishes any potential benefit (patients younger than 55 years with normal ventricular function, no complex ventricular ectopy, and no angina).

Although the data supporting the use of beta blockers in patients withAMI who do not present with ST-segment elevation are limited, the available evidence suggests that even among such patients, the use of beta blockers decreases the rates of cardiovascular mortality and reinfarction, and increases the probability of long-term survival.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors reduce the mortality rate afterAMI, and the mortality benefits are additive to those achieved with aspirin and beta blockers. The maximum benefit is seen in high-risk patients (those who are elderly or have an anterior infarction, a prior infarction, and/or globally depressedLVfunction), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with AMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see "Ventricular Dysfunction," below) with a subsequent reduction in the risk of congestive heart failure (CHF). The rate of recurrent infarction also may be lower in patients treated chronically with ACE inhibitors after infarction.

ACEinhibitors should be prescribed within 24 h to all patients withAMI and overtCHF as well as to hemodynamically stable patients with ST-segment elevation or left bundle branch block. There is little evidence to support the immediate use of ACE inhibitors in patients with AMI who present without ST-segment changes or only with ST-segment depression without CHF. Before hospital discharge,LVfunction should be assessed with an imaging study. ACE inhibitors should be continued indefinitely in patients who have clinically evident CHF, in patients whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who are hypertensive.

OTHER AGENTS

Although the actual impact on the mortality rate is slight (three to four lives saved per 1000 patients treated), *nitrates* (intravenous or oral) may be useful in the relief of pain associated withAMI. Favorable effects on the ischemic process and ventricular remodeling (see below) have led many physicians to routinely use intravenous nitroglycerin (5 to 10 ug/min initial dose and up to 200 ug/min as long as hemodynamic stability is maintained) for the first 24 to 48 h after the onset of infarction.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients withAMI, in contrast to the more consistent data that exist for other drugs (e.g., beta blockers, aspirin, thrombolytic

agents). The routine use of calcium antagonists cannot be recommended.

A metabolic supportive measure that has shown promise in several small-scale trials of patients withAMI is the administration of a solution of glucose-insulin-potassium (GIK). A GIK infusion lowers the concentration of plasma free fatty acids and improves ventricular performance. Strict control of blood glucose in diabetic patients with AMI has been shown to reduce the mortality rate. It remains to be determined whether infusions of GIK should be administered to all patients with AMI.

Intracellular *magnesium* levels are frequently reduced in patients withAMI, but this deficit is not adequately reflected in serum measurements, as magnesium is predominantly an intracellular ion and <1% of its total body stores is intravascular. Whether giving routine empirical supplemental infusions of magnesium to high-risk patients with AMI is beneficial remains an open question. At present, serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias. There does not appear to be any benefit in the routine use of magnesium when it is administered relatively late (after more than 6 h) or to patients with an uncomplicated AMI who have a low mortality risk. Its role in high-risk patients is under investigation.

COMPLICATIONS AND THEIR TREATMENT

VENTRICULAR DYSFUNCTION

AfterAMI, theLVundergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evidentCHF in the months to years after infarction (Fig. 243-CD7). Soon after AMI, the LV begins to dilate. Acutely, this results from expansion of the infarct (i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone). Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the apex of the LV and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy withACEinhibitors and other vasodilators (e.g., nitrates) (Fig. 243-CD8). Thus, in patients with an ejection fraction <40%, regardless of whether or not heart failure is present, ACE inhibitors should be prescribed.

HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death fromAMI. The extent of ischemic necrosis correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and S_3 and S_4gallop rhythms. Pulmonary congestion is also frequently seen on the chest roentgenogram. ElevatedLVfilling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (Chap. 231).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases, S_3gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0 to 5%; class II, 10 to 20%; class III, 35 to 45%; and class IV, 85 to 95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as one-third to one-half.

Hemodynamic evidence of abnormalLVfunction appears when contraction is seriously impaired in 20 to 25% of the LV. Infarction of ³40% of the LV usually results in cardiogenic shock (see below). Positioning of a balloon flotation catheter in the pulmonary artery permits monitoring of LV filling pressure; this technique is useful in patients who exhibit hypotension and/or clinical evidence ofCHF(Fig. 243-CD9). Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intraarterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients withAMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indexes [>2.6 and>3.6 L/(min/m_2)], while others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indexes. The former patients usually benefit from diuresis, while the latter may respond to volume expansion by means of intravenous administration of colloid-containing solutions.

Hypovolemia Hypovolemia is an easily corrected condition that may contribute to the hypotension and vascular collapse associated withAMI in some patients. It may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with AMI and hypotension before more vigorous forms of therapy are begun. Central venous pressure reflectsRVrather thanLVfilling pressure and is an inadequate guide for adjustment of blood volume, since LV function is almost always affected much more adversely than RV function in patients with AMI. The optimal LV filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally ~20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output level plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

TREATMENT

The management ofCHF in association withAMI is similar to that of acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic support) (Chap. 232), except that the benefits of digitalis administration to patients with AMI are unimpressive. By contrast, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic heart failure. Left ventricular filling pressure falls and orthopnea and

dyspnea improve after the intravenous administration of furosemide or other loop diuretics. These drugs should be used with caution, however, as they can result in a massive diuresis with associated decreases in plasma volume, cardiac output, systemic blood pressure, and hence coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, or intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation ofLVfilling pressure. The patient with pulmonary edema is treated as described inChap. 232, but vasodilators must be used with caution to prevent serious hypotension. As noted earlier,ACEinhibitors are an ideal class of drugs for management of ventricular dysfunction after AMI, especially for the long term.

CARDIOGENIC SHOCK

In recent years, efforts to reduce infarct size and prompt treatment of ongoing ischemia and other complications ofMIappear to have reduced the incidence of cardiogenic shock from 20% to about 7%. Only 10% of patients with this condition present with it on admission, while 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of "piecemeal" necrosis extending outward from the original infarct zone (Fig. 243-4).

Cardiogenic shock should be considered to be a form of severeLVfailure. This syndrome is characterized by marked hypotension with systolic arterial pressure of <80 mmHg and a markedly reduced cardiac index [<1.8 L/(min/m_2)] in the face of an elevated LV filling (pulmonary capillary wedge) pressure (>18 mmHg). Hypotension alone is not a basis for the diagnosis of cardiogenic shock, because many patients who make an uneventful recovery have serious hypotension (systolic pressure of<80 mmHg) for several hours. Such patients often have low LV filling pressures, and their hypotension usually resolves with the administration of intravenous fluids. In contrast to hypovolemic hypotension, cardiogenic shock is generally associated with a mortality rate of>70%; however, recent efforts to restore perfusion by coronary angioplasty or surgical revascularization suggest that this high mortality rate can be lowered by as much as one-half.

Risk factors for the in-hospital development of shock include advanced age, a depressedLVejection fraction on admission, a large infarct, previousMI, and a history of diabetes mellitus. Patients with several of these risk factors should be considered for cardiac catheterization and mechanical reperfusion (byPCI or surgery) before the development of shock.

Pathophysiology of Severe Power Failure A marked reduction in the quantity of contracting myocardium is the cause of cardiogenic shock inAMI. The initial insult reduces arterial pressure, and the reduction in coronary perfusion pressure and myocardial blood flow initiates a vicious cycle that impairs myocardial function further and may increase the size of the infarct (Fig. 243-4). Arrhythmias and metabolic acidosis also contribute to this deterioration, because they are the result of inadequate perfusion. This positive feedback loop accounts for the high mortality rate associated with the shock syndrome.

TREATMENT

The physiology and ominous prognosis of cardiogenic shock dictate that all patients with this condition should, if possible, have continuous monitoring of arterial pressure and ofLVfilling pressure (as reflected in the pulmonary capillary wedge pressure measured with a pulmonary artery balloon catheter) as well as frequent determinations of cardiac output. When pulmonary edema coexists, endotracheal intubation may be necessary to ensure oxygenation. The relief of pain is important, as some vasodepressor reflex activity may be a response to severe pain. However, narcotics should be used cautiously, in view of their propensity to lower arterial pressure. The primary objective of treatment is to maintain coronary perfusion by raising the arterial blood pressure with vasopressors (see below), intraaortic balloon counterpulsation, and manipulation of blood volume to a level that ensures an optimum LV filling pressure (~20 mmHg). The latter may require either infusion of crystalloid or diuresis.

Vasopressors Various intravenous drugs may be used to augment arterial pressure and cardiac output in patients with cardiogenic shock. All have important disadvantages or problems, and none has been shown to change the outcome in patients with established shock. *Isoproterenol* is a sympathomimetic amine that is now rarely used in the treatment of shock due toMI. Although this agent increases contractility, it also produces peripheral vasodilation and increases the heart rate. The resulting increase in myocardial oxygen consumption and reduction of coronary perfusion pressure may extend the area of ischemic injury. *Norepinephrine* (Chap. 72) is a potenta-adrenergic agonist with powerful vasoconstrictor properties that also possesses b-adrenergic activity and therefore enhances contractility. Because the increase in afterload and contractility associated with its use causes a marked increase in myocardial oxygen consumption, norepinephrine should be reserved for patients in desperate situations or for those with cardiogenic shock and reduced systemic vascular resistance. It should be started at a dosage of 2 to 4 ug/min. If pressure cannot be maintained with a dosage of 15 ug/min, it is unlikely that a further increase will be beneficial.

Dopamine (Chap. 72) is useful in many patients with severe power failure. At low doses (2 to 10 ug/kg per min), the drug has positive chronotropic and inotropic effects as a consequence ofb receptor stimulation. At higher doses, a vasoconstrictor effect results from a receptor stimulation. At lower doses (£2 ug/kg per min), dopamine also has the unique effect of dilating the renal and splanchnic vascular beds, and it apparently has little effect on myocardial oxygen consumption. Intravenous dopamine is started at an infusion rate of 2 to 5 ug/kg per min, and the dosage is increased every 2 to 5 min up to a maximum of 20 to 50 ug/kg per min. Systolic arterial blood pressure should be maintained at ~90 mmHg. *Dobutamine* is a synthetic sympathomimetic amine with positive inotropic action and minimal positive chronotropic or peripheral vasoconstrictive activity in the usual dosage range of 2.5 to 10 ug/kg per min. It should not be used when a vasoconstrictor effect is required. However, in patients with less profound degrees of hypotension, dobutamine may be an extremely useful agent, particularly if positive chronotropy is to be avoided.

Amrinone and *milrinone* are positive inotropic agents without catecholamine structure or activity that inhibit phosphodiesterase. These drugs resemble dobutamine in

pharmacologic activity, although they have a more potent vasodilating action. For amrinone, an initial loading dose of 0.75 mg/kg is given over 2 to 3 min. If effective, it is followed by an infusion of 5 to 10 ug/kg per min. If necessary, the dose may then be increased up to 15 ug/kg per min for short periods. Milrinone is given as a loading dose of 50 ug/kg over 10 min followed by a maintenance infusion of 0.375 to 0.75 ug/kg per min.

Aortic Counterpulsation In cardiogenic shock, mechanical assistance with an intraaortic balloon pumping (IABP) system capable of augmenting both diastolic pressure and cardiac output may be helpful. A sausage-shaped balloon at the end of a catheter is introduced percutaneously into the aorta via the femoral artery, and the balloon is automatically inflated during early diastole, thereby augmenting coronary blood flow. The balloon collapses in early systole, thereby reducing the afterload against whichLVejection takes place. Improvement in hemodynamic status has been achieved with balloon pumping in a large number of patients. In the absence of early revascularization, however, long-term survival after this mode of therapy in patients with cardiogenic shock is still disappointing. Intraaortic balloon pumping may best be reserved for patients whose condition merits mechanical (surgical or angioplastic) intervention (e.g., patients with continuing ischemia, ventricular septal rupture, or mitral regurgitation) and in whom a successful result is likely to reverse the cardiogenic shock. This technique is contraindicated if aortic regurgitation is present or aortic dissection is suspected.

Therapy for the shock syndrome secondary toMI, while improving gradually as a result of meticulous attention to the details outlined above, continues to be disappointing overall because a large fraction of patients with the syndrome have large areas of infarcted myocardium with severe, diffuse coronary atherosclerosis. The SHOCK trial was a randomized study comparing emergency revascularization (PCI or coronary artery bypass grafting) with initial medical stabilization and delayed revascularization as clinically indicated for patients with cardiogenic shock. Although the 30-day mortality rates in the two groups did not differ significantly, the 6-month and 1-year mortality rates in the emergency revascularization group were significantly lower than the corresponding rates in the stabilization and delayed revascularization group. Patients younger than 75 years showed particular benefit from emergency revascularization. However, few patients developing cardiogenic shock have prompt access to these expensive techniques. It is hoped that the widespread and early application of thrombolytic therapy will reduce the amount of myocardium that becomes necrotic and thereby reduce the incidence of this syndrome.

RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferoposterior infarction demonstrate at least a minor degree ofRVnecrosis. An occasional patient with inferoposteriorLVinfarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure [jugular venous distention, Kussmaul's sign (Chap. 225), hepatomegaly] with or without hypotension. ST-segment elevations of right-sided precordialECGleads, particularly lead V_4R, are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV

dysfunction. Catheterization of the right side of the heart often reveals a distinctive hemodynamic pattern resembling cardiac tamponade or constrictive pericarditis (steep right atrial "y" descent and an early diastolic dip and plateau in right ventricular waveforms) (Chap. 239). Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

MECHANICAL CAUSES OF HEART FAILURE

Free Wall Rupture Myocardial rupture is a dramatic complication ofAMI that is most likely to occur during the first week after the onset of symptoms; its frequency increases with the age of the patient. First infarction, a history of hypertension, no history of angina pectoris, and a relatively large Q-wave infarct are associated with a higher incidence of cardiac rupture. The clinical presentation typically is a sudden loss of pulse, blood pressure and consciousness while theECGcontinues to show sinus rhythm (apparent electromechanical dissociation or pulseless electrical activity). The myocardium continues to contract, but forward flow is not maintained as blood escapes into the pericardium. Cardiac tamponade (Chap. 239) ensues, and closed-chest massage is ineffective. This condition is almost universally fatal, although dramatic cases of urgent pericardiotensis followed by successful surgical repair have been reported.

Ventricular Septal Defect The pathogenesis of perforation of the ventricular septum is similar to that of free wall rupture, but the chance of successful therapy is greater. Patients with ventricular septal rupture present with sudden, severeLVfailure in association with the appearance of a pansystolic murmur, often accompanied by a parasternal thrill. It is often impossible to differentiate this condition from rupture of a papillary muscle with resulting mitral regurgitation (MR), and the presence in both conditions of a tall "v" wave in the pulmonary capillary wedge pressure further complicates the differentiation. The diagnosis of ventricular septal defect can be established by the demonstration of a left-to-right shunt (i.e., an oxygen step-up at the level of the RV) by means of limited cardiac catheterization performed at the bedside with a flow-directed balloon catheter. Color flow Doppler echocardiography can also be extremely useful for making this diagnosis at the bedside (Fig. 243-CD10). A prolonged period of hemodynamic compromise may produce end-organ damage and other complications that can be avoided by early intervention, including nitroprusside infusion and intraaortic balloon counterpulsation.

The pathophysiology of acuteMR is similar to that of acute ventricular septal perforation in that the level of aortic systolic pressure partly determines the regurgitant volume, the principal difference being the chamber into which the regurgitant fraction is ejected. In septal perforation, a fraction ofLVoutput is ejected into the right ventricle. As in MR, lowering of the aortic systolic pressure by mechanical (intraaortic balloon counterpulsation) and/or pharmacologic (nitroglycerin or nitroprusside) means can decrease the hemodynamic compromise caused by perforation.

Mitral Regurgitation (See alsoChap. 236) The reported incidence of apical systolic murmurs ofMRduring the first few days after the onset ofAMIvaries widely (from 10 to 50% of patients) depending on the population studied and the acumen of the observers. While MR causes acute hemodynamic compromise in only a minority of these patients,

it is a risk factor for late CHF and reduced survival.

The most common cause of MR after AMI is dysfunction of the mitral valve due to ischemia or infarction. Left ventricular dilatation or alteration in the size or shape of the LV due to impaired contractility or to aneurysm formation causes disordered contraction of the papillary muscles and failure of coaptation of the mitral valve leaflets. Rarely, a papillary muscle, or, more commonly, the head of a papillary muscle, may rupture. Then, LV function deteriorates dramatically, with superimposition of severe MR. The major element in the differential diagnosis is perforation of the ventricular septum as discussed above. Surgical repair or replacement of the mitral valve may lead to dramatic improvement in patients in whom acute heart failure results primarily from severe MR due to papillary muscle rupture or dysfunction and in whom global ventricular function is relatively good.

If aortic systolic pressure is lowered in patients with MR, a greater fraction of the LV output will be ejected antegrade, thus lessening the regurgitant fraction. To this end, both intraaortic balloon counterpulsation (IABC), which lowers the aortic systolic pressure mechanically, and the infusion of nitroglycerin or sodium nitroprusside, which reduce systemic vascular resistance, have been used with success in the interim management of patients with severe MR in the presence of AMI. Ideally, definitive operative treatment should be postponed until pulmonary congestion has cleared and the infarct has had time to heal. However, if the patient's hemodynamic and/or clinical condition does not improve or stabilize, surgical treatment should be undertaken, even in the acute stage.

ARRHYTHMIAS (See also Chaps. 229 and 230)

The incidence of arrhythmias after AMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Since most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of myocardial infarction.

Ventricular Premature Beats Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with AMI and do not require therapy. Whereas in the past, frequent, multifocal, or early diastolic ventricular extrasystoles (so-called warning arrhythmias) were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either intravenous lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias, as such therapy may actually increase the mortality rate. b-Adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with AMI and in the prevention of ventricular fibrillation. As described above (see "b-Adrenoceptor Blockers"), they should be used routinely in

patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with AMI; the serum potassium concentration should be adjusted to approximately 4.5 mmol/L and magnesium to about 2.0 mmol/L.

Ventricular Tachycardia and Fibrillation Within the first 24 h of AMI, ventricular tachycardia and fibrillation can occur without prior warning arrhythmias. The occurrence of ventricular fibrillation can be reduced by prophylactic administration of intravenous lidocaine. However, prophylactic use of lidocaine has not been shown to reduce overall mortality from AMI. In fact, in addition to causing possible noncardiac complications, lidocaine may predispose to an excess risk of bradycardia and asystole. For these reasons, and with earlier treatment of active ischemia, more frequent use of beta-blocking agents, and the nearly universal success of electrical cardioversion or defibrillation, routine prophylactic antiarrhythmic drug therapy is no longer recommended. It should be reserved for patients who cannot reach a hospital or for those treated in hospitals that lack the constant presence in the coronary care unit of a physician or nurse trained in the recognition and treatment of ventricular fibrillation.

Sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an intravenous regimen of lidocaine (bolus of 1.0 to 1.5 mg/kg; infusion of 20 to 50 ug/kg per min), procainamide (bolus of 15 mg/kg over 20 to 30 min; infusion of 1 to 4 mg/min), or amiodarone (bolus of 75 to 150 mg over 10 to 15 min followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min); if it does not stop promptly, electroversion should be used (Chap. 230). An unsynchronized discharge of 200 to 300 J (defibrillation) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with epinephrine (1 mg intravenously or 10 mL of a 1:10,000 solution via the intracardiac route), bretylium (a 5 mg/kg bolus), or amiodarone (a 75 to 150 mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as *torsade de pointes* (Chap. 230), may occur in patients with AMI as a consequence of other concurrent problems (such as hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of an agent being administered to the patient (such as digoxin or quinidine). A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is good in patients who survive to hospital discharge after *primary* ventricular fibrillation, i.e., ventricular fibrillation that is a primary response to acute ischemia and is not associated with predisposing factors such as CHF, shock, bundle branch block, or ventricular aneurysm. This result is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation *secondary* to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for electrophysiologic study (Chap. 230).

Accelerated Idioventricular Rhythm Accelerated idioventricular rhythm (AIVR, "slow ventricular tachycardia"), a ventricular rhythm with a rate of 60 to 100 beats per minute,

occurs in 25% of patients withAMI. It often occurs transiently during thrombolytic therapy at the time of reperfusion. The rate of AIVR is usually similar to that of the sinus rhythm that precedes and follows it, and this similarity of rate plus the relatively minor hemodynamic effects make this rhythm more difficult to detect except by electrocardiographic monitoring. For the most part, AIVR is benign and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully, as degeneration into a more serious arrhythmia is rare, and, if it occurs, AIVR can generally be readily treated with a drug that increases the sinus rate (atropine).

Supraventricular Arrhythmias Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause (such as anemia, fever, heart failure, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be due to sympathetic overstimulation, for example, as part of a hyperdynamic state, then treatment with a beta blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary toLVfailure. Digoxin is usually the treatment of choice for supraventricular arrhythmias if heart failure is present. If heart failure is absent, beta blockers, verapamil, or diltiazem are suitable alternatives for controlling the ventricular rate, as they may also help to control ischemia. If the abnormal rhythm persists for >2 h with a ventricular rate in excess of 120 beats per minute, or if tachycardia induces heart failure, shock, or ischemia (as manifested by recurrent pain orECGchanges), a synchronized electroshock (100 to 200 J) should be used.

Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromisedLVfunction, the loss of appropriately timed atrial systole results in a marked decrease in cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

Sinus Bradycardia Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing heart rate and should be given intravenously in doses of 0.5 mg initially. If the rate remains below 50 to 60 bpm, additional doses of 0.2 mg, up to a total of 2.0 mg, may be given. Persistent bradycardia (<40 bpm) despite atropine may be treated with electrical pacing. Isoproterenol should be avoided.

Atrioventricular and Intraventricular Conduction Disturbances (See alsoChap. 229) Both the in-hospital mortality rate and the post-discharge mortality rate of patients who have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone and/or the release of adenosine and therefore is transient. In anterior wall infarction, heart block is usually related to ischemic malfunction of the conduction system, which commonly is associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia due to AVblock. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and

complete heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics, however. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with heart failure, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RVinfarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive pacing electrodes should be positioned in a "demand" mode for patients with sinus bradycardia (rate <50 bpm) that is unresponsive to drug therapy, Mobitz II second-degreeAVblock, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death due to bradyarrhythmias in the rare patient who develops combined persistent bifascicular and transient third-degree heart block during the acute phase ofMI.

OTHER COMPLICATIONS

Recurrent Chest Discomfort Recurrent angina develops in ~25% of patients hospitalized forAMI. This percentage is even higher in patients who undergo successful thrombolysis. Since recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a doubling of risk after AMI, patients with these symptoms should be considered for repeat thrombolysis or referred for prompt coronary arteriography and mechanical revascularization. Repeat administration of a thrombolytic agent is an alternative to early mechanical revascularization.

Pericarditis (See alsoChap. 239) Pericardial friction rubs and/or pericardial pain are frequently encountered in patients with transmuralAMI. This complication can usually be managed with aspirin (650 mg qid). It is important to diagnose the chest pain of pericarditis accurately, since failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain and/or infarct extension, with resulting inappropriate use of anticoagulants, nitrates, beta blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful since such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

Thromboembolism Clinically apparent thromboembolism complicatesAMI in ~10% of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be at least an important contributing cause of death in 25% of patients with AMI who die after admission to the hospital. Arterial emboli originate fromLV mural thrombi, while most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior),CHF, and a LVthrombus detected by echocardiography. The incidence of

arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis when the cerebral circulation is involved or hypertension if the renal circulation is compromised. When a thrombus has been clearly demonstrated by echocardiographic or other techniques or when a large area of regional wall motion abnormality is seen even in the absence of a detectable mural thrombus, systemic anticoagulation should be undertaken (in the absence of contraindications), as the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3 to 6 months is probably prudent.

Left Ventricular Aneurysm The term *ventricular aneurysm* is usually used to describe *dyskinesis* or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications ofLVaneurysm do not usually occur for weeks to months afterAMI; they includeCHF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this *pseudoaneurysm* enlarges, maintaining communication with theLVcavity through a narrow neck. Because a pseudoaneurysm often ruptures spontaneously, it should be surgically repaired if recognized.

POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical factors have been identified that are associated with an increase in cardiovascular risk after initial recovery fromAMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressedLVejection fraction (<40%), rales above the lung bases on physical examination or congestion on chest radiograph, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of previous myocardial infarction, age over 70 years, diabetes, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina ("silent ischemia"), an abnormal signal-averagedECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction and death after recovery fromAMI has led to strategies to evaluate risk after infarction. Early after AMI, this evaluation generally involves the use of noninvasive testing. In stable patients, submaximal exercise stress

testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4 to 6 weeks after infarction. Evaluation ofLVfunction at rest and during exercise is usually warranted as well. Recognition of a depressed LV ejection fraction by echocardiography or radionuclide ventriculography identifies patients who should receiveACEinhibitors (see "Angiotensin-Converting Enzyme Inhibitors," above). Patients in whom angina is induced at relatively low workloads, those who have a large reversible defect on perfusion imaging or a depressed ejection fraction, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrentMI or death from arrhythmia; and cardiac catheterization with coronary angiography and/or invasive electrophysiologic evaluation is advised.

Exercise tests also aid in formulating an individualized exercise prescription, which can be much more vigorous in patients who tolerate exercise without any of the above-mentioned adverse signs. Additionally, predischarge stress testing may provide an important psychological benefit, building the patient's confidence by demonstrating a reasonable exercise tolerance. Furthermore, particularly when no arrhythmias or signs of ischemia are identified, the patient benefits by the physician's reassurance that objective evidence suggests no immediate jeopardy.

In many hospitals a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Ideally, such programs should include an educational component that informs patients about their disease and its risk factors.

The usual duration of hospitalization for an uncomplicatedAMI is about 5 days. The remainder of the convalescent phase may be accomplished at home. During the first 2 weeks, the patient should be encouraged to increase activity by walking about the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician must regulate the patient's activity on the basis of exercise tolerance. Most patients will be able to return to work within 2 to 4 weeks.

SECONDARY PREVENTION OF INFARCTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates afterAMI. Long-term treatment with an antiplatelet agent (usually aspirin) after AMI is associated with a 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). In addition, in patients taking aspirin chronically, AMIs tend to be smaller and are more likely to be non-Q-wave in nature. An alternative antiplatelet agent that may be used for secondary prevention in patients intolerant of aspirin is the ADP receptor antagonist clopidogrel (75 mg orally daily).ACEinhibitors should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

The chronic routine use of oral b-adrenoceptor blockers for at least 2 years afterAMI is supported by well-conducted, placebo-controlled trials that have convincingly

demonstrated reductions in the rates of total mortality, sudden death, and, in some instances, reinfarction. In contrast, calcium antagonists are not recommended for routine secondary prevention.

Evidence suggests that warfarin lowers the risk of late mortality and the incidence of reinfarction afterAMI. Since studies comparing aspirin and warfarin therapy separately or in combination have not yet been completed, most physicians prescribe aspirin routinely for all patients without contraindications and add warfarin for patients at increased risk of embolism (see "Thromboembolism," above).

Finally, risk factors for *atherosclerosis* (Chap. 241) should be discussed with the patient, and, when possible, favorably modified. In particular, efforts should be made to ensure the cessation of smoking and the control of hypertension and hyperlipidemia (the target low-density lipoprotein level is<100 mg/dL). In addition, regular physical exercise and reduction of emotional stress should be encouraged. The benefits of hormone replacement therapy in postmenopausal women recovering fromMIremain controversial. The initiation of a combination of estrogen plus progestin is associated with an increased risk of cardiovascular events within the first year but may reduce events in later years (HERS Trial). Thus, hormone replacement therapy prevention of coronary events should not be given *de novo* to postmenopausal women afterAMI. Postmenopausal women already taking estrogen plus progestin at the time of AMI may continue that therapy.

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244. ISCHEMIC HEART DISEASE - *Andrew P. Selwyn*, *Eugene Braunwald*

ETIOLOGY AND PATHOPHYSIOLOGY

Ischemia refers to a lack of oxygen due to inadequate perfusion, which results from an imbalance between oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of epicardial coronary arteries. Ischemic heart disease (IHD) is the most common, serious, chronic, life-threatening illness in the United States, where more than 11 million persons have IHD. This condition causes more deaths and disability and incurs greater economic costs than any other illness in the developed world.

By reducing the lumen of the coronary arteries, atherosclerosis reduces myocardial perfusion in the basal state or limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. Coronary blood flow can also be limited by spasm (Fig. 244-CD1), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to luetic aortitis. Congenital abnormalities, such as anomalous origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults. Myocardial ischemia can also occur if myocardial oxygen demands are markedly increased, as in severe ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, is a rare cause of myocardial ischemia. Not infrequently, two or more causes of ischemia will coexist, such as an increase in oxygen demand due to left ventricular hypertrophy and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Often such a combination leads to clinical manifestations of ischemia.

Although the large epicardial coronary arteries are capable of constriction and relaxation, in healthy persons they serve largely as conduits and are referred to as *conductance vessels*, while the intramyocardial arterioles normally exhibit striking changes in tone and are therefore referred to as *resistance vessels*. Abnormal constriction or failure of normal dilation of the coronary resistance vessels can also cause ischemia. When it causes angina this condition is referred to as *microvascular angina*.

The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and therefore blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate an immense capacity for dilation. For example, the changing oxygen needs with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure in order to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

CORONARY ATHEROSCLEROSIS (See also Chap. 241)

Epicardial coronary arteries are a major site of atherosclerotic disease. The major risk factors for atherosclerosis [high plasma low-density lipoprotein (LDL), low plasma high-density lipoprotein (HDL), cigarette smoking, hypertension, and diabetes mellitus] are thought to disturb the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an anticoagulant surface, and defense against inflammatory cells. The loss of these defenses leads to inappropriate constriction, luminal clot formation, and abnormal interactions with blood monocytes and platelets. The latter leads to subintimal collections of fat, cells, and debris (i.e., atherosclerotic plaques), which develop at irregular rates in different segments of the epicardial coronary tree and lead eventually to segmental reductions in cross-sectional area (stenosis). The relationship between pulsatile flow and luminal stenosis is complex, but experiments have shown that when a stenosis reduces the cross-sectional area by approximately 75%, a full range of increases in flow to meet increased myocardial demand is not possible. When the luminal area is reduced by more than approximately 80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice can reduce coronary flow dramatically and cause myocardial ischemia.

Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is subject to fissuring, hemorrhage, and thrombosis. Any of these events can temporarily worsen the obstruction, reduce coronary blood flow, and cause clinical manifestations of myocardial ischemia, as described below. The location of the obstruction will influence the quantity of myocardium rendered ischemic and thus determine the severity of the clinical manifestations. Severe coronary narrowing and myocardial ischemia are frequently accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can, by themselves, provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.

Once stenosis of a proximal epicardial artery has reduced the cross-sectional area by more than approximately 70%, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances ischemia in the region perfused by the stenotic artery can be precipitated by increases in myocardial oxygen demands caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery due to physiologic vasomotion, loss of endothelial control of dilation, pathologic spasm, or small platelet plugs can all upset the critical balance between oxygen supply and demand and thus precipitate myocardial ischemia.

EFFECTS OF ISCHEMIA

The inadequate perfusion induced by coronary atherosclerosis may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium. The abrupt development of severe ischemia, as occurs with total or subtotal occlusion, is associated with almost instantaneous failure of normal muscle

contraction and relaxation. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall. Ischemia of large portions of the ventricle will cause transient left ventricular failure, and if the papillary muscles are involved, mitral regurgitation can complicate this event. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction (Chap. 243). Coronary atherosclerosis is a focal process that usually causes nonuniform ischemia. Regional disturbances of ventricular contractility cause segmental akinesis or, in severe cases, bulging (dyskinesia), which can greatly reduce myocardial pump function.

Underlying these mechanical disturbances are a wide range of abnormalities in cell metabolism, function, and structure. When oxygenated, the normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is broken down to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, ATP, and creatine phosphate. Impaired cell membrane function leads to potassium leakage and the uptake of sodium by myocytes. The severity and duration of the imbalance between myocardial oxygen supply and demand will determine whether the damage is reversible (0 to 20 min for total occlusion) or whether it is permanent, with subsequent myocardial necrosis (>20 min).

Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion of the T wave and, when more severe, by displacement of the ST segment (Chap. 226). Transient ST-segment depression often reflects subendocardial ischemia, while transient ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to ventricular tachycardia or ventricular fibrillation (Chap. 230). Most patients who die suddenly fromIHD do so as a result of ischemia-induced malignant ventricular tachyarrhythmias (Chap. 39).

ASYMPTOMATIC VERSUS SYMPTOMATIC ISCHEMIC HEART DISEASE (IHD)

Postmortem studies on accident victims and military casualties in western countries have shown that coronary atherosclerosis often begins to develop prior to age 20 and is widespread even among adults who were asymptomatic during life. When all age groups are considered, IHD is the most common cause of death not only in men but also in women (Chap. 6). Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-inducedECGchanges not accompanied by angina; coronary angiographic studies of such persons may reveal obstructive [coronary artery disease (CAD) (Chap. 228)]. Postmortem examination of patients with obstructive CAD without a history of any clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries. According to population studies, approximately 25% of patients who survive acute myocardial infarction may not reach medical attention, and these patients carry the same adverse prognosis as those who present with the classic clinical syndrome (Chap. 243). Sudden death may be unheralded and is a common presenting manifestation of IHD (Chap. 39). Patients can

also present with cardiomegaly and heart failure secondary to ischemic damage of the left ventricular myocardium that may have caused no symptoms prior to the development of heart failure; this condition is referred to as *ischemic cardiomyopathy*. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized by chest discomfort due to either angina pectoris or acute myocardial infarction (Chap. 243). Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or suddenly die.

STABLE ANGINA PECTORIS

This episodic clinical syndrome is due to transient myocardial ischemia. Various diseases that cause myocardial ischemia as well as the numerous forms of discomfort with which it may be confused are discussed in Chap. 13. Males constitute approximately 70% of all patients with angina pectoris and an even greater fraction of those younger than 50 years of age.

HISTORY

The typical patient with angina is a 50- to 60-year-old man or 65- to 75-year-old woman who seeks medical help for chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she will typically press on the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort. This symptom is usually crescendo-decrescendo in nature and lasts 1 to 5 min. Angina can radiate to the left shoulder and to both arms and especially to the ulnar surfaces of the forearm and hand. It can also arise in or radiate to the back, neck, jaw, teeth, and epigastrium.

Although episodes of angina are typically caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they may also occur at rest (see "Unstable Angina Pectoris," p. 1408) and at night while the patient is recumbent (angina decubitus). The patient may be awakened at night distressed by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia or activities such as micturition. It can also be due to the expansion of the intrathoracic blood volume that occurs with recumbency, which causes an increase in cardiac size and myocardial oxygen demand that lead to ischemia and transient left ventricular failure.

The threshold for the development of angina pectoris varies from person to person and may vary by time of day and emotional state. Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity. In these patients coronary stenosis and myocardial oxygen supply are fixed and ischemia is precipitated by an increase in myocardial oxygen demand. In other patients the threshold for angina may vary considerably within any given day and from day to day. In such patients variations in oxygen supply, most likely due to changes in coronary vascular tone, may play an important role. A patient may report symptoms upon minor exertion in the morning (a short walk or shaving) yet by midday may be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar tasks, a heavy meal, or exposure to cold.

Sharp, fleeting chest pain or prolonged, dull aches localized to the left submammary area are rarely due to myocardial ischemia. However, angina pectoris may be atypical in location and may not be strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, being more frequent in the winter in temperate climates. Anginal "equivalents" are symptoms of myocardial ischemia other than angina. These include dyspnea, fatigue, and faintness and are more common in the elderly.

Systematic questioning of the patient with suspectedIHD is important to uncover a positive family history of premature IHD (under the age of 45 years in first-degree male relatives and under 55 in female relatives), diabetes, hyperlipidemia, hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis. The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. In patients with atypical angina (Chap. 13), coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis (Chap. 241) increase the likelihood of important coronary disease.

PHYSICAL EXAMINATION

The physical examination is often normal in the patient with stable angina. Rarely, the general examination reveals signs of risk factors associated with coronary atherosclerosis such as xanthelasma, xanthomas (Chap. 241), or diabetic skin lesions. There may also be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking. Palpation can reveal thickened or absent peripheral arteries, signs of cardiac enlargement, and abnormal contraction of the cardiac impulse (left ventricular akinesia or dyskinesia). Examination of the fundi may reveal increased light reflexes and arteriovenous nicking as evidence of hypertension (Table 35-2), while auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left decubitus position. Aortic stenosis, aortic regurgitation (Chap. 236), pulmonary hypertension (Chap. 260), and hypertrophic cardiomyopathy (Chap. 238) must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient left ventricular failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema.

LABORATORY EXAMINATION

Although the diagnosis ofIHD can be made with confidence from the clinical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease, since both of these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol -- total, low density, high density -- and triglycerides), glucose, creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray is important, since it may show the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the

degree of cardiac damage and the effects of treatment for heart failure.

Electrocardiogram A 12-leadECGrecorded at rest is normal in about half the patients with typical angina pectoris, but there may be signs of an old myocardial infarction (Chap. 226). Although repolarization abnormalities, i.e., T-wave and ST-segment changes and intraventricular conduction disturbances at rest, are suggestive ofIHD, they are nonspecific, since they can also occur in pericardial, myocardial, and valvular heart disease or transiently with anxiety, changes in posture, drugs, or esophageal disease. Typical ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific. The most characteristic changes include displacement of the ST segment that is similar in every way to that induced during a stress test (see below). The ST segment is usually depressed during angina but may be elevated -- sometimes strikingly so -- in Prinzmetal's angina.

Stress Testing The most widely used test both widenfects of yc drugs, most widely c apex, mitraee of pros, mostinvolvglyt restraee of recorded abe ofor ena burmal coore srtercisiennnd/oe mdverlgealusss tesbicyon, ergtrike s(Fig dia4-CD2segmentwidenes oistment est al d vazed lightualled light reway txke e, sworkloadcultatits with typ

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although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

The physician should be present throughout the exercise test, and it is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as a stage of exercise), and the internal cardiac work performed; the last is represented by the heart rate-blood pressure product. The depth of the ST-segment depression and the time needed for recovery of theseECGchanges are also important. Because the risks of exercise testing are small but real -- estimated at one fatality and two nonfatal complications per 10,000 tests -- equipment for resuscitation should be available. Modified (heart rate-limited rather than symptom-limited) exercise tests can be performed safely in patients as early as 6 days after myocardial infarction. Contraindications to exercise stress testing include acute myocardial infarction (<4-5 days), rest angina <48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, and active infective endocarditis.

The normal response to graded exercise includes a progressive increase in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease in blood pressure with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global left ventricular dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and ST-segment depression that persists for more than 5 min after the termination of exercise increases the specificity of the test and suggests severe ischemic heart disease and a high risk of future adverse events.

When the restingECG is abnormal (e.g., Wolff-Parkinson-White syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial perfusion imaging after the intravenous administration of a radioisotope such as thallium 201 or technetium 99m sestamibi during exercise (or a pharmacologic stress) (Chap. 227); the imaging is carried out both immediately after cessation of exercise to detect reversible ischemia and 4 h later to confirm reversible ischemia and regions of infarction (Fig. 244-2;Fig. 244-CD3).

An important fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal disease, exertional dyspnea, or deconditioning. In these circumstances intravenous dipyridamole or adenosine can be used in place of exercise. The development of a transient perfusion defect with a tracer such as radioactive thallium or technetium 99m sestamibi is used to detect myocardial ischemia. Ambulatory monitoring of theECG can assess myocardial ischemia as episodes of ST-segment depression. These techniques are sensitive and capable of identifying patients with ischemia who are at increased risk of coronary events (Figs. 244-CD4 and244-CD5).

Two-dimensional echocardiography of the left ventricle can assess both global and regional wall motion abnormalities due to myocardial infarction or persistent ischemia (Chap. 227). Stress (exercise or dobutamine) echocardiography may cause the