МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
ХАРКІВСЬКИЙ ДЕРЖАВНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

THE MAIN INFECTIOUS DISEASES OF CHILDREN

for English medium medical students

ОСНОВНІ ІНФЕКЦІЙНІ ХВОРОБИ У ДІТЕЙ

для студентів вищих медичних навчальних закладів з англійською мовою навчання

Харків ХДМУ 2012

УДК 616.9 - 053.2(075.8)

THE MAIN INFECTIOUS DISEASES OF CHILDREN. Book for English medium medical students / Comp.: S.V. Kuznetchsov, O.N. Olkhovskaya, A.N. Tatarkina, T.A. Kirsanova. – Kharkov: KNMU, 2012. – 188 p.

The questions of an etiology, epidemiology, pathogenesis, clinical picture, diagnosis, treatment and prophylaxis of the main infectious diseases of children are reported. Alongside with treating of classical variants of illness, the major attention is given to features of an infectious pathology of children of the first year of life, immunoprophylactic measures.

ОСНОВНІ ІНФЕКЦІЙНІ ХВОРОБИ У ДІТЕЙ. Навчальний посібник для студентів вищих медичних навчальних закладів з англійською мовою навчання / Укладачі: С.В. Кузнєцов, О.М. Ольховська, А.М. Татаркіна, Т.О. Кірсанова. – Харків: ХНМУ, 2012.– 188 с.

В посібнику на сучасному рівні розкриті питання етіології, епідеміології, патогенезу, клініки, діагностики, лікування і профілактики основних інфекційних захворювань дитячого віку. Велика увага приділена особливостям інфекційної патології у дітей першого року життя, профілактиці та імунопрофілактиці інфекційних захворювань.

Рецензенты: Ходак Л.А. - д-р.мед.наук, професор кафедри дитячих інфекційних хвороб Харківської медичної академії післяґдипломної освіти

Полукчи А.К. - д-р.мед.наук, професор кафедри інфекційних хвороб Харківської медичної академії післяґдипломної освіти

Затверджено вченою радою ХДМУ. Протокол № 6
від 17.05.2012 р.

PART 1 **INTRODUCTORY PART**

Infection or infectious process is the interaction of a pathogenic microorganism and a microorganism under the influence of environment. If, as a result, the equilibrium of the organism's interaction with its environment is disturbed an infectious disease ensues manifested by clinical symptoms.

An infectious disease is a form of infectious process. The specific feature of an infectious (epidemic) disease is its contagiosity, i.e. transmissibility from one body to another.

The General Character of an Infectious Disease. A characteristic of acute infectious diseases is their cyclic course, which is distinctly divided into the following individual stages: the incubation period, or stage of latency, the prodromal stage (premonitory symptoms), the stage of development, the stage of subsidence, and the period of convalescence.

The incubation period begins from the moment of infection and ends with the appearance of the first signs of the disease. Every disease has an incubation period of definite length.

During incubation the causative agent multiplies producing toxic products in the process. In addition a reconstruction of the organism takes place as it reacts to the action of the extreme irritant.

A prodromal or premonitory period is not observed in all infectious diseases. It is characterized by the appearance of the first indefinite signs of illness (mild chill, low fever, malaise, headache, etc.). It does not usually last long (one to three days).

The stage of development of a disease has its own complex of symptoms appearing and developing in a definite sequence, and then gradually declining in the stage of subsidence. The general symptoms of all the acute infectious diseases are fever, the development of inflammatory processes, and a more or less pronounced toxemia.

Fever occurs when various infectious and noninfectious processes interact with the host's defense mechanism. In most children fever is either due to an identifiable microbiologic agent or subsides after a short time. Fever in children may be categorized as (1) fever of short duration with localizing signs for which the diagnosis can be established by clinical history and physical examination, with or without laboratory tests; (2) fever without localizing signs, for which the history and physical examinations do not suggest a diagnosis but laboratory tests may establish an etiology; and (3) fever of unknown origin (FUO).

Bacteraemia and virusaemia are very important in the pathogene-sis and development of clinical signs of some infectious diseases. An important sign of an infectious disease is a more or less marked intoxication. Toxicoses caused by endotoxins, the products of decomposition of bacteria, tissues, products of disordered metabolism, are not specific.

Many infectious diseases are attended by neurotoxicosis which is characterized by affections of the central nervous system. Hyperther-mic, meningeal, and convulsive syndromes, oedema of the brain, during which the danger of brain protrusion into the great foramen arises, are very important. The Waterhouse-Friderichsen syndrome, which is characterized by a violent onset,

hyperthermia, marked adynamia, loss of consciousness, frequent vomiting, fall of arterial pressure to a circulatory collapse, is especially dangerous.

Acute intestinal infections, and sometimes other infectious processes in children to 2 years of age, may be attended by toxicosis with dehydration due to loss of the body water caused by frequent stools and vomiting. Metabolic acidosis develops due to the loss of the electrolyte (as a result of the upset water-ionic balance, haemo-dynamics, and the disordered acid-base equilibrium). The degree and character of dehydration may be different. Isotonic, water-deficit and salt-deficit dehydrations are differentiated.

With convalescence there is more or less rapid elimination of all symptoms of the disease, but complete restoration of the organism's normal functional condition is often a lengthy process. Adynamia, rapid mental fatiguability, and lability of the cardiovascular system are common.

Not infrequently exacerbation is observed in the stage of subsidence of the clinical manifestations of an infectious disease, and relapse or recurrence of almost the whole symptom complex in the period of recovery.

Superinfection – there is a new infection, mostly by another type of the same causative agent (dysentery, scarlet fever).

Mixed infections, in which the infectious process is complicated by involvement of two and more causative agents, occur frequently. Various associations of causative "gents are possible: mixed bacterial, bacterial-fungal, viral-bacterial, and viral infections are differentiated.

Clinical Forms and Complications. Infectious diseases have a great variety of clinical forms. The-manifestations and severity of a disease depend both on the properties (virulence) of the causative agent and on individual peculiarities of the organism's reactivity, which are determined by age, type of higher nervous activity, physical state, previous illnesses, etc.

Hypertoxic forms of infectious disease (diphtheria, scarlet fever,. dysentery, etc.) are apparently associated with previous sensitization of the child's organism.

Atypical forms are of great practical interest, and are often difficult to diagnose. They include so-called formes frustes with rudimentary symptoms (viz. angina scarlatinosa, whooping-cough without paroxysms, the catarrhal form of diphtheria, etc.) which are especially common when carrier state is encountered. They therefore play a great role in the epidemiology of infectious diseases.

Complications are pathological processes closely linked genetically with the main disease and developing during the course of the latter or during convalescence. Their incidence depends on the severity of the disease (its clinical form), peculiarities of the organism's reactivity (particularly of age reactivity), the conditions of the patient's environment, and on nursing and treatment.

Features of infection and immunity in children

Physiological immaturity is the cause of imperfect protective reaction of the newborns. Atypical inflammatory processes, inability to form the cell barrier round the infection focus, i.e. to localize it and to preclude its propagation, are found in infants.

The non-specific mechanism of protection against viruses, interferonogenesis, also depends on maturity of the body and its age. Production of interferon is minimal in infants under one year of age, or they are interferon-negative. This is encourage to develop deferent viruses diseases.

The source or the natural reservoir of an infection is an infected human animal (the sick and carriers). Not only patients with clinically manifest forms of the disease are dangerous as regards infection but also those suffering from atypical forms frustes.

The mechanism of infection is specific for each infectious disease and depends on localization of the causative agent in the human (of animal) organism, i.e. or the source of infection. This localization determines the route of discharge of the microbe into the environment.

In diseases in which the causative agents are discharged from the organism mainly in the secretions of the mucous membranes of the nose, throat, pharynx, and upper respiratory tract infection is direct, by the aerial-droplet route (respiratory infections – measles, german measles, influenza, whooping-cough, diphtheria, scarlet fever, chickenpox, mumps).

The causative agent can also be spread by direct contact of a healthy person with a source of infection. The transmission of infection via infected objects, i.e. by indirect contact (through dishes, toys, towels, handkerchiefs, patient clothes.

The alimentary method of transmission of infection (by food) is characteristic of intestinal infections. Foodstuffs can become infected by a sick person or a carrier during transportation, sale, or cooking. Water-borne infection can occur through drinking infected water, accompanying extensive epidemics with an explosive onset and course.

Transmission of the causative agents by living vectors (the transmissive route) is characteristic of many infection diseases (flies, blood-sucking arthropod parasites, mosquitoes, ticks).

The problem of congenital infectious diseases is transplacental transmission of the causative agent from a sick mother to the foetus.

A most important factor in the epidemic process is the susceptibility of a population. This is usually defined by the so-called index of contagion, of more correctly, the index of susceptibility.

Diagnosis. Precise and early diagnosis of acute infections in children is of great practical significance not only because it largely determines the efficacy of the treatment, but also because it is indispensable for the most important anti-epidemic measure early isolation of the source of infection.

The various laboratory tests and other auxiliary methods of examination are of vital importance. The most reliable are methods of detecting the infective agent in the patient's organism.

Laboratory diagnosis of bacterial infections

Gram stain. The examination of a Gram stain should be carried out on all fluids to be cultured. In addition to giving rapid results, the Gram stain may be useful in interpreting the subsequent cultural data because it allows identification of cellular exudate and the predominant organisms.

Special cultures. Most medically important bacteria can be cultivated on blood agar, chocolate agar, and eosin methylene blue or MacConkey agar. New media preparations en-

hance the recovery of anaerobic organisms. For collection of anaerobic cultures, material should be rapidly transported to the laboratory in a capped syringe, or special swabs supplied in oxygen-free tubes should be used.

Blood culture. Culturing the blood is one of the most fruitful procedures in the diagnosis of bacterial disease. It should be done carefully before administration of antibiotics, using iodine-alcohol for skin disinfection. A number of different blood culture techniques are now available, most of which use 50- to 100-mL bottles containing broth nutritious for bacteria into which not more than 5–10 mL of blood are introduced. Some blood culture bottles also contain an oxygen-free carbon dioxide–enriched atmosphere that allows the recovery of anaerobes. Repeating blood cultures may be necessary to determine (1) whether treatment has been successful particularly in high-risk patients who have infections that are difficult to treat and (2) whether the isolate is a contaminant when the organism reported is usually nonpathogenic. Whether an organism isolated from blood is a pathogen or a contaminant should be carefully considered, since "nonpathogens" such as coagulase-negative staphylococci may cause disease.

Examination of cerebrospinal fluid. Fluid obtained by lumbar puncture or ventricular tap should be collected in sterile, capped containers and transported quickly to the laboratory, where centrifugation is done to concentrate organisms. Gram stains of cerebrospinal fluid (CSF) sediment are helpful; the presence of organisms distinguishes bacterial from viral disease, but stains should not be relied on for the identification of a specific organism. It is better to use broad-spectrum initial therapy in life-threatening disease and to wait for the culture report before ordering specific treatment. Counterimmunoelectrophoresis and agglutination of antibody-coated latex beads are additional rapid, accurate methods for diagnosis. Specific antisera can be used to detect antigens of Haemophilus influenzae type b, Neisseria meningitidis, Staphylococcus pneumonia, group B streptococci, and Escherichia coli K1.

Urine culture. Urine for culture and colony count can be obtained in midstream (clean-catch), by catheterization, or by suprapubic puncture. The last method is the most reliable; urine so obtained should normally be sterile. Urine collected by catheter is likely to reflect infection if there are 103 organisms/mL or more. Clean-catch urine, if obtained after adequate cleansing, can be considered abnormal if 105 or more organisms/mL are present, and possibly abnormal if between 104 and 105 organisms/mL are counted. Clean-catch urine specimens from girls who have inadequately washed, and specimens allowed to sit at room temperature for some time before being transported to the laboratory, may result in unreliable cultures.

Culture of feces. Rectal swabs or stool specimens are cultured either to identify common bacterial pathogens such as Salmonella and Shigella or to determine the predominant flora of the intestine in a patient with weakened host defenses whose endogenous flora may become pathogenic. Since feces contain mostly anaerobic bacteria, routine cultures identify only the predominant aerobic organisms among the billions of bacteria contained in each gram of feces.

A number of organisms have recently been added to the list of bacterial pathogens found in feces, including Helicobacter pylori, Yersinia enterocolitica, Clostridium difficile, Aeromonas spp., Plesiomonas spp., Vibrio spp., and E. coli 0157:H7. DNA probes, anti-

gen detection methods, and toxin detection have all been applied to the rapid diagnosis of enteric pathogens.

Exudates and transudates. Abscesses, pleural fluids, joint fluids, urethral exudates, and other miscellaneous exudates and transudates can be cultured directly on agar. In addition to cultures and stains, glucose and cell count determinations should be done on all transudates for the same reasons they are done on CSF.

Nasopharyngeal, throat, and skin swabs. A dry rayon, Dacron, or calcium alginate swab is most efficient for collecting specimens from the skin and mucous membranes. Since drying rapidly destroys some pathogenic bacteria, swab specimens should be placed promptly in a transport medium. Interpretation of results of cultures from skin and mucous membranes is difficult because microbial flora are normally recovered from these areas. Some organisms are considered pathogenic wherever found, such as Corynebacterium diphtheriae, Bordetella pertussis, and Neisseria gonorrhoeae; others, such as Streptococcus pyogenes, N. meningitidis, H. influenzae, or staphylococci, may be pathogenic or non-pathogenic, depending on circumstances. Still others, such as Streptococcus viridans, are rarely considered pathogenic. In respiratory tract disease there is little correlation between flora of the upper airway and that of the lower airway. Because sputum cultures are seldom reliable in children, bronchoalveolar lavage, tracheal aspirates, and lung punctures are sometimes necessary for accurate diagnosis. If bacteria such as C. diphtheriae or Bordetella sp. (which grow poorly in ordinary media) are suspected, the laboratory should be informed prior to receipt of the specimen.

Antibody-based techniques. Fluorescent antibody (FA) techniques have increased the diagnostic scope of direct microscopy. Specific antisera are now available commercially for several common pathogens. In these sera the antibody molecules have been conjugated with a fluorescein dye. The specific dye-labeled serum is added to the smear containing the suspected organism, and the slide is microscopically examined for fluorescence under ultraviolet light. Indirect FA methods are also applicable in the absence of conjugated antibodies. FA is used principally for identifying B. pertussis, Legionella pneumophila, and N. gonorrhoeae.

Antibiotic sensitivity tests. Most laboratories routinely test bacterial isolates for sensitivity to various antibiotics. The most prevalent technique of antibiotic testing is the agar disk diffusion method, in which a standardized inoculum of the organism is seeded onto a plate. Filter paper disks, each impregnated with an antibiotic, are placed on the agar surface, and after 18–24 hr of incubation, the zone of inhibition of bacterial growth around each disk is measured. Standard zone diameters indicating sensitivity or resistance have been defined according to previous test results correlating zone sizes with sensitivity determined by inhibition of bacteria inoculated into dilutions of antibiotics in culture broth.

Dna probes. The greatest revolution in microbiologic diagnosis to date has occurred through the use of DNA probes. Among those bacteria for which commercial probes are now available, Mycoplasma pneumoniae, M. tuberculosis, Mycobacterium avium–intracellulare, and enteric organisms figure prominently.

Laboratory diagnosis of viruses. If viral disease is a diagnostic possibility, specimens should be obtained for viral culture and rapid viral detection. Serologic tests are much less useful for viral diagnosis but obtaining an acute phase sample is sometimes indicated for later comparison with convalescent antibody titers.

Rapid viral detection. Fluorescent-antibody techniques or other methods that use antibodies to detect viral antigens in clinical specimens provide rapid identification of viruses. For example, smears of mucosal cells stained by immunologic reagents can identify the antigens of respiratory viruses, such as respiratory syncytial virus or influenza, for which there is a polyclonal or monoclonal antiserum. Rotaviruses, which cause infantile gastroenteritis, and hepatitis B surface antigen can be detected by enzyme-linked immuno-sorbent assay (ELISA) using specific antisera.

Cytologic examination aids in diagnosis when inclusion bodies or syncytia are found but these methods are not sensitive enough to be relied upon for the diagnosis of life-threatening infections, such as neonatal herpes. All rapid detection assays should be done in parallel with and confirmed by viral culture.

Isolation. Viruses require living cells for propagation; the cells used most often are human or animal cell tissue cultures. Because some viruses are difficult to isolate and many require a variety of culture systems for their isolation, the clinician should describe the clinical signs, for example, pneumonia or skin lesions, when the specimen is sent to the laboratory. Specimens should be delivered to the laboratory promptly.

Viral genome and virion detection. New methods for viral diagnosis rely upon the use of probes constructed of sequences complementary to the genome sequences of DNA or RNA viruses. Polymerase chain reaction (PCR) detects viral gene sequences using complementary nucleotides as primers to amplify a conserved region of the genome. These methods are technically complex and difficult to standardize, but reliable commercial assays are available to detect some viruses. False-positive results are common, particularly with PCR methods. While electron microscopy (EM) provides a tool for direct visualization of virions within infected cells, its use in clinical diagnosis has been replaced for the most part by viral antigen or genome detection methods. Its usefulness is also limited because different viruses in the same family, such as herpes simplex, cytomegalovirus, and other herpesviruses, are indistinguishable by EM morphology.

Serologic tests. Correct diagnosis requires at least two blood specimens: the first should be obtained during the early acute phase of the disease "acute serum", and the second "convalescent serum" 14–21 days later. If the second is taken earlier than 14 days after the first, it is advisable to take a third blood specimen 4–6 wk after the onset, since the rise of antibodies may be delayed, especially in infants. If it is not possible to send blood to the laboratory promptly, serum may be removed for preservation by freezing. Whole blood should never be frozen. To establish the etiologic diagnosis, it is necessary to demonstrate a fourfold rise in titer of antibody to an agent in the convalescent as opposed to the acute phase serum, when all specimens are tested together. IgM antibody titers should never be relied upon as the only diagnostic test for a serious viral infection. IgG antibody assays are often useful for establishing immune status because viral pathogens usually induce humoral immunity that persists for years after primary infection.

Methods of Detecting Antibody. Antibody can be detected by a variety of specific serologic methods; some are more appropriate than others for specific viruses. Complement-fixation (CF) antigens are available for a great range of viruses, and CF antibodies have the advantage of correlating with recent infection but are less useful for showing past infection. Hemagglutination-inhibition (HI) antibodies correlate fairly well with neutralizing antibodies. Fortunately, many viruses such as the myxoviruses, rubella, and some enteroviruses can agglutinate erythrocytes. Antibodies can be detected by the indirect fluorescence technique. ELISA and latex agglutination tests are now used most often to detect antibodies to viral antigens. These depend on the attachment of viral antigens to plastic wells or latex beads.

Physical examination. Sweating in a febrile child should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration from vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine.

Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral conjunctivitis in the febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, cat-scratch disease, or Newcastle disease virus infection. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki syndrome or leptospirosis. Petechial conjunctival hemorrhages suggest endocarditis. Uveitis suggests sarcoidosis, juvenile rheumatoid arthritis, systemic lupus erythematosus, Kawasaki syndrome and vasculitis. Chorioretinitis suggests cytomegalovirus, toxoplasmosis, and syphilis. Proptosis suggests orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, Wegener granulomatosis, or pseudotumor. A careful ophthalmic examination is important in most patients with FUO.

The ophthalmoscope should also be used to examine for nailfold capillary abnormalities that are associated with connective tissue diseases such as dermatomyositis and systemic scleroderma. Emersion oil or lubricating jelly is placed on the skin adjacent to the nailbed, and the capillary pattern is observed with the ophthalmoscope set on +40.

Fever of unknown origin is sometimes due to hypothalamic dysfunction. A clue to this disorder is failure of pupillary constriction due to absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Lack of tears or an absent corneal reflex may suggest fever resulting from familial dysautonomia. A smooth tongue may reflect absence of fungiform papillae and also suggest this diagnosis. Tenderness to tapping over the sinuses and teeth should be sought, and the sinuses should be transilluminated. Oral candidiasis may be a clue to various disorders of the immune system.

Fever blisters are common findings at patients with pneumococcal, streptococcal, malarial, and rickettsial infection. They also are common in children with meningococcal meningitis (which usually does not present as FUO) but rarely are seen in children with meningococcemia. Fever blisters also are rarely seen with salmonella or staphylococcal infections.

Repetitive chills and temperature spikes are common in children with septicemia (regardless of etiology), particularly when associated with renal disease, liver or biliary disease, endocarditis, malaria, brucellosis, rat-bite fever, or loculated collections of pus.

Hyperemia of the pharynx, with or without exudate, may suggest infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki syndrome, or leptospirosis.

The muscles and bones should be palpated carefully. Point tenderness over a bone may suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiaphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki syndrome, or mycoplasma or arboviral infection.

Rectal examination may reveal pararectal adenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained on any stool found on the examining finger; occult blood loss may suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

The general activity of the patient and the presence or absence of rashes should be noted. Hyperactive deep tendon reflexes may suggest thyrotoxicosis as the cause of FUO.

Laboratory studies. Diagnostic tests most likely to provide a prompt definitive diagnosis should be used. Ordering a large number of tests in every child with FUO according to a predetermined sequence may waste time and money. Alternatively, prolonged hospitalization for sequential tests may be more costly. The tempo of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed more slowly and deliberately, and, usually, in the ambulatory setting.

A complete blood cell count with a differential cell count and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count <5,000 mm^3 is evidence against nonfulminant bacterial infection other than typhoid. Conversely, patients with >10,000 polymorphonuclear leukocytes or >500 nonsegmented polymorphonuclear leukocytes/mm3 have a high chance of having a severe bacterial infection. Direct examination of the blood smear treated with Giemsa or Wright stain may reveal malaria, trypanosomiasis, babesiosis, or relapsing fever.

An elevated erythrocyte sedimentation rate (ESR >30 mm/hr, Westergren method) indicates inflammation and the need for further evaluation for infectious, autoimmune, or malignant diseases. A low ESR does not eliminate the possibility of infection or juvenile rheumatoid arthritis, but an ESR of >100 mm/hr suggests tuberculosis, Kawasaki syndrome, malignancy, or autoimmune disease.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should only be obtained if there are specific reasons to suspect an anaerobic infection. Repeated blood cultures may be required to diagnose endocarditis, osteomyelitis, or deep-seated abscesses producing bacteremia. Polymicrobial bacteremia suggests factitious self-induced infection or gastrointestinal pathology. The isolation of leptospires, Francisella, or Yersinia may require selective media or specific conditions not routinely employed. Urine culture should be obtained routinely.

Tuberculin skin testing should be performed carefully with polysorbate 80 (Tween) stabilized purified protein derivative (PPD) that has been kept appropriately refrigerated. Other appropriate antigens should be placed to test for anergy.

Roentgenographic examination of the chest, sinuses, mastoids, or gastrointestinal tract may be suggested by specific historical or physical findings. Roentgenographic evaluation of the gastrointestinal tract for inflammatory bowel disease may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow may reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic diseases; and histiocytosis, hemophagocytosis, or storage diseases. If a bone marrow aspirate is performed cultures for bacteria, Mycobacterium, and fungi should be obtained.

Serologic tests may aid in the diagnosis of infectious mononucleosis, cytomegaloviral disease, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, and, on some occasions, juvenile rheumatoid arthritis. As serologic tests for more diseases become available through commercial laboratories, it is important to ascertain the sensitivity and specificity of each test before relying on these results to make a diagnosis. Serologic tests for Lyme disease are notoriously unreliable.

Radioactive scans may be helpful in detecting osteomyelitis and abdominal abscesses. Gallium citrate localizes in inflammatory tissues (leukocytes) associated with tumors or abscesses. 99mTc phosphate is useful for detecting osteomyelitis before plain roentgenograms demonstrate bone lesions. Indium-III granulocytes or iodinated IgG may be useful in detecting localized pyogenic processes. Echocardiograms may suggest the presence of vegetation on the leaflets of heart valves, as in subacute bacterial endocarditis. Ultrasonography may identify intra-abdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total body computed tomography (CT) or magnetic resonance imaging (MRI) scanning permits the detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT scanning is helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intra-abdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT or ultrasound-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. Although scanning procedures can be very helpful in confirming a suspected diagnosis, they rarely lead to an unsuspected one.

Biopsy is occasionally helpful in establishing a diagnosis of FUO. Bronchoscopy, laparoscopy, mediastinoscopy, and gastrointestinal endoscopy may provide direct visualization and biopsy material when organ-specific manifestations are present.

Treatment. Treatment of patients suffering from an infectious disease should be aetiopathogenic, complex, systemic, individualized, and as early as possible.

Regimen, nursing, and diet. The most important element in the treatment of infectious patients is correct organization of the regimen. Children are especially sensitive patients. The growing body with its characteristic reactivity requires special care on the part of the medical personnel during performance by them of medical, diagnostic, and prophylactic measures. Psychic perception of the child is quite different from that of an adult.

Much attention should be paid to giving an adequate amount of fluid; this is particularly important in toxaemia and exsiccosis. Children should be fed at definite intervals, depending on their age, and meal times should be strictly observed.

Causal treatment

Various methods are employed in order to eliminate or render harmless the organism causing or maintaining the infectious process, and to detoxicate bacterial toxins (chemotherapy, immunotherapy, and phagotherapy).

1. Chemotherapy (anti-malarial drugs, derivatives of arsenic and antimony, sulphonamides, antibiotics, etc.) is the treatment of an infectious disease by chemical agents acting on the causative agent.

2.Immunotherapy is divided on 2 groups -active (vaccinotherapy, anatoxynotherapy) and passive (serotherapy, immunoglobulin).

3. Phagotherapy is another method of acting on the causative agent of a disease. Bacteriophages are strictly specific, acting only on definite species of microbe, causing complete lysis. Specific bacteriophages are indicated in dysentery and salmonellosis.

4. Therapy with biological preparations is close to the latter two methods. The preparations are obtained from microbes of normal intestinal microflora that are antagonists to some pathogenic microbes. These preparations are bifidumbacterin, bificol, lactobacteria, etc.; giving these preparations to treat dysbacteriosis caused by various diseases favours the restoration of normal biocenosis.

Non-specific pathogenetic therapy

Apart from aetiological therapy, of great importance in infectious diseases is pathogenetic therapy, i.e. action on the mechanisms determining the development of pathological processes, and developing the organism's protective, compensatory, and restorative reactions.

The methods of pathogenetic therapy include many elements with aetiotropic action. Strict separation of aetiologic and pathogenetic therapy is impossible.

The various methods of pathogenetic therapy employed in infectious diseases may provisionally be grouped as follows, according to their principal action:

(a) non-specific methods of eliminating toxaemia (blood and plasma transfusion (polyglucin), intravenous injection of hypertensive glucose solution, increased fluid intake, use of corticosteroids, saturation with vitamins);

(b) action on the pathologically changed reactivity of the organism through stimulation, desensitization (hormone therapy, use of anti-histamine drugs, general ultraviolet irradiation, etc.);

(c) restoration of disturbed physiological functions and their regulation (normalization of metabolism, for example, of water-mineral metabolism in toxic dysentery; restoration of disturbed cardiovascular activity, restoration of normal lung ventilation, etc.);

(d) depression of excessive and pathologically altered reactions (inflammation, hyperthermia, cough in croup and whooping-cough, intestinal spasm in dysentery, etc.);

(e) replacement therapy (blood transfusion in anaemia, enzyme therapy in dysentery, vitamins in hypovitaminoses, corticosteroids in disturbed funct'on of suprarenals, etc.).

Prophylaxis

General prophylactic measures are of the utmost importance, but to be continuous (even during periods that are favourable epidemicwise). Preventive measures desirable in an epidemic focus are as follows:

1. Isolation of the source of infection.
2. To send the urgent massage to sanepidemic station
3. Quarantine of contact children.
4. Immunization of contact children (active of passive).
5. Disinfections (concurrent and terminal).
6. Follow-up of the epidemic focus.

When a case of nosocomial infection is discovered, the patient should be immediately isolated, and the ward ventilated, and when the infection is caused by a stable agent, disinfected. With aerial-droplet infections (except German measles) the whole department or an individual ward is quarantined, depending on the infection, the type of patients, and the conditions in the ward. Children who have not had the infection previously are no longer admitted, and the discharge of contacts is delayed. The question of what group of patients to quarantine, and on the need for this measure in such infections as chickenpox, mumps, whooping-cough, and influenza, is decided individually in each case, depending on the specific conditions; but it is desirable to consult an epidemiologist. An important item in control of nosocomial measles infection is properly organized serum prophylaxis among unimmunized contacts, thanks to which this very dangerous nosocomial infection is now relatively harmless in well-organized hospitals, and mortality has been reduced to zero. Each individual case of nosocomial infection needs to be analysed and recorded in a special journal of hospital infections.

To avoid the danger of spread of infection from a hospital, or to reduce it to the minimum, it is necessary to observe strictly the rules for dismissal of infectious patients. Officially recommended terms for isolation of contagious patients should be strictly adhered to. Before discharge convalescents are given a bath or shower, and dressed in disinfected clothes. When a convalescing child is dismissed from the hospital, the parents are given an epicrisis where contacts (or absence of contacts) with infectious patients are indicated. The rules for caring for convalescents and the prophylactic measures needed at home, are explained to the relatives taking a child away from hospital.

Sanitary, prophylactic, and anti-epidemic measures need to be skillfully combined with the treatment and the therapeutic regimen. It is of great importance in combating nosocomial infections to maintain the moral of patients and the general non-specific resistance of their organisms at a high level.

PART 2 VIRAL HEPATITIS

S.P. Botkin regarded epidemic virus hepatitis as an independent infection. Viral hepatitis is a major health problem in developing and developed countries.

Causative agents. Recent advances in the field of molecular biology have aided identification and understanding of the pathogenesis of the five viruses that are now known to cause hepatitis as their primary disease manifestation. These hepatotropic viruses are designated hepatitis A, B, C, D, and E.

The five hepatitis viruses are a heterogenous group of viruses that cause similar acute clinical illness. Hepatitis A, C, D, and E are RNA viruses representing four different families, and hepatitis B is a DNA virus.

The viruses of hepatitis are stable to the environmental factors (temperature in particular).

Hepatitis A

Etiology. HAV is a 27-nm diameter, RNA-containing virus that is a member of the Picornavirus family. It was isolated originally from stools of infected patients. Laboratory strains of HAV have been propagated in tissue culture.

Epidemiology. Hav infections occur throughout the world but are most common in developing countries, where the prevalence rate approaches 100 % in children by the age of 5 yr. Hepatitis A causes only acute hepatitis. The illness is much more likely to be symptomatic in adults; most infections in children younger than 5 yr are asymptomatic or have mild, nonspecific manifestations. The transmission of HAV is almost always by person-to-person contact. Spread is predominantly by the fecal-oral route; percutaneous transmission is a rare occurrence and maternal-neonatal transmission is not recognized as an epidemiologic entity. Fecal excretion of the virus occurs late in the incubation period, reaches its peak just before the onset of symptoms, and is minimal in the week after the onset of jaundice. The mean incubation period for HAV is about 4 wk.

Pathology and pathogenesis. The acute response of the liver to HAV is similar to that of the other four hepatitis viruses. The entire liver is involved with necrosis, most marked in the centrilobular areas, and increased cellularity, which is predominant in the portal areas. The lobular architecture remains intact, although balloon degeneration and necrosis of parenchymal cells occur initially. When the course of the disease is protracted, regeneration, sclerosis, dystrophic-necrotic processesare found. Injury in acute hepatitis is caused by several mechanisms. The initial injury in hepatitis A is thought to be cytopathic. Regardless of the mechanism of initial injury to the liver, damage from the five hepatitis viruses is evident in three main ways. The first is a reflection of injury to the hepatocytes, which release alanine aminotransferase (ALT) and aspartate aminotransferase (AST) into the bloodstream. The affection of hepatocytes and deranged permeability of cell membranes account for the increased activity in the blood of the enzyme aminotransferase. The ALT is more specific to the liver than the AST, which also can be elevated after injury to erythrocytes, skeletal muscle,

or myocardial cells. Protein, fat, carbohydrate, pigment, and water-salt metabolism are affected. There is hypoproteinaemia, accumulation of metabolites, and a considerable increase in blood bilirubin content. The liver loses its capacity to produce and store glycogen. There is a deficiency of vitamins A, B1, and B2; disturbance of vitamin K assimilation leads to reduction of prothrombin level and as a result to haemorrhagic phenomena. The height of aminotransferaseelevation does not correlate with the extent of hepatocellular necrosis and has little prognostic value. In some cases, a falling aminotransferase level may predict a poor outcome if the decline occurs in conjunction with a rising bilirubin and prolonged prothrombin time (PT). This combination of findings indicates that massive hepatic injury has occurred, resulting in few functioning hepatocytes. Viral hepatitis is also associated with cholestatic jaundice, in which both direct and indirect bilirubin levels are elevated. Jaundice results from obstruction of biliary flow and damage to hepatocytes. Elevations of serum alkaline phosphatase, 5-nucleotidase, g-glutamy-l-transpeptidase, and urobilinogen all can reflect injury to the biliary system. Increased PT reflects abnormal protein synthesis by hepatocytes. Because of the short half-life of these proteins, the PT is a sensitive indicator of damage to the liver. Serum albumin is another liver-manufactured serum protein, but its longer half-life limits its relevance for monitoring acute liver injury. Cholestasis results in a decreased intestinal bile acid pool and decreased absorption of fat-soluble vitamins.

Clinical picture

The incubation period of epidemic hepatitis A is between 15 and 50 days. The course of epidemic hepatitis has a cyclic character and consists of three stages, the preicteric, icteric, and convalescent. The preicteric stage, lasting from three to ten days, is met in most patients. Its most constant symptoms are dyspeptic, namely: anorexia, nausea, vomiting, abdominal pain, and sometimes diarrhoea or, on the contrary, constipation.

There is prostration, moderate or slight elevation of temperature, and headache, but the temperature often remains normal. Catarrh of the respiratory tract, i.e. rhinitis, cough, pain all over the body, and headache are met less often. In some cases the leading symptom is rheumatoid pain in the joints and neuralgia (more common in adults than in children). A certain enlargement and slight tenderness of the liver are already noted at the preicteric stage, and sometimes (mostly in nursing babies) there is also enlargement of the spleen. Blood bilirubin content rises by the end of this period; there is also increased activity of the enzymes - aldolase and transaminase. Bile pigments appear in the urine, often rendering it dark yellow; the stool becomes pale. The ESR is usually normal or decreased.

As a rule, the icteric stage is accompanied with a fall of temperature and improvement in the patient's condition. Jaundice develops gradually; initially the sclera and the soft palate are involved, and then the skin. The severity of the jaundice does not always conform to that of the disease. Hepatitis with a mild form of jaundice, or even without it, may sometimes end in cirrhosis, or change to toxic dystrophy of the liver. The jaundice is sometimes accompanied with slight pruritus of the skin, and epistaxis and a haemorrhagic rash are occasionally displayed. When the hepatitis runs a benign course the neuropsychic phenomena are usually mild, only adynamia, listlessness, and sometimes sleepiness and

irritability, being noted. Cardiovascular findings are bradycardia and enfeebled and impure cardiac sounds; but bradycardia is not met, as a rule, in nursing babies. The dyspeptic symptoms noted during the preicteric stage often become intensified: there is sharp loss of appetite, some patients have diarrhoea, and others constipation. The stool is usually pale (achylous).

The liver is enlarged, hard, and moderately tender. Spontaneously arising pain in the hepatic region is common. The spleen is enlarged in one-fifth to one-third of patients. The affection of the liver is accompanied with its disturbed function detectable by examination of the blood and urine and by special functional tests. There is a marked increase in blood bilirubin content especially conjugate bilirubin. Bilirubinaemia increases significantly in severe cases mainly due to indirect bilirubin (free bilirubin). The onset of jaundice is marked by decreased diuresis.

The urine becomes dark yellow or brownish-yellow in colour. Bilirubin and sometimes a little protein and individual erythrocytes are found in it. At the height of the disease, when no bile at all enters the intestine, urobilin disappears, but it reappears at the beginning of convalescence. Urobilinuria ceases after restoration of hepatic function.

The deranged liver function (which corresponds to the gravity of the disease) involves (in addition to the pigment disorders) a decrease in the total protein content of the blood serum, dysproteinaemia, which develops mainly due to the increased gamma globulin content. Dysproteinaemia is also confirmed by positive sedimentation tests (thymol and sublimate tests) characterizing the stability and dispersion of the serai proteins. The coagulating factors (prothrombin and proconvertin) are decreased. The activity of the blood serum enzyme aldolase and aminotransferase increases. The increased activity of sorbitdehydrogenase and fructosomonophosphate aldolase is especially important. These enzymes are regarded as organospecific of the liver. Fat and carbohydrate metabolism is also upset.

Blood findings. Erythrocyte count and haemoglobin content are often reduced particularly when the process is protracted. In the initial period leucocyte count usually remains within the range normal for the given age, but in the icteric stage slight leucopenia and relative lymphocytosis are often noted. The ESR remains normal or decreases.

The icteric stage is divided into phases of progress, maximum development and abatement of icterus. Jaundice persists for ten to twenty days, on the average, but is sometimes as short as seven, or as long as 40 and more. As a rule, subsidence is slower than progress. As blood bilirubin falls and the other symptoms of the disease disappear, there is increased diuresis and improvement of the patient's general condition.

Gradual restorations of hepatic function and decrease in the size of the liver proceed during the convalescent stage, which is sometimes protracted. There may be exacerbations and relapses. The residual phenomena (enlargement of the liver and mild icterus) may last for several months. The younger a child, however, the more rapid is convalescence.

This description of the clinic of virus hepatitis equally holds for its inoculation variant (hepatitis B). The latter only has the following special characteristics: shorter duration of the preicteric period and more frequent absence of this period; more pronounced intoxication; gradual intensification of jaundice, its longer duration and more pronounced bilirubinaemia; relatively low indices of the thymol test and relatively low increase in IgM; more frequent enlargement of the spleen and a more severe course in general. Compared with hepatitis A, hepatitis B is more characterized by its protractedness and chronic forms. But it should be noted that this, to a certain extent, might be due to the special reactivity of infants less than 1 year of age in whom the inoculation hepatitis mostly occurs. The more severe course of inoculation hepatitis can probably be partially associated with the initial development of the infection against the background of another severe disease, for which some manipulations were carried out (e.g. blood transfusion).

Epidemic hepatitis has various clinical forms. Acute, protracted, and chronic hepatitis is distinguished. Hepatitis is considered protracted if it lasts for over three months and chronic if it continues over six months. The latter term is however only conventional and chronic hepatitis may (especially in severe cases) develop at earlier terms. At the same time, the process of recovery may continue for a few months, which may be due to the so-called post-hepatic astheno-dyspeptic syndrome with functional disorders. Acute hepatitis is divided by severity into mild, moderately severe, severe, and grave; the last-named follows the course of toxic dystrophy of the liver. Hepatitis without clinical jaundice is distinguished as an atypical form; this form presents considerable diagnostic difficulties.

The form without clinical jaundice is much more common, but is not always recognized. Many clinicists regard hepatitis occurring without jaundice and bilirubinaemia (as established at the laboratory) as the nonicteric hepatitis. It has the symptoms of the pre-icteric stage of hepatitis. Of-particular importance for diagnosis are pain in the hepatic region, swelling or slight tenderness of the liver, increased activity of aldolase and transaminase, positive thymol turbidity test, and increase of urobilin content in the urine. Although this form is mild, it sometimes leads to toxic dystrophy of the liver or to cirrhosis.

The grave form (toxic dystrophy of the liver) may begin as common hepatitis. The change to malignancy usually occurs during the first seven or ten days of the icteric stage. Adynamia progresses rapidly; anorexia, persistent vomiting and specific mouth smell is noted. Bilirubinaemia increases significantly at the expense of indirect bilirubin; residual nitrogen increases, and the alkali reserve of the blood decreases sharply (acidosis). There is a picture of very grave toxaemia with fulminant neuropsychic symptoms (including maniac excitation, motor agitation, and delirium followed by a lapse into a comatose state). Most patients display a rapidly progressive contraction of the liver, a haemorrhagic tendency, arterial hypotension, and tachycardia. The disease is often fatal, but active treatment may bring recovery.

Epidemic hepatitis may become chronic (this being particularly facilitated by repeated exacerbations and relapses), and last for months or even years. The outcome is either recovery, usually with residual phenomena, or cirrhosis of the liver. Virus hepatitis is often aggravated by affection of the bile

ducts (mostly their dyskinesia). The late periods of the disease may be marked by cholecystitis and cholangitis, which develop as a result of secondary bacterial infection.

Diagnosis. Great difficulties are encountered in recognizing the disease during the preicteric stage or in cases without clinical jaundice. Examination of the blood for bilirubin, and of urine for bile pigments and urobilin, and the epidemiological anamnesis are of diagnostic value in these cases. For early diagnosis of hepatitis, particularly of the form without apparent jaundice, of great aid is the determination of the activity of the following enzymes: aldolase, aspartate amino-transferase and alanin aminotransferase. The content of the latter two substances increases several times in virus hepatitis. Protein sedimentation tests (with thymol and sublimate) are also used.

Anti-HAV is detected at the onset of symptoms of acute hepatitis A and persists for life. The acute infection is diagnosed by the presence of IgM anti-HAV, which can be detected for 3–12 mo; thereafter, IgG anti-HAV is found. The virus is excreted in stools from 2 wk before to 1 wk after the onset of illness. The PT should always be measured in a child with hepatitis to help assess the extent of liver injury; prolongation is a serious sign mandating hospitalization.

Hepatitis B

Etiology. HBV is a 42-nm diameter member of the hepadnavirus family, a noncytopathogenic, hepatotropic group of DNA viruses. The surface of the virus includes two particles designated hepatitis B surface antigen (HbsAg) The inner portion of the virion contains hepatitis B core antigen (HBcAg) and a nonstructural antigen called hepatitis B e antigen (HBeAg). Replication of HBV occurs predominantly in the liver but also occurs in lymphocytes, spleen, kidney, and pancreas.

Epidemiology. The most important risk factor for acquisition of hepatitis B infection in children is perinatal exposure to an HBsAg-positive mother. The risk of transmission is greatest if the mother also is HBeAg positive; 70-90 % of their infants becomes chronically infected if untreated. In most cases, antigenemia appears later, suggesting that transmission occurred at the time of delivery; virus contained in amniotic fluid or in maternal feces or blood may be the source. Although most infants born to infected mothers become antigenemic from 2–5 mo of age, some infants of HBsAg-positive mothers are not affected until later ages.

HBsAg has been demonstrated inconsistently in milk of infected mothers. Breastfeeding of unimmunized infants by infected mothers does not appear to confer a greater risk of hepatitis on offspring than does artificial feeding despite the possibility that cracked nipples may result in the ingestion of contaminated maternal blood by the nursing infant.

HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen. For these reasons, efficient transmission occurs through blood exposure and sexual contact. The incubation period ranges from 45–160 days, with a mean of about 100 days.

Pathogenesis. Hepatitis B, unlike the other hepatitis viruses, is a noncytopathic virus that causes injury by immune-mediated mechanisms. The first step in the process of acute

hepatitis is infection of hepatocytes by HBV, resulting in the appearance of viral antigens on the cell surface. These antigens, in combination with class I major histocompatibility (MHC) proteins, make the cell a target for cytotoxic T-cell lysis.

Clinical manifestations. Many cases of HBV infection are asymptomatic. The usual acute, symptomatic episode is similar to HAV and hepatitis C virus (HCV) infections but may be more severe and is more likely to include involvement of skin and joints. The first clinical evidence of HBV infection is elevation of ALT, which begins to rise just before the development of lethargy, anorexia, and malaise, about 6–7 wk after exposure. The illness may be preceded in a few children by a serum sickness–like prodrome including arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Papular acrodermatitis, the Gianotti-Crosti syndrome, also may occur. Jaundice, which is present in about 25 % of infected individuals, usually begins about 8 wk after exposure and lasts for about 4 wk. Splenomegaly and lymphadenopathy are common. Chronic hepatitis occurs, and the chronic active form can result in cirrhosis and hepatocellular carcinoma.

Virus hepatitis in infants under 1 year of age has special characteristics. They can probably be partially associated with the fact that the disease in infants is mostly evoked by virus B. The course of virus hepatitis in infants under 1 is more severe than in older children; toxic dystrophy of the liver occurs more frequently in them. The preicteric period in infants is short and is often overlooked. Jaundice, on the contrary, is longer (30-40 days) and is attended by pronounced hyperbilirubinaemia and a marked enlargement of the liver. Secondary bacterial (staphylococcal) infection often supervenes in these infants to account for the intermittent course of the disease.

Diagnosis. The serologic pattern for HBV is more complex than for HAV and difference depending on whether the disease is acute, subclinical, or chronic. HBsAg is the first serologic marker of infection to appear and is found in almost all infected persons; its rise coincides closely with the onset of symptoms and disappeared soon. In chronic carriers HbsAg may persist longer than 6 months or even indefinitely. Same time HbsAg may be present in healthy carrier. HBeAg is often present during the acute phase and indicates a highly infectious state. HbcAg never presents in blood, it can be found only in hepatocytes by biopsy.

Antibody to hepatitis B surface antigen (Anti-HBs) is diagnostic of previous HBV infection or immunization conferring immunity against HBV. Only anti-HBsAg is present in persons immunized with hepatitis B vaccine, whereas anti-HBsAg and anti-HBcAg are detected in persons with resolved infection.

Because HBsAg levels fall before the end of symptoms, IgM antibody to hepatitis B core antigen (IgM anti-HBcAg) also is required because it rises early after infection and persists for many months before being replaced by IgG anti-HBcAg, which persists for years. Presence of IgM anti-HBcAg more than 6 months is considered evidence of ongoing HBV replication. IgM anti-HBcAg usually is not present in perinatal HBV infections.

Antibody to the “e”-antigen (anti-HbeAg) appears with the reduction of acute infection. Its presence in chronic carries is associated with relatively low infectivity and a good prognosis.

Complications. Acute fulminant hepatitis occurs more frequently with HBV than with the other hepatitis viruses, and the risk of fulminant hepatitis is further increased when there is coinfection or superinfection with HDV. Mortality from fulminant hepatitis is greater than 30 %. HBV infections also can result in chronic hepatitis, which can lead to cirrhosis and primary hepatocellular carcinoma. Interferon alpha-2b is available for treatment of chronic hepatitis B in person's 18 years of age or older with compensated liver disease.

Prevention. Universal immunization of infants with hepatitis B vaccine is now recommended. Two recombinant DNA vaccines are available in the United States; both have proven to be highly immunogenic in children. The AAP recommends that infants born to HBsAg-negative women receive the first dose of vaccine at birth, the second at 1–2 mo of age, and the third between 6 and 18 mo of age. Infants born to HBsAg-positive women should receive vaccine at birth, 1 mo, and 6 mo of age. The first dose should be accompanied by administration of 0.5 mL of hepatitis B immunoglobulin (HBIG) as soon after delivery as possible because the effectiveness decreases rapidly with increased time after birth.

Hepatitis C

Etiology. HCV is a single-strand RNA virus that has been classified as a separate genus within the Flaviviridae family. HCV is an enveloped virus, 50–60 nm in size that is transmitted mainly by blood or blood products, intravenous drug use, and sexual contact. Chronic liver disease is common in infected individuals.

Epidemiology. The most important risk factors for HCV transmission are the use of intravenous drugs (40 %), transfusions (10 %), and occupational and sexual exposure (10 %). The incubation period is range7–9 wk (2–24 wk).

Pathogenesis. HCV appears to cause injury primarily by cytopathic mechanisms, but immune-mediated injury also may occur. The cytopathic component appears to be mild, because the acute form is typically the least severe of all hepatitis virus infections; HCV rarely is fulminant.

Clinical manifestations. The clinical picture of the acute infection is usually similar to that of the other hepatitis viruses. HCV is the most likely hepatitis virus to cause chronic infection; about two thirds of post-transfusion infections and about one third of sporadic, community-acquired cases will become chronic. Although chronic elevations of aminotransferase levels are common, chronic HCV will progress to cirrhosis in only about half of the patients, or about 25 % of all those initially infected.

Diagnosis. The clinically available serologic assays for HCV are based on development of antibodies to HCV antigens because no detectable antigens have been found in blood. The assays are used mainly for detection of chronic hepatitis C because they remain negative for at least 1–3 mo after the clinical onset of illness. Assays for viral RNA (polymerase chain reaction [PCR]) are costly.

Complications. The risk of fulminant hepatitis is low with HCV, but the risk for chronic hepatitis is the highest among the hepatitis viruses. The usual chronic course is mild even when cirrhosis develops.

Prevention. There is no vaccine available, and none may be developed because animal studies suggest that HCV infection does not lead to protective immunity; the same individual can be infected multiple times with the same virus.

Hepatitis D

Etiology. Hepatitis D virus (HDV), the smallest known animal virus, is considered defective because it cannot produce infection without a concurrent HBV infection.

Epidemiology. HDV infection cannot occur without HBV as a helper virus. Hepatitis D infections are uncommon in children but must be considered when fulminant hepatitis occurs. The incubation period for HDV superinfection is about 2–8 wk; with coinfection, the incubation period is similar to that of HBV infection.

Pathophysiology. In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. Many of the most severe cases of hepatitis B appear to be due to combined infection with HBV and HDV.

Clinical manifestations. The symptoms of hepatitis D infection are similar to but usually more severe than those of the other hepatitis viruses. The clinical outcome for HDV infection depends on the mechanism of infection. In coinfection, acute hepatitis, which is much more severe than for HBV alone, is common, but the risk for chronic hepatitis is low. In superinfections, acute illness is rare, whereas chronic hepatitis is common. However, the risk of fulminant hepatitis is highest in superinfection. Hepatitis D should be considered in any child who experiences acute hepatic failure.

Diagnosis. Detecting IgM antibody to HDV makes the diagnosis; the antibodies to HDV develop about 2–4 wk after coinfection and about 10 wk after superinfection.

Complications. HDV must be considered in all cases of fulminant hepatitis.

Prevention. There is no vaccine for hepatitis D. However, because HDV cannot occur without hepatitis B infection, HBV prevention eliminates HDV. HBIG and hepatitis B vaccines are used for the same indications as hepatitis B.

Hepatitis E

Etiology. Hepatitis E virus (HEV) has not been isolated but has been cloned using molecular techniques. This RNA virus is similar to the caliciviruses. Infection is associated with shedding of 27- to 34-nm particles in the stool.

Epidemiology. Infection is transmitted enterically, the highest prevalence has been reported in the Indian subcontinent, the Middle East, and Southeast Asia. The mean incubation period is about 40 days (range, 15–60 days).

Pathogenesis. HEV appears to act as a cytopathic virus.

Clinical manifestations. The clinical illness in hepatitis E is similar to that of hepatitis A, the other enterically transmitted virus, but it is often more severe. Both viruses produce only acute disease; chronic illness does not occur. In addition to causing more severe illness than HAV, hepatitis E affects older patients, with a peak incidence between 15 and 34 yr. Another important clinical difference is that HEV has a high fatality rate in pregnant women.

Diagnosis. IgM antibody to viral antigen becomes positive after about 1 wk of illness.

Complications. HEV is associated with a high prevalence of death in pregnant women.

Prevention. No vaccines are available.

Diagnosis. Puncture biopsy should only be resorted to in separate doubted cases to diagnose chronic hepatitis. It should be remembered that the method is not sufficiently accurate since healthy tissue may be taken during the biopsy.

Data of epidemiological anamnesis may be useful for establishment of the diagnosis. The diagnosis can only be confirmed by determining antigens and antibodies to its.

Acute respiratory infections and other diseases characterized by fever during their initial period should be excluded in differential diagnosis. Enlarged liver, dark colour of the urine and colourless faeces, and especially increased activity of aminotransferase are very important for correct diagnosis. Haemolytic and obstructive jaundice may also interfere with correct diagnosis in the icteric period. Haemolytic jaundice is characterized by the absence of bilirubin in the urine, the faeces are not colourless but on the contrary are coloured more intensely. Free bilirubin content of blood increases. Obstructive jaundice, which is caused by obstruction of the bile ducts by stones, parasites, etc., is characterized by the absence of biochemical indices of liver affection; the indices of aminotransferase activity are normal. For differential diagnosis of leptospiral jaundice see the corresponding section.

Prognosis. The overwhelming majority of patients recover. There may be a transition to a chronic form (in 5 per cent of cases on average) with subsequent cirrhosis of the liver. It is more common in hepatitis B. The death rate is now low (fractions of 1 per cent) but is higher in nursing babies and in hepatitis B.

Treatment. Hepatitis patients must be hospitalized. Physical and mental quiet is of utmost importance. Bed rest is prescribed for the whole course of epidemic hepatitis; the patient is only allowed to leave his bed during the recovery period.

Close attention has to be given to diet, which must be planned with due consideration of the disturbed function of the liver, the extent of the toxaemia, and the patient's appetite. It should be mainly carbohydrates with adequate amount of animal protein. Limited intake of proteins and even complete eradication of proteins from the diet is only indicated in grave intoxication when a precomatose state develops. The menu should include milk products (cottage cheese, sour milk, yoghourt), vegetables, fruit, stewed fruit, sweet jellies, sugar, jam, honey. A minimum of fat and salt, and no extracts, hot spices, cocoa, or chocolate should be given. Adequate fluid (tea, fruit juices, alkaline mineral water, etc.) must be ensured.

The patient's food should be enriched with vitamins. In addition it should be supplemented by synthetic vitamin preparations, like ascorbic acid (100 to 300 mg daily), nicotinic acid (30 to 50 mg), and vitamins E1 and A. Vitamin K (vikasol) is indicated for three to five days (0.005 to 0.01 g, depending on age, three times a day) when there are haemorrhagic symptoms.

In mild hepatitis bed rest and diet supplemented by these vitamins suffice for the majority.

When the course of hepatitis is grave special measures are sometimes required to control the toxaemia. To this end a special diet, consisting only of fruit, sugar, jam, yoghourt, and abundant fluids, is recommended for one or two days. Cleansing or syphon enemas are prescribed to rid the bowel of accumulated toxic products. Intravenous drip infusions of 5 per cent glucose solution (300-500 ml and over) or Ringer's solution with ascorbic acid are recommended.

Transfusion of plasma substitutes and albumin solution is employed for detoxication, stimulation of hepatic function, and desensitization.

Steroid hormones (prednisolone, 2 mg/kg daily for seven to ten days) which possess an antiphlogistic, detoxifying, and desensitizing effect, are valuable, and are included in the general therapeutic complex in severe forms of hepatitis. Definite indications for their prescription in increased doses (up to 5 ml/kg intramuscularly or intravenously) are a precomatose condition, and subacute or acute dystrophy of the liver.

Plasma transfusion and hormone therapy are also employed when the disease has a protracted course. Physiotherapy (UHF, paraffin and ozokerite therapy) is also prescribed in these cases. Antibiotic therapy (ampicillin, chloramphenicol, etc.) is prescribed.

Children who have had an attack of epidemic hepatitis should be kept under medical observation for six months and longer (up to 2 years) after discharge from hospital. They should be forbidden excessive physical strain and put on a light, digestible diet. No prophylactic vaccinations and no antihelminthic agents (apart from oxygen) should be prescribed during that period. Sanatorium treatment is recommended for children with long-term residual phenomena.

PART 3 INFECTIOUS DISEASES OF ELEMENTARY TRACT (Shigellosis, Sallmonellosis, Escherichiosis)

30 to 40 percent of diarrheal episodes are caused by viruses, of which rotavirus is the best example. About 50 percent are due to bacterial infections of the gut. The presence of bacteria in the stools by itself is not a proof of these being causative agents. Bacteria cause diarrhea by two mechanisms: 1) through the action of toxins and 2) direct invasion of the intestinal mucosa.

Shigellosis

Four species of Shigella are responsible for illness: S. dysenteriae (serogroup A), S. flexneri (serogroup B), S. boydii (serogroup C), and S. sonnei (serogroup D). There are 12 serotypes in group A, 6 serotypes and 13 subserotypes in group B, 18 serotypes in group C, and 1 serotype in group D.

Pathophysiology. The shigellae have the ability to invade colonic epithelial cells. This characteristic is encoded on a large (120–140 MD) plasmid that is responsible for synthesis of a group of polypeptides involved in cell invasion and killing. Shigellae that lose the virulence plasmid no longer act as pathogens. Escherichia coli that naturally or

artificially harbor this plasmid behave like shigellae. Shigatoxin, a potent protein synthesis–inhibiting exotoxin, is produced in significant amounts only by S. dysenteriae serotype 1 and certain E. coli (enterohemorrhagic E. coli or shiga-like toxin–producing E. coli).

Shigellae require very low inocula to cause illness. Ingestion of as few as 10 S. dysenteriae serotype 1 organisms can cause dysentery in some susceptible individuals. This is in contrast to organisms such as Vibrio cholerae, which require ingestion of 108–1010 organisms to cause illness. The inoculum effect explains the ease of person-to-person transmission of shigellae in contrast to V. cholerae. Secretory IgA and serum antibodies develop within days to weeks after infection with Shigella.

Pathology. The colon is the target organ for shigellae. The changes are most intense in the distal colon, although pancolitis may occur. Grossly, localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may be seen. The following forms of intestinal affection are distinguished in dysentery: catarrhal, follicular, croupous, and diphtheritic.

Epidemiology. Infection with shigellae occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. The sexes are affected equally. Although infection can occur at any age, it is most common in the 2nd and 3rd yr of life. Infection in the first 6 mo is rare. Breast milk, which in endemic areas contains antibodies to both virulence plasmid-coded antigens and lipopolysaccharides, may explain the age-related incidence.

In industrialized societies, S. Sonnei is the most common cause of bacillary dysentery, with S. Flexneri second in frequency; in preindustrial societies, S. Flexneri is most common with S. Sonnei second in frequency. S. Dysenteriae serotype 1 tends to occur in massive epidemics, although it is also endemic in Asia.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. However, person-to-person transmission is probably the major mechanism of infection in most areas of the world.

Clinical manifestations. The most convenient and widespread classification of the clinical forms of dysentery is Kaltupin classification. There are typical and atypical forms of dysentery. Typical dysentery is divided into mild, moderately severe, and severe forms, the last-named may show prevalence either of local or of general phenomena (toxic form).

After ingestion of shigellae there is an incubation period of several days before symptoms ensue. Characteristically, severe abdominal pain, high fever, emesis, anorexia, generalized toxicity, urgency, and painful defecation occur. Physical examination at this point may show abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination.

The diarrhea may be watery and of large volume initially, evolving into frequent small-volume, bloody mucoid stools; however, some children never progress to the stage of bloody diarrhea, whereas in others the first stools are bloody.

In mild cases the frequency of defaecation is three to eight times a day; the stool remains faecal in character, but assumes a greenish hue; pathological admixtures are not copious. In more severe cases bowel movements are very frequent (15 to 20 times

a day and more times). The stools are scanty, lose their faecal character, consist almost entirely of thick, almost transparent mucus, and are practically odorless. Later the mucus with pus and blood.

A leading place in the clinical picture of dysentery is taken by symptoms reflecting a spastic condition in the large intestine, namely, abdominal pain (spasmodic in character and precedes and accompanies each bowel movement, localized more frequently in the left iliac region), tenesmus, spastic contraction of the sigmoid colon. As severe dysentery progresses, paresis or paralysis replaces spasm of the sphincter, with result in gaping of the anus.

Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40 % of hospitalized infected children. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea.

Untreated diarrhea may last 1–2 wk; only about 10 % of patients have diarrhea persisting for more than 10 days. Chronic diarrhea is uncommon except in malnourished infants.

The colitic syndrome is relatively mild in infants, and is usually not fully expressed. The stool often retains its faecal character but becomes liquid and greenish in colour. Mucus is almost always present, but blood flecks occur much less frequently. The stool may be dyspeptic in character. In most cases there is no tenesmus, but the baby shrieks and becomes red in the face during defaecation. Gaping of the anus is quite rare; much more frequently anal responsiveness is observed. The abdomen is inflated. Significant dehydration related to the fluid and electrolyte losses in both feces and emesis can occur at young children.

The most common complication of shigellosis is dehydration with its attendant risks of renal failure and death. Other major complications, particularly in very young, malnourished children, include sepsis and disseminated intravascular coagulation. Complications caused by secondary infection are common in dysentery, particularly in infants (disbacteriosis, bronchopneumonia, stomatitis, gingivitis, nephritis, dystrophy, avitaminosis and anaemia).

Differential diagnosis. The dysentery closely resembles many other intestinal diseases. Mild dysentery in infants under 1 should be differentiated from simple dyspepsia. It develops from overfeeding or from other negligence; its course is marked by apyrexia; stools are liquid, green, with insignificant admixtures of mucus (4-6 defaecations a day). Adherence to normal feeding rules will normally give a rapid positive effect.

An erroneous diagnosis of dysentery in infants with intestinal invagination can lead to grave results. Invagination begins abruptly at a normal temperature, and the baby becomes very restless. There is tenesmus; stool consists of mucus and blood alone without faecal matter; no gases are evacuated. Usually the abdomen is soft, and a sausage-like tumour is palpable. Invagination can sometimes be revealed by digital examination of the rectum. Roentgenography of the abdominal cavity can help diagnosis.

Salmonella infections

Salmonella infections occur worldwide. Acute gastroenteritis, the most frequent presentation, is usually self-limited, although bacteremia and focal extraintestinal infections may develop, especially in immunocompromised patients. Enteric fever, a severe systemic disease typically caused by Salmonella typhi, is found mainly in developing countries, but it is seen elsewhere because of international travel.

Etiology. Salmonella is a genus that belongs to the family Enterobacteriaceae and contains three species: S. typhi, S. choleraesuis, and S. enteritidis. The former two species have one serotype each, but S. enteritidis contains more than 1800 distinct serotypes.

Salmonellae are motile, nonsporulating, nonencapsulated, gram-negative rods. Most strains ferment glucose, mannose, and mannitol to produce acid and gas, but they do not ferment lactose or sucrose. S. typhi does not produce gas. They are resistant to many physical agents. Like other members of the Enterobacteriaceae, Salmonella possesses somatic O antigens and flagellar H antigens. The O antigens are the heat-stable lipopolysaccharide components of cell wall; the H antigens are heat-labile proteins. The Kauffmann-White scheme commonly used to classify salmonellae serotypes is based on O and H antigens. Another antigen is a virulence (Vi) capsular polysaccharide present on S. typhi and rarely found on strains of S. paratyphi C.

Nontyphoidal Salmonellosis

Epidemiology. The major reservoir of nontyphoidal salmonellae is infected animals, which constitute the principal source of human disease. Infected animals are often asymptomatic. Salmonella organisms have been isolated from many animals, including poultry (i.e., chickens, turkeys, and ducks), sheep, cows, pigs, pets, and birds. Animal-to-animal transmission may occur. Animal feeds containing fishmeal or bone meal contaminated with Salmonella are an important source of infection for animals. Moreover, subtherapeutic concentrations of antibiotics are often added to animal feed. Such practices promote the emergence of antibiotic-resistant bacteria, including Salmonella, in the gut flora of the animals. Data suggest that animal antibiotic exposure may be responsible for antibiotic-resistant Salmonella infections in man.

Poultry and poultry products (mainly eggs), raw or powdered milk and dairy products caused about half of the common-source outbreaks. Because of the high infecting dose, person-to-person transmission by direct fecal-oral spread is unusual but can occur, especially in young children who are not yet toilet-trained and do not maintain proper hygiene.

Nosocomial infections have been related to contaminated medical instruments (particularly endoscopes) and diagnostic or pharmacologic preparations, particularly those of animal origin (e.g., pancreatic extracts, pituitary extracts, bile salts, pepsin, gelatin, vitamins, and carmine dye).

During the period of Salmonella excretion, the individual may infect others, directly by the fecal-oral route or indirectly by contaminating foods. If one household

member becomes infected, the probability that another will also become infected is about 60 %.

Pathology. Enterocolitis is the typical disorder caused by nontyphoidal Salmonella infection. Salmonella organisms are capable of penetrating the intestinal mucosa. Intestinal inflammation, with polymorphonuclear leukocytes and macrophages, usually involves the lamina propria. Hyperplasia of the reticuloendothelial system is seen also within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration of almost any organ.

Pathogenesis. Ingested Salmonella organisms reach the stomach, where acidity is the first protective barrier. The acidity inhibits multiplication of the salmonellae, and when gastric pH reaches 2.0, most organisms are rapidly killed. Neonates and young infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to symptomatic salmonellosis. Because the transit time through the stomach is faster for drinks than for foods, a lower inoculum may cause disease in waterborne infection.

Heat-labile, cholera-like enterotoxin is produced by many Salmonella isolates. This toxin and the prostaglandins that are produced locally increase cyclic adenosine monophosphate levels within intestinal crypts, causing a net efflux of electrolytes and water into the intestinal lumen. Bacteremia, however, is theoretically possible with any Salmonella strain, especially in individuals with reduced host defenses.

Clinical manifestations. Acute Gastroenteritis. This is the most common clinical presentation. After an incubation period of 6–72 hr (mean, 24 hr), there is an abrupt onset of nausea, vomiting, and abdominal pain primarily in the periumbilical area and right lower quadrant, followed by mild to severe watery diarrhea and sometimes by dysenteric diarrhea, containing blood and mucus. Moderate fever of (38.5–39 C) affects about 70 % of patients. Some children develop severe disease with high fever, headache, drowsiness, confusion, meningismus, seizures, and abdominal distention. Abdominal examination reveals some tenderness. The stool, which is usually not bloody, typically contains a moderate number of polymorphonuclear leukocytes and occult blood. Mild leukocytosis may be detected. Symptoms subside within 2–7 days in healthy children; fatalities are rare.

Neonates, young infants, and children with primary or secondary immune deficiency may have symptoms persisting for several weeks. At patients with AIDS, the infection may become widespread and overwhelming, causing multisystem involvement, septic shock, and death.

Bacteremia. Salmonella bacteremia is associated with fever, chills, and often with a toxic appearance. Children with certain underlying conditions who have Salmonella gastroenteritis are at increased risk of bacteremia, which may lead to extraintestinal infection.

Asymptomatic Infection. After clinical recovery from Salmonella gastroenteritis, asymptomatic fecal excretion of salmonellae occurs for several weeks. A chronic carrier state is defined as asymptomatic excretion of Salmonella organisms for more than 1 yr.

Differential diagnosis. Salmonella gastroenteritis should be differentiated from other bacterial, viral, and parasitic causes of diarrhea. Etiologic diagnosis on the basis of the clinical picture is not possible. In children with gastroenteritis, cultures of stools have higher yields than rectal swabs. Epidemiologic data may be helpful.

Prognosis. Complete recovery is the rule in healthy children who develop Salmonella gastroenteritis. Young infants and immunocompromised patients often have systemic involvement, a prolonged course, and complications. The prognosis is poor for children with Salmonella meningitis (~50 % mortality rate) or endocarditis.

Escherichia coli

Etiology and pathogenesis. Five classes of E. coli are recognized as agents associated with pediatric gastroenteritis.

Enterotoxigenic E. coli (ETEC). These E. coli serogroups produce a heat-labile enterotoxin (LT) and/or a heat-stable enterotoxin (ST). LT related to cholera toxin produced by Vibrio cholerae, stimulates adenylate cyclase, resulting in increased cyclic AMP. Due to colonization factor antigens (CFAs) E. coli adhere to intestinal epithelium, the ETEC release ST or LT.

Enteroinvasive E. coli (EIEC). These E. coli serogroups behave like shigellae in their capacity to invade gut epithelium and produce a dysentery-like illness because these E. coli possess a large virulence plasmid closely related to the Shigella plasmid. Invasion of epithelium causes cell death and a brisk inflammatory response (clinically recognizable as colitis).

Enteropathogenic E. coli (EPEC). These diarrheagenic E. coli belong to serogroups that have been associated with outbreaks of infantile gastroenteritis but do not produce conventional enterotoxins or invade epithelial cells. The EPEC adhere to the intestinal mucosa in a distinctive way. The lesion consists of loss of microvilli with adherence of bacteria to the epithelial cells, which form a cup or pedestal in which the bacteria can be seen. Attachment results in increased intracellular calcium concentration and dense polymerization of actin at the site of attachment.

Enterohemorrhagic E. coli (EHEC). These E. coli serogroups produce one or more toxins that kill mammalian cells. Two major toxins are produced by EHEC. One is essentially identical to shigatoxin, the protein synthesis–inhibiting exotoxin of Shigella dysenteriae serotype 1. The second is more distantly related to shigatoxin. The first toxin is called SLT-I (VT-1) and the second SLT-II (VT-2). These toxins kill cells by protein synthesis inhibition and cell death.

Enteroaggregative E. coli (EAggEC). These E. coli serogroups have the ability to adhere to HEp-2 cells in tissue culture. They are also referred to as autoagglutinating and enteroadherent-aggregative E. coli. It is likely that this group will be further subdivided, and some of these organisms will be shown to be nonpathogens.

Epidemiology. In the developing world, the various diarrheagenic serogroups of E. coli cause frequent infections in the first few years of life. They occur with increased frequency during the warm months in temperate climates and during rainy season months in tropical climates. Most E. coli strains (except EHEC and perhaps

some EPEC) require a large inoculum of organisms to induce disease; person-to-person spread is atypical, but foodborne or waterborne illness is common.

Clinical manifestations

As might be expected from the different mechanisms of disease production, the clinical features of E. coli–associated diarrhea vary from group to group.

ETEC are a major cause of dehydrating infantile diarrhea in the developing world. The typical signs and symptoms include explosive watery diarrhea, abdominal pain, nausea, vomiting, and little or no fever. Resolution usually occurs in a matter of days.

EIEC cause an illness that is indistinguishable from classic bacillary dysentery. Fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency with water or bloody diarrhea are characteristic.

EPEC usually are isolated from infants and children in the first few years of life who have a nonbloody diarrhea with mucus; fever may occur. Unlike ETEC, EIEC, or EHEC, these organisms often cause a prolonged diarrheal disease.

EHEC may cause an illness characterized by abdominal pain with diarrhea that is initially watery but within a few days becomes grossly bloody (hemorrhagic colitis). Although this pattern resembles that of shigellosis or EIEC disease, it differs in that fever is an uncommon manifestation. The major risk with EHEC is that approximately 10 % of symptomatic infections are complicated by development of hemolytic-uremic syndrome.

EAggEC cause significant fluid losses with dehydration, but vomiting and grossly bloody stools are relatively infrequent. These organisms, like the EPEC, are often associated with prolonged diarrhea.

Complications

The major complications are those related to dehydration and electrolyte loss. Infection with EHEC is frequently associated with the hemolytic-uremic syndrome.

Diagnosis

Positive bacteriological study of the faeces is of decisive importance. The best bacteriological results are obtained when the culture medium is inoculated with fresh faeces directly at the patient's bedside and before the beginning of treatment with antibiotics and sulphonamides, and when tests are repeated several times. Culture of both stool and rectal swab specimens optimizes the chance of diagnosing intestinal infection.

Indirect haemagglutination test, which is carried out with the blood serum of the patient, deserves special attention. The reaction becomes positive during the first week of the disease and it is highly sensitive.

Coprology, i.e. microscopic study of faeces for pathological admixtures (mucus, leucocytes, and erythrocytes), is widely employed as an auxiliary method.

In children who appear to be toxic, blood cultures should be obtained; this is particularly important in very young or malnourished infants because of their increased risk of bacteremia.

Treatment

As with gastroenteritis of other causes, the first concern about a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance. In general, this therapy should include oral replacement and maintenance with rehydrating solutions such as those

specified by the World Health Organization. Early refeeding with breast milk or dilute formula should be encouraged as soon as dehydration is corrected. Prolonged withholding of feeding frequently leads to chronic diarrhea and malnutrition.

Drugs that retard intestinal motility should not be used because of the risk of prolonging the illness.

In severe form nursing babies are given boiled water, salt solutions, tea. An adequate amount of fluid, namely 150 ml per kg of body weight, should be given. When vomiting is frequent, fluid must be given in small portions by spoon (one to two teaspoonfuls every five or ten minutes) or dripped from a pipette. Water diet is followed by fractional feeding with expressed breast milk (10-50 ml ten times per 24 hours, with fluid added up to the volume required for the given age.

APPROXMATE AMOUNT OF ORS SOLUTION TO GIVE IN THE FIRST 4 HOURS:						
Age	Less then 4 months	4-11 months	12-23 months	2-4 years	5-14 years	15 years or older
Weight:	Less than 5kg	5-7.9 kg	8-10.9 kg	11-15.9 kg	16-29.9 kg	30 kg or more
in ml	200-400	400-600	600-400	800-1200	1200-2200	2200-4000

Antibiotics and chemotherapeutic agents. The next concern is a decision about the use of antibiotics. Some authorities recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, and the risk of emergence of resistant organisms. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

Since viruses or toxigenic bacteria cause a large majority of cases of diarrhea and there is little evidence of inflammation of gut mucosa, it is neither necessary nor desirable to use antibacterial substance. Antimicrobial should be used only for infectious agents such as shigella, cholera vibrio, Entamoeba histolytic and giardia. They may be prescribed for very small and sick newborns infected with enteropathogenic strains of E. coli. They may have a role in some cases of diarrhea persisting for more than 3-4 weeks.

Resistance to nalidixic acid is uncommon. Treatment regimens involve a 5-day course. For strains known to be susceptible to ampicillin, this drug is given at 100 mg/kg/24 hr divided into four doses each day, cefixime (8 mg/kg/24 hr in two divided doses given orally for 5 days), ceftriaxone (50 mg/kg/24 hr as a single daily dose given parenterally for 2–5 days), or nalidixic acid (55 mg/kg/24 hr in four divided doses for 5 days) can be given. Oral first- and second-generation cephalosporins are inadequate as alternative drugs.

Complex of urgent measures should be taken to control intoxication. The appropriate treatment should be given in the presence of neurotoxicosis and the corresponding syn-

dromes (hyperthermic, convulsive, etc.). In the presence of exsiccosis, measures should be taken to control it with due consideration of the degree and character of dehydration.

Treatment with a bacteriophage in tablets coated with an acid-proof material is indicated. Biological preparations such as coli-bacterin, bifidumbacterin, lactobacterin, linex and other preparations should be used to prevent and to treat dysbacteriosis.

At patients with gastroenteritis, antimicrobial agents do not shorten the clinical course, nor do they eliminate fecal excretion of Salmonella. By suppressing normal intestinal flora, antimicrobial agents may prolong the excretion of Salmonella and increase the risk of creating the chronic carrier-state. They should be used in young infants and other children who are at increased risk of a disseminated disease and in those with a severe or protracted course. In children with severe disease, initial treatment with a third-generation cephalosporin is recommended until antibiotic susceptibility is known.

Symptomatic treatment. If a child vomits during oral rehydration therapy, it is best to stop ORT for ten minutes and then restart ORT by spoon. One or more doses of metoclopramide 0.1 to 0.2 mg/kg or phenothiazine (0.5 mg/kg) may be given in cases of severe vomiting, but should preferably be avoided since these can cause oculogyric spasms. Convulsions associated with diarrhea may be due to hypo - or hypematremia, meningitis, encephalitis, hypocalcemia following bicarbonate herapy for acidosis. If hypo-or hypernatremia can be excluded, lumbar puncture must be done. The treatment of convulsions depends on the cause. Symptomatic control of seizures can be achieved either with diazepam (0.2 mg/kg/dose IV, max. 5 mg) phenobarbitone (5 to 10 mg/kg dose IM), or phenytoin (10 mg/kg/initially I.V. slowly followed by 5 mg/kg/day).

Prevention

Two simple measures decrease the risk of intesyinal infection in children. The first is to encourage prolonged breast-feeding. The second measure is to educate families in handwashing techniques, especially after defecation and before food preparation and consumption. Chlorinated water, proper sanitary systems, and adequate food hygiene practices are necessary to prevent nontyphoidal salmonellosis in humans. Handwashing is of paramount importance in controlling person-to-person transmission by means of food. Individuals with symptomatic or asymptomatic excretion of Salmonella strains should be excluded from activities that involve food preparation or childcare until repeated stool cultures are negative. Control of the transmission of Salmonella infections to humans requires control of the infection in the animal reservoir.

PART 4 INFECTIOUS DISEASES OF ELEMENTARY TRACT (Campylobacter, Yersiniosis, Rotavirus and other agents of viral gastroenteritis)

Initially considered animal pathogens only, Campylobacter organisms are now recognized as an important cause of bacterial gastroenteritis and of systemic infections, primarily in neonates and compromised patients.

Etiology. The genus Campylobacter (meaning curved rod) includes 14 species, of which eight are considered pathogenic for humans: C. jejuni, C. fetus, C. coli, C. hypointestinalis, C. laridis, C. cinaedi, C. fennelliae, and C. upsaliensis. There are more than

90 different serotypes of C. jejuni. Helicobacter pylori (formerly C. pylori) is a new genus, differentiated from Campylobacter by RNA sequence differences. The clinical presentation depends on the species of campylobacter organisms. Intestinal disease is usually associated with C. jejuni, and extraintestinal and systemic infections are associated with C. fetus. Less frequently, enteritis is caused by C. coli, C. laridis, or C. fetus; systemic infections may rarely be caused by C. jejuni or C. coli. Campylobacter organisms are thin, gram-negative rods; they are short and S-shaped or long, multispiraled, and filamentous. In older cultures, coccal forms may be seen. The organism is motile, with a flagellum at one or both poles. The organisms appear as small (0.51 mm), slightly raised, smooth colonies on solid media. Visible growth in blood culture is often not apparent until 5-14 days after the initial inoculation. Campylobacter organisms are microaerophilic, requiring reduced oxygen tension for growth, with optimal growth occurring in 5-6 % oxygen. They neither oxidize nor ferment carbohydrates.

Epidemiology. Campylobacter infections are among the most frequent causes of bacterial gastroenteritis worldwide. In developed countries, C. jejuni gastroenteritis is usually more common than Salmonella or Shigella infections. C. coli also causes gastroenteritis, although the frequency is about 400-fold lower than for C. jejuni. Population-based studies in the United States showed isolation rates of Campylobacter ranging from 28 to 71 per 100,000 inhabitants annually.

Campylobacter gastroenteritis occurs most often in summer and fall; in subtropical areas, it peaks in the rainy season.

The age distribution of Campylobacter gastroenteritis in developed countries is bimodal, with one peak in children younger than 4 yr of age and a second in adolescents and young adults. The highest incidence occurs in the first year of life. In developing countries, infections occur early in life, usually below the age of 5 yr. Many infections are asymptomatic, especially in older children.

Campylobacter enteritis is a worldwide zoonosis. The gastrointestinal tract of many domestic and wild animals is the main reservoir of infection. C. jejuni has been isolated from the feces of 30100 % of chickens, turkeys, and water fowl. Most farm animals, meat sources, and pets can harbor the organisms. Transmission of C. jejuni from animals to persons occurs most often by the fecal-oral route by ingestion of contaminated food, especially undercooked poultry, unpasteurized milk, and untreated water. Perinatal and person-to-person transmission occurs but is much less common. Household transmission from young dogs and cats with diarrhea also occurs. Outbreaks of Campylobacter diarrhea are reported in nurseries and day-care centers.

Communicability is greatest during the acute phase of the illness and can last as long as 2–3 wk, but appropriate antibiotic treatment can shorten this period to 2–3 days. Chronic carriage is uncommon. Homosexual men are at increased risk for C. cinaedi and C. fennelliae infections.

Pathology. C. jejuni infection involves the terminal ileum and colon, often producing inflammatory diarrhea. Macroscopically, mucus, pus, and blood are present in the lumen of the bowel, with friable, ulcerated mucosa. Microscopically, rectal biopsies of such patients demonstrate colitis with acute inflamma-

tory infiltrates and swelling of the lamina propria and crypt abscesses. These findings are similar to those seen in shigellosis. Damage to the intestinal mucosa may also be minimal.

Pathogenesis. Invasion, enterotoxin production, and cytotoxin production have been demonstrated in C. jejuni infections. Mucosal invasion, which is mediated by bacterial surface proteins and occurs after specific binding, seems to be the most important virulence trait. Low levels of cytotoxins that damage mammalian cells are produced by some isolates and may help in the invasion process. Some strains of C. jejuni produce a cholera-like enterotoxin, which may explain the watery diarrhea seen clinically. It is not clear that all C. jejuni possess virulence traits. Asymptomatic infection may reflect this phenomenon. C. fetus tends to penetrate the intestinal mucosa without significantly damaging it, reaching the reticuloendothelial system and bloodstream. This organism contains a surface protein capsule that inhibits opsonophagocytosis and enables a systemic infection.

Clinical manifestations. Several clinical presentations of Campylobacter infections are possible, depending on the species involved and host factors, such as age, immunosuppression, and underlying conditions.

Acute Gastroenteritis. This is the most common presentation of Campylobacter infections, usually caused by C. jejuni (95-99 % of cases); C. coli and C. laridis are responsible for the remaining 1-5 % of cases. The incubation period is 1-7 days. Diarrhea consists of loose, watery stools or blood- and mucus-containing stools (typically dysentery). Blood appears in the stools 2–4 days after the onset of symptoms. Fever, vomiting, malaise, and myalgia are common. Fever may be the only initial manifestation, but 6090 % of older children also complain of abdominal pain. The abdominal pain is periumbilical; cramping may precede other symptoms or persist after the stools return to normal. Abdominal pain mimics appendicitis or intussusception.

Mild infection lasts only 1 to 2 days and resembles viral gastroenteritis. Most patients recover in less than one week, but 20 % have a relapse or prolonged or severe illness. Persistent or recurrent Campylobacter gastroenteritis and emergence of erythromycin resistance during therapy are reported in patients with hypogammaglobulinemia (congenital or acquired) and acquired immunodeficiency syndrome (AIDS). Persistent infection mimics acute inflammatory bowel disease. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 wk, with a range of a few days to several months.

Bacteremia. Bacteremia without localized infection is the most common systemic infection caused by Campylobacter. C. jejuni or C. coli gastroenteritis rarely (<1 %) cause bacteremia. C. fetus usually causes bacteremia without diarrheal symptoms; diarrhea caused by this organism is seen in debilitated or immunocompromised patients.

Bacteremia presents with fever, headache, and malaise. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion are common, but specific neurologic signs are unusual in the absence of cerebrovascular disease or meningitis. Abdominal pain is fre-

quent; diarrhea, jaundice, and hepatomegaly are less common. Cough may occur, but pulmonary parenchymal involvement is unusual. There may be a moderate leukocytosis. Transient asymptomatic bacteremia that clears without antibiotic therapy occurs, as does rapidly fatal septicemia. Prolonged bacteremia of 8-13 wk is described with spontaneous remissions and relapses, especially in the immunocompromised host.

Focal Extraintestinal Infections. Focal infections caused by C. jejuni such as meningitis, pancreatitis, cholecystitis, urinary tract infection, arthritis, and peritonitis occur mainly in neonates or immunocompromised patients. C. fetus bacteremia is more often associated with focal infections. This organism shows a predilection for vascular endothelium, causing endocarditis, pericarditis, thrombophlebitis, and mycotic aneurysms; focal infections include meningitis, septic arthritis, urinary tract infections, lung abscess, and cholangitis.

Perinatal Infections. Severe perinatal infections are usually caused by C. fetus and rarely by C. jejuni. C. fetus tends to colonize the genital tract and infect fetal tissue. Maternal C. fetus and C. jejuni infections, which may be asymptomatic, cause abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Newborn infection with C. jejuni is associated with diarrhea that may be bloody; C. fetus rarely causes diarrhea.

Complication. Guillain-Bar syndrome has been reported 1-3 wk after culture-proven C. jejuni gastroenteritis. Stool cultures obtained from patients with Guillain-Bar syndrome at the onset of neurologic symptoms have yielded C. jejuni in more than 25 % of the cases. Serologic studies suggest that 20-40 % of patients with Guillain-Bar syndrome have evidence of recent C. jejuni infection.

Reactive arthritis is an immunoreactive complication seen in adolescents and adults; it appears 5-40 days after onset of diarrhea, involves mainly large joints, and resolves in 1-21 wk without any sequelae. Typically, the arthritis is migratory, but the child is afebrile. Synovial fluid is always sterile. Reiter syndrome (i.e., reactive arthritis with conjunctivitis, urethritis, and rash) and erythema nodosum occur less commonly. IgA nephropathy and immune complex glomerulonephritis with C. jejuni antigens in the kidneys are reported. Other complications are hemolytic anemia and rectal bleeding.

Diagnosis. The diagnosis of Campylobacter is usually confirmed by identification of the organism in culture. Selective media, such as Skirrow's or Batzler's media, microaerophilic conditions (5-10 % oxygen), and, for C. jejuni, an optimal temperature of 42 C are necessary. For rapid diagnosis of Campylobacter enteritis, direct carbolfuchsin stain of fecal smear, indirect fluorescence antibody test, darkfield microscopy, or latex agglutination can be use. Species-specific DNA probes and specific gene amplification by PCR have been described, although clinical experience is limited. Serologic diagnoses have been reported, using enzyme-linked immunoassays to measure antibody (IgG, IgM, IgA) levels to C. jejuni. This method may help delineate individuals with acute, chronic, or no exposure to C. jejuni antigens but is not yet a standard diagnostic approach.

Treatment. Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays in the management of children with Campylobacter gastroenteritis. Antimotility agents may cause prolonged or fatal disease and should not be used. Controversy

exists regarding the need for antibiotic therapy in patients with uncomplicated gastroenteritis. Several studies showed no improvement in clinical symptoms or shortening of the course of the disease. When erythromycin ethylsuccinate suspension is initiated early in the course of the disease in patients with the dysenteric form of Campylobacter enteritis, the duration of symptoms and shedding is shortened. Antibiotic therapy significantly shortens fecal excretion of Campylobacter from 2-3 wk without treatment to about 2 days with treatment.

Erythromycin (50 mg/kg/24 hr in four divided doses for 5 days) is the drug of choice. Late therapy (4 or more days after onset of symptoms) does not cause clinical improvement, although it still decreases shedding. Alternative antibiotic agents are tetracycline (useful in children >7 yr), ciprofloxacin (useful in older adolescents >17 yr), and furazolidone. The new macrolides, clarithromycin and azithromycin, show good in vitro activity, but clinical evaluation is needed. Antibiotics are recommended for patients with the dysenteric form of the disease, high fever, or a severe course; children attending childcare centers or other institutions; and children who are immunosuppressed or have underlying disturbances.

Campylobacter bacteremia or extraintestinal infection caused by C. fetus requires parenteral antibiotic therapy for 3-4 wk. Gentamicin is the recommended treatment until antibiotic susceptibility of the isolate is known; C. fetus isolates resistant to erythromycin are reported.

Prognosis. Although Campylobacter gastroenteritis is usually self-limited, immunosuppressed children, including those with AIDS, may experience a protracted, prolonged, or severe course. Septicemia in the newborn and immunocompromised host has a poor prognosis, with an estimated mortality rate of 30-40 %.

Prevention. As with many enteric infections, prolonged breast-feeding decreases the risk of symptomatic Campylobacter infection. Proper food handling, particularly of chicken, decreases the frequency of C. jejuni infections.

Yersinia enterocolitica

Infections due to Y. enterocolitica far outnumber infections due to Y. pseudotuberculosis and Y. pestis. Disease is usually manifested as an acute enteritis with fever, diarrhea, abdominal pain, nausea, and vomiting. Stools may be mucoid and bloody or, less commonly, watery.

Etiology. The genus Yersinia was transferred from the family Pasteurellaceae to the family Enterobacteriaceae on the basis of DNA-DNA hybridization studies and the presence of the enterobacterial common antigen. They resemble "atypical" coliforms morphologically and biochemically. Y. enterocolitica organisms are oxidase-negative, non-lactose-fermenting, gram-negative bacilli that are motile at 22 C but not at 37 C. Strains resembling Y. enterocolitica are isolated from extraintestinal infections and stool from asymptomatic patients or patients with mild gastroenteritis. These strains are considered to be nonenteropathogenic in that they lack the genes required for invasion and have now been assigned to a new species.

Epidemiology. Animals, food, and water are the major reservoirs for Y. enterocolitica. Many animal species harbor Yersinia, but swine, cattle, goats, dogs, and cats are more commonly involved. Y. enterocolitica has been isolated or detected by the polymerase chain reaction in commercial meat products, especially pork. Infections occur primarily in children and young adults, with most occurring in children under 7 yr of age. Infecting serogroups show variable geographic distributions with O:3, O:5, O:8, and O:9 strains predominant. Disease is more common in the colder months and in males than females. Common source outbreaks due to contaminated food or water are reported with incubation periods ranging from 1 to 11 days. Institutional and hospital person-to-person spread, including neonatal transmission from a symptomatic mother and transfusion-related disease from red blood cell-containing products are reported. Extraintestinal infections due to Y. enterocolitica are rare.

Pathology and pathogenesis. Y. enterocolitica pathogenesis is multifactorial, involving chromosomal and plasmid genes. All strains pathogenic for humans carry a related virulence plasmid that encodes several calcium- and thermally regulated virulence factors. The essential mechanisms involved in pathogenesis appear to be adherence, toxin production, and invasion. Adherence and production of a heat-stable enterotoxin appear to be sufficient to produce a watery diarrhea, with elaboration of cytotoxin and one or more invasin genes necessary to produce the classic enteric pathology: a superficial ulcerative ileocolitis with mesenteric adenitis, lymphoid hyperplasia, and abscesses of the Peyer patches. Necrotizing granulomas in the mesenteric nodes seen with Y. pseudotuberculosis are absent.

Several features of the organism are important for transfusion-acquired disease. First, pathogenic strains require iron and survive only in red blood cell-containing products. This cold-enhanced growth is useful for isolating the organism from mixed sources, such as stool, but increases the bacterial load in stored meat products and blood products.

Clinical manifestations. The most common presenting signs and symptoms are fever (occasionally to 40{degree} C), abdominal pain (usually colicky), and diarrhea (watery or mucoid with fecal leucocytes). Illness may be as short as 2 days or persist for 3-4 wk. It is usually self-limiting in older children, but bacteremia develops in 20-30 % of infants younger than 3 mo of age. Fever occurs in 40-50 % of cases, abdominal pain in 20-80 %, and diarrhea in 80-95 %. Asymptomatic infections are readily detected in family contacts.

Complications are uncommon in children. Erythema nodosum, hemolytic anemia, thrombocytopenia, and bacteremic spread to other sites with meningitis, hepatic abscess, and pneumonia have all been reported, but the most frequent complication is reactive arthritis. Joints of the extremities are usually affected, with one to four joints involved. Intact organisms are not detected in synovial specimens known to contain bacterial antigen, suggesting only stable degradation products or immune complexes trapped from the circulation are associated with Yersinia-triggered reactive arthritis.

Diagnosis. The history may suggest enterocolitis due to Y. enterocolitica based on contact with animals or ingestion of uncooked meat products, espe-

cially pork. Direct examination of diarrheal stool for fecal leukocytes is helpful in establishing invasive diarrhea. Culture is the most useful diagnostic test. Because many laboratories do not routinely culture for Yersinia, it is important to notify the laboratory of suspected cases. Yersinia-selective agar is inoculated with stool and incubated at reduced temperatures of 25 or 32 C. Some laboratories use cold enrichment methods and subculture material held at 4 C for as long as 4 wk. Isolations from nonstool sources and sterile body fluids may be made on routine media. Speciation is important from nonenteric sources. Pathogenic stool strains of Y. enterocolitica can be differentiated from nonpathogenic strains using Congo red-magnesium oxalate agar, the pyrazinamidase test, salicin fermentation, and esculin hydrolysis.

Serotyping of isolates and serodiagnosis in culture-negative cases is of value for epidemiologic purposes only.

Differential diagnosis. Enterocolitis due to Y. enterocolitica is similar in clinical presentation to invasive diarrheal disease due to other enteric pathogens, such as Shigella or enteroinvasive Escherichia coli, mesenteric adenitis due to Y. pseudotuberculosis, inflammatory bowel disease, and reactive arthritis due to other causes.

Prevention. Infection is preventable by careful attention to the preparation of meat, especially the slaughter of swine, and by avoiding ingestion of uncooked meat, precooked pork products held at 4 C, potable water of questionable purity, and unpasteurized milk or milk products made from unpasteurized milk. Person-to-person transmission can be reduced by careful personal hygiene, especially handwashing, and institution of enteric precautions in hospitalized patients. Vaccines are not available.

Treatment. Uncomplicated enterocolitis due to Y. enterocolitica is a self-limited disease, and the benefit of antimicrobial therapy has not been established. Culture-proven septicemia at any age and patients under 3 mo of age who have a high rate of septicemia should be treated. In one retrospective study, aminoglycosides in combination with third-generation cephalosporins, fluoroquinolones, or other agents, such as rifampin and trimethoprim-sulfamethoxazole, were effective, whereas other b{beta}-lactams, such as amoxicillin with or without clavulanate and benzylpenicillin were associated with treatment failures.

Rotavirus and other agents of viral gastroenteritis

Diarrhea is probably the leading cause of childhood mortality in the world, accounting for 5–10 million deaths per year. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteritis viruses are not only major causes of pediatric mortality but also lead to significant morbidity as a result of malnutrition. Worldwide, up to 1 million deaths per year are estimated to occur from rotavirus infection alone. In the United States, rotavirus causes millions of episodes of diarrhea per year with 70,000 hospitalizations and more than 100 deaths.

Etiology. Rotavirus, astrovirus, adenovirus, and caliciviruses, are the known, medically important pathogens of human viral gastroenteritis such as the Norwalk agent,.

Rotaviruses are classified by group (A, B, C, D, E), subgroup (I or II), and serotype. Group A, which has no antigenic relationship to the other groups, includes the common human pathogens as well as a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China but not elsewhere. Occasional human outbreaks of group C rotavirus are reported. The other groups are limited to animal strains. Astroviruses are the second most important agent of viral gastroenteritis in young children. The recent availability of convenient immunoassays for astrovirus infection has allowed investigators to demonstrate its high incidence in both the developing and developed worlds. There are five known human serotypes. Enteric adenoviruses are the third most common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in stool, especially during and after typical upper respiratory tract infections, only serotypes 40 and 41 cause gastroenteritis. These strains do not cause respiratory symptoms and are very difficult to grow in tissue culture. Other caliciviruses may cause a rotavirus-like illness in young infants. Several other viruses that may cause diarrheal disease in animals have been postulated but not yet well established as human gastroenteritis viruses. These include coronaviruses and pestiviruses.

Epidemiology. Rotavirus infection is most common in winter months in temperate climates. Peak incidence spreads from the west to the east in the United States. Unlike other winter viruses such as influenza, this wave of increased incidence is not due to a single prevalent strain or serotype. Typically, several serotypes predominate in a given community for one or two seasons while nearby locations may harbor unrelated strains. Most clinical cases occur in children younger than 2 yr (but older than 3 mo), with serologic evidence of infection developing in virtually all children by age 4 or 5 yr. Subclinical infections are common in newborn nurseries and in adults with intimate contact with infected children. Some rotavirus strains have stably colonized newborn nurseries where for years virtually all newborns have been infected with the colonizing strain without any overt illness. Rotavirus and the other gastroenteritis viruses spread efficiently via a fecal-oral route, and outbreaks are common in children's hospitals and day-care centers. The virus is shed in stool at very high concentration before and for days after the clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

The epidemiology of astroviruses is not as thoroughly studied as rotavirus, but it is a common cause of mild to moderate watery diarrhea in children and infants and an uncommon pathogen in adults. Hospital outbreaks are common. Enteric adenovirus gastroenteritis occurs year-round, mostly in children younger than 2 yr. Nosocomial outbreaks occur but are less common than in rotavirus and astrovirus. Norwalk virus is best known for causing large explosive outbreaks among older children and adults, particularly in settings such schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source.

Pathology and pathophysiology. Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Observed pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the resolution of diarrhea.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions such as hydrolysis of disaccharides and absorptive functions such as the transport of water and electrolytes via glucose and amino acid cotransporters. The crypt enterocytes are undifferentiated. Selective viral infection of intestinal villus tip cells thus leads to (1) an imbalance of the ratio of intestinal fluid absorption to secretion, and (2) malabsorption of complex carbohydrates, particularly lactose. Most evidence supports the first mechanism as the most important factor in the genesis of viral diarrhea. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk of food allergies.

Clinical manifestations. Rotavirus infection typically begins after an incubation period of fewer than 48 hr with mild to moderate fever and vomiting followed by the onset of frequent watery stools. Vomiting and fever typically abate during the 2nd day of illness, but diarrhea often continues for 5–7 days. The stool is without gross blood or white cells. Dehydration may develop and progress rapidly, particularly in infants. Malnourished children and children with underlying intestinal disease such as short-bowel syndrome are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children will experience severe and prolonged illness. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of astrovirus appears to be quite similar to that of rotavirus with the notable exception that the disease tends to be milder, with less significant dehydration. Adenovirus enteritis tends to cause diarrhea of longer duration, often 10 -14 days. The Norwalk virus has a short (12-hr) incubation period. Vomiting and nausea tend to predominate in illness associated with the Norwalk virus, and the duration is brief, usually 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as Staphylococcus aureus or Bacillus cereus.

Laboratory findings. Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

Diagnosis and differential diagnosis. The differential diagnosis includes other infectious causes such as bacteria and protozoa. Occasionally surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis. In most cases, a satisfactory diagnosis can be made on the basis of the clinical and epidemiologic features. Commercial immunoassays, which offer approximately 90 % specificity and sensitivity, are available for group A rotavirus and enteric adenovirus. More obscure cases can be studied by electron microscopy of stools, RNA electrophoresis, nucleic acid hybridization, and polymerase

chain reaction assays. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent high fever, blood or white cells in the stool, or persistent severe or bilious vomiting (especially in the absence of diarrhea).

Treatmen. Avoiding and treating dehydration are the main goals in treatment of viral enteritis.A secondary goal is maintainance of the nutritional status of the patien.

Rehydration can be accomplished in most patients via the oral route. Modern rehydration solutions containing appropriate quantities of sodium and glucose promote optimum absorption of fluid from the gut. There is no evidence that a particular carbohydrate source (i.e., rice) or addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids such as flat soda, fruit juice, and sports drinks are inappropriate for rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric if needed) route should be done over 6-8 hr and feedings begun immediately thereafter. Rehydration solution should be continued as a supplement to make up for ongoing excessive stool losses. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hr) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breast-feeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (such as soy formula or lactose-free cow's milk) for several days, although this is not necessary for most children. The use of hypocaloric diets low in protein and fat such as BRAT (bananas, rice, cereal, applesauce, and toast) have not been shown to be superior to a regular diet. There is no role for drug treatment of viral gastroenteritis. Controlled studies have shown no benefit from antiemetics or antidiarrheal drugs, and there is a real risk of serious side effects. Obviously, antibiotics are similarly of no benefit. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus gastroenteritis, but this treatment is currently considered experimental therapy.

Prevention. Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses, particularly rotavirus. Strict hand-washing and isolation procedures can help control nosocomial outbreaks. The role of breast-feeding in prevention or amelioration of rotavirus infection is probably small given the variable protection observed in a number of studies.

The most promising prospect for prevention is the development of an effective vaccine. To date, a number of live rotavirus vaccine candidates have been extensively tested. Most have been animal or human-animal hybrid rotaviruses that are attenuated in humans. None have consistently protected infants in a variety of settings, but new candidates are under development. A successful rotavirus vaccine would substantially reduce morbidity and mortality among children throughout the world.

PART 5 **EXANTHEMAS (measles, rubella)**

Measles, an acute communicable disease, is characterized by three stages: (1) an incubation stage of approximately 10–12 days with few, if any, signs or symptoms; (2) a prodromal stage with an enanthem (Koplik spots) on the buccal and pharyngeal mucosa, slight to moderate fever, mild conjunctivitis, coryza, and an increasingly severe cough; and (3) a final stage with a maculopapular rash erupting successively over the neck and face, body, arms, and legs and accompanied by high fever.

Etiology. Measles is an RNA virus of the family Paramyxoviridae, genus Morbillivirus. Only one antigenic type is known. During the prodromal period and for a short time after the rash appears, it is found in nasopharyngeal secretions, blood, and urine. It can remain active for at least 34 hr at room temperature.

Measles virus may be isolated in cultures of human embryonic or rhesus monkey kidney tissue. Cytopathic changes, visible in 5–10 days, consist of multinucleated giant cells with intranuclear inclusions. Circulating antibody is detectable when the rash appears.

Infectivity. Maximal dissemination of virus is by droplet spray during the prodromal period (catarrhal stage). Transmission to susceptible contacts often occurs prior to diagnosis of the original case. An infected person becomes contagious by the 9th-10th day after exposure (beginning of prodromal phase), in some instances as early as the 7th day. Isolation precautions, especially in hospitals or other institutions, should be maintained from the 7th day after exposure until 5 days after the rash has appeared.

Epidemiology. Measles is endemic over most of the world. In the past, epidemics tended to occur irregularly, appearing in the spring in large cities at 2- to 4-yr intervals as new groups of susceptible children were exposed. Measles is very contagious; approximately 90 % of susceptible family contacts acquire the disease. It is rarely subclinical. Prior to the use of measles vaccine, the age of peak incidence was 5-10 yr; most adults were immune. At present in the United States, measles occurs most often in unimmunized preschool-aged children and in teenagers and young adults who have been immunized. Epidemics have occurred in high schools and colleges where immunization levels were high. These epidemics are thought to be due primarily to vaccine failure. A prevalence of more than 90 % immunization of infants has been shown to produce disease-free zones.

Pathology. The essential lesion of measles is found in the skin; in the mucous membranes of the nasopharynx, bronchi, and intestinal tract; and in the conjunctivae. Serous exudate and proliferation of mononuclear cells and a few polymorphonuclear cells occur around the capillaries. There is usually hyperplasia of lymphoid tissue, particularly in the appendix, where multinucleated giant cells of up to 100 m{mu}m in diameter (Warthin-Finkeldey reticuloendothelial giant cells) may be found. In the skin, the reaction is particularly notable about the sebaceous glands and hair follicles. Koplik spots consist of serous exudate and proliferation of endothelial cells similar to those in the skin lesions. A general inflammatory reaction of the buccal and pharyngeal mucosa extends into the lymphoid tissue and the tracheobronchial mucous membrane. Interstitial pneumonitis resulting from

measles virus takes the form of Hecht giant cell pneumonia. Bronchopneumonia may be due to secondary bacterial infection.

In fatal cases of encephalomyelitis, perivascular demyelinization occurs in areas of the brain and spinal cord. In Dawson subacute sclerosing panencephalitis (SSPE), there may be degeneration of the cortex and white matter with intranuclear and intracytoplasmic inclusion bodies.

Clinical manifestations. The incubation period of measles is usually from 8 to 17 days. In children who have had serum prophylaxis, or been treated with blood or plasma transfusion, the incubation period may even be as long as 21 days.

The onset of the disease is characterized by symptoms of the initial catarrhal period, viz. a rise in temperature up to 38-39°G, headache, rhinitis, and a hacking cough, coryza, and conjunctivitis. These nearly always precede Belsky-Filatov-Koplik spots, the pathognomonic sign of measles, by–3 days. An enanthem or red mottling is usually present on the hard and soft palates. Belsky-Filatov-Koplik spots are grayish white dots, usually as small as grains of sand, with slight, reddish areolae; occasionally they are hemorrhagic. They tend to occur opposite the lower molars but may spread irregularly over the rest of the buccal mucosa. Rarely they are found within the midportion of the lower lip, on the palate, and on the lacrimal caruncle. They appear and disappear rapidly, usually within 12–18 hr. As they fade, red, spotty discolorations of the mucosa may remain. The conjunctival inflammation and photophobia may suggest measles before Belsky-Filatov-Koplik spots appear. In particular, a transverse line of conjunctival inflammation, sharply demarcated along the eyelid margin, may be of diagnostic assistance in the prodromal stage. As the entire conjunctiva becomes involved, the line disappears.

There is general malaise, adynamia, poor appetite, and insomnia; the child is listless and fretful. The temperature usually falls on the second or third day, sometimes to a subfebrile level. But the symptoms of affection of the mucous membrane increase. The cold in the nose gets worse; the patient begins sneezing an5 there is a more or less copious serous discharge. A perturbing dry hacking cough develops, and there is a sensation of irritation in the respiratory tract. Hoarseness is sometimes noted, and with it a change in the cough, which becomes hard and harsh. Conjunctivitis expresses itself in hyperaemia of the conjunctiva, watering of the eyes, and photophobia, which may be so strong that the eyelids close spasmodically and involuntary (blepharospasm). The look of the patient is characteristic: the face is swollen, the eyelids slightly hyperaemic and oedematous, the eyes water, photophobia is apparent, and there is a serous discharge from the nose.

Very typical alterations of the mucous membranes of the mouth and soft palate occur. One or two days before the outbreak of rash on the skin red irregular spots varying in size from the head of a pin to a lentil can be seen on the mucosa of the soft, and in part of the hard, palate. This eruption, known as enanthema, is an important early diagnostic sign of measles. Fusing in one or two days, these spots become indistinguishable against the general background of hyperaemic mucosa.

The eruptive stage begins with a new rise of temperature, which reaches its maximum on the second or third day, and falls to the normal in a short irregular lysis towards the fifth to seventh day of eruption.

The appearance of the rash coincides with the rise of temperature. Its first elements are found behind the ears and in the centre of the face. Within 24 hours it spreads rapidly over the whole face, neck, and upper part of the chest; it also covers the skin of the circumoral region. On the second day the exanthema rapidly spreads over the trunk and the proximal parts of the extremities and on the third day covers the limbs. This order of succession in the spread of the eruption is typical of measles. Outbreak of the rash may, however, sometimes be accelerated or retarded, or may appear first on the trunk.

At first the elements of the rash look like pink papules of a soft consistency, the size of a grain of millet or buckwheat. Within a few hours each papule becomes surrounded by a zone of bright erythema. Soon adjacent maculopapules become confluent, forming large blotches of irregular outline, with the initial papules in the centre. Large maculopapular elements have a tendency to fuse further. The unaffected pale areas of the skin show up distinctly against the background of the bright rash.

Elements of the rash 'effloresce' for three days; from the fourth day they begin to fade in order of their appearance. Quite often the rash on the face loses its brightness on the third day when it appears on the extremities. The subsiding rash becomes less prominent and assumes a cyanotic tinge; its elements, gradually fading, leave spots of a light-brown pigmentation which persists for one or two weeks. Fine branny desquamation (on the face and trunk) sometimes is following the subsidence of eruption lasts around five to seven days.

The general malaise and symptoms of functional disturbance of the central nervous system first seen-during the catarrhal stage progress during the eruptive stage. General inhibition and adynamia are observed; headache becomes worse; there is loss of appetite. Sleep is disturbed and the child is sometimes restless and delirious during the night. The catarrh of the mucosa of the respiratory passages and conjunctiva (running nose, cough, suffused eyes, and intolerance of light) becomes more pronounced.

At the end of the incubation period the blood picture shows mild leucocytosis and netrophilosis, at the end of the catarrhal stage leucopenia and neutropenia, and at the eruptive stage leucopenia, often with a relative neutropnilosis, eosinopenia and thrombopenia.

During convalescence, even when all clinical manifestations of the disease have already subsided, the restorative process is far from completed. The indices of general immunological reactivity have fallen sharply.

Lymph nodes at the angle of the jaw and in the posterior cervical region are usually enlarged, and slight splenomegaly may be noted. Mesenteric lymphadenopathy may cause abdominal pain. Characteristic pathologic changes of measles in the mucosa of the appendix may cause obliteration of the lumen and symptoms of appendicitis. Changes of this type tend to subside with the disappearance of Koplik spots. Otitis media, bronchopneumonia, and gastrointestinal symptoms, such as diarrhea and vomiting, are more common in infants and small children (especially malnourished ones) than in older children.

Clinical Forms. Mild, moderately severe, and severe forms of measles are distinguished, according to its severity. Atypical forms (measles with a toxic, abortive, or rudimentary course) are also encountered.

The severe form has marked symptoms of toxaemia (hyperthermia, affection of the nervous system with disturbances of consciousness, adynamia, and acute cardiovascular failure). In the hemorrhagic type of measles (black measles), bleeding may occur from the mouth, nose, or bowel

An abortive or rudimentary form of measles is encountered quite rarely among the unimmunized.

Measles sometimes runs an atypical (but not mitigated) course in children treated with antibiotics.

In children subjected to serum prophylactic|immunization mitigated (attenuated) measles is observed, in which the incubation period is protracted to a maximum of 21 days, but the initial and eruptive periods are shortened. Catarrhal symptoms in the mucous membrane are usually mild or absent; and the enanthema and Belsky-Filatov-Koplik spots may also not appear. Rash is usually sparse or even represented by a few elements. Temperature is sometimes only subfebrile and lasts for two or three days. The patient's general condition is usually not disturbed, or only slightly affected. In mild cases the rash may be less macular and more nearly pinpoint, somewhat resembling that of scarlet fever or rubella.

The diagnosis. The diagnosisof measles is frequently delayed in adults because practitioners providing health care for adults are not used to encountering the disease and rarely include it in the differential diagnosis.Diagnosis is based on the clinical symptoms, with due account of the epidemiological anamnesis laboratory confirmation is rarely needed. This is usually made from the typical clinical picture; laboratory confirmation is rarely needed. During the prodromal stage multinucleated giant cells can be demonstrated in smears of the nasal mucosa. Virus can be isolated in tissue culture, and diagnostic rises in antibody titer can be detected between acute and convalescent sera. The white blood cell count tends to be low with a relative lymphocytosis. Lumbar puncture in patients with measles encephalitis usually shows an increase in protein and a small increase in lymphocytes. The glucose level is normal. In the catarrhal stage diagnosis of measles must rest on the presence of the typical complex of catarrhal symptoms. An important early diagnostic symptom is spotty enanthema on the palatal mucosa. The finding of Belsky-Filatov-Koplik spots is indisputable evidence of measles.

The catarrhal stage of measles can simulate influenza and other respiratory viral infections. When measles is suspected the patient should be isolated and observed for a day or two until diagnosis is clarified by the appearance of typical symptoms.

During the eruptive stage there are usually no difficulties in recognizing measles, and errors can only occur when its course is atypical.

In developing countries and in recent outbreaks in the United States, measles frequently occurs in infants younger than 1 yr, possibly because malnutrition is concomitant there, the disease is very severe and has a high mortality.

Differential diagnosis. The rash of rubeola must be differentiated from exanthem subitum, rubella, infections resulting from echovirus, coxsackie virus, and adenovirus, infectious mononucleosis, toxoplasmosis, meningococcemia, scarlet fever, rickettsial diseases, serum sickness, Kawasaki disease, and drug rashes.

Koplik spots are pathognomonic for rubeola, and the diagnosis of unmodified measles should not be made in the absence of cough.

Roseola infantum (exanthem subitum) is distinguished from measles in that the rash of the former appears as the fever disappears. The rashes of rubella and of enteroviral infections tend to be less striking than that of measles, as do the degree of fever and severity of illness. Although cough is present in many rickettsial infections, the rash usually spares the face, which is characteristically involved in measles. The absence of cough or the history of injection of serum or administration of a drug usually serves to identify serum sickness or drug rashes. Meningococcemia may be accompanied by a rash that is somewhat similar to that of measles, but cough and conjunctivitis are usually absent. In acute meningococcemia the rash is characteristically petechial purpuric. The diffuse, finely papular rash of scarlet fever with a "goose flesh" texture on an erythematous base is relatively easy to differentiate.

The milder rash and clinical picture of measles modified by gamma globulin or by partial immunity induced by measles vaccine, or in infants by maternal antibody, may be difficult to differentiate.

Complications. The chief complications of measles are otitis media, pneumonia, and encephalitis. Noma of the cheeks may occur in rare instances. Gangrene elsewhere appears to be secondary to purpura fulminans or disseminated intravascular coagulation following measles.

Pneumonia may be caused by the measles virus itself; the lesion is interstitial. Measles pneumonia in patients with HIV infection is often fatal and not always accompanied by rash. Bronchopneumonia is more frequent, however; it is due to secondarily invading bacteria, particularly the pneumococcus, streptococcus, staphylococcus, and Haemophilus influenzae. Laryngitis, tracheitis, and bronchitis are common and may be due to the virus alone.

One of the potential dangers of measles is exacerbation of an existing tuberculous process. There may also be a temporary loss of hypersensitivity to tuberculin.

Myocarditis is an infrequent serious complication; transient electrocardiographic changes are said to be relatively common.

Neurologic complications are more common in measles than in any of the other exanthems. The incidence of encephalomyelitis is estimated to be 1-2/1,000 reported cases of measles. There is no correlation between the severity of the measles and that of the neurologic involvement or between the severity of the initial encephalitic process and the prognosis. Rarely, encephalitis has been reported in association with measles modified by gamma globulin or by live attenuated measles virus vaccine. Infrequently, encephalitic involvement is manifest in the pre-eruptive period, but more often the onset occurs 2-5 days after the appearance of the rash. The cause of measles encephalitis remains controversial. It is suggested that when encephalitis occurs early in the course of the disease, viral invasion plays a large role, although measles virus has rarely been isolated from brain tissue; encephalitis that occurs later is predominantly demyelinating and may reflect an immunologic reaction. In this demyelinating type the symptoms and course do not differ from those of other parainfectious en-

cephalitides. Fatal encephalitis has occurred in children receiving immunosuppressive treatment for malignancies. Other central nervous system complications, such as Guillain-Barrй{acute-e} syndrome, hemiplegia, cerebral thrombophlebitis, and retrobulbar neuritis, are rare.

Subacute sclerosing panencephalitis is due to measles virus.

Prognosis. Case fatality rates in the United States have decreased in recent years to low levels for all age groups, largely because of improved socioeconomic conditions but also because of effective antibacterial therapy for the treatment of secondary infections.

When measles is introduced into a highly susceptible population, the results may be disastrous. Such an occurrence in the Faroe Islands in 1846 resulted in the deaths of about one fourth, nearly 2,000, of the total population regardless of age.

Treatment. Sedatives, antipyretics for high fever, bed rest, and an adequate fluid intake may be indicated. Humidification of the room may be necessary for laryngitis or an excessively irritating cough, and it is best to keep the room comfortably warm rather than cool. The patient should be protected from being exposed to strong light during the period of photophobia. The complications of otitis media and pneumonia require appropriate antimicrobial therapy.

With complications such as encephalitis, subacute sclerosing panencephalitis, giant cell pneumonia, and disseminated intravascular coagulation, each case must be assessed individually. Good supportive care is essential. Gamma globulin, hyperimmune gamma globulin, and steroids are of limited value. Currently available antiviral compounds are not effective. Treatment with oral vitamin A (400,000 IU) reduces morbidity and mortality in children with severe measles in the developing world.

Prophylaxis. Quarantine is of little value because of the contagiousness during its prodromal stage, when measles may not be suspected.

Active Immunization. The initial measles immunization may be given at 12 to 15 mo but may be given earlier in areas where disease is occurring. Because the seroconversion rate following immunization is not 100 % and there may be some waning of immunity with time, a second immunization against measles, usually given as measles-mumps-rubella (MMR), is indicated. This dose can be given when the child enters school or later on entry to middle school. Adolescents entering college should also have received a second measles immunization.

The response to live measles vaccine is unpredictable if immune globulin has been administered in the 3 mo preceding immunization. Anergy to tuberculin may develop and persist for 1 mo or longer after administration of live, attenuated measles vaccine. A child with active tuberculous infection should be receiving antituberculosis treatment when live measles vaccine is administered. A tuberculin test prior to or concurrent with active immunization against measles is desirable.

Use of live measles vaccine is not recommended for pregnant women or for children with untreated tuberculosis. Live vaccine is contraindicated in children with leukemia and in those receiving immunosuppressive drugs because of the risk of persistent, progressive infection such as giant cell pneumonia. After exposure of these sus-

ceptible children to measles, measles immune globulin (human) should be given intramuscularly in a dose of 0.25 mL/kg as soon as possible. A larger dose may be advisable in children with acute leukemia, even those in remission. Children with HIV infection should receive measles vaccine because mortality from measles is high in this group and they tolerate the vaccine well. Despite a history of having received measles immunization, these children should receive gamma globulin after exposure to measles in a dose of 0.5 mL/kg (maximum 15 mL). This is twice the usual recommended dose. Measles vaccine can be given following exposure to the disease. Reactions are not increased, and measles may be prevented. The use of inactivated (killed) virus vaccine is not recommended.

Passive Immunization. Passive immunization with pooled adult serum, pooled convalescent serum, placental globulin, or gamma globulin of pooled plasma is effective for prevention and attenuation of measles. Measles can be prevented by using immune serum globulin (gamma globulin) in a dose of 0.25 mL/kg given intramuscularly within 5 days after exposure but preferably as soon as possible. Complete protection is indicated for infants, for children with chronic illness, and for contacts in hospital wards and children's institutions. Attenuation may be accomplished by the use of gamma globulin in a dosage of 0.05 mL/kg. Gamma globulin is approximately 25 times as potent in antibody titer as pooled adult serum, and it avoids the risk of hepatitis. Attenuation is variable, and the modified clinical patterns may vary from those with few or no symptoms to those with little or no modification. Encephalitis may follow measles modified by gamma globulin.

After the 7th-8th day of incubation the amounts of antibody administered must be increased greatly for any degree of protection. If the injection is delayed until the 9th, 10th, or 11th day, slight fever may already have started and only slight modification of the disease may be expected.

Rubella

Rubella is a common communicable disease of childhood characterized ordinarily by mild constitutional symptoms, a rash similar to that of mild rubeola or scarlet fever, and enlargement and tenderness of the postoccipital, retroauricular, and posterior cervical lymph nodes. In older children and adults, especially adult women, the infection may occasionally be severe, with manifestations such as joint involvement and purpura.

Rubella in early pregnancy may cause severe congenital anomalies. The congenital rubella syndrome is an active contagious disease with multisystem involvement, a wide spectrum of clinical expression, and a long postnatal period of active infection with shedding of virus.

Etiology. Rubella is caused by a pleomorphic, RNA-containing virus currently listed in the family Togaviridae, genus Rubivirus. The virus is usually isolated in tissue culture, and its presence is demonstrated by the ability of rubella-infected African green monkey kidney (AGMK) cells to resist challenge with enterovirus. During clinical illness the virus is present in nasopharyngeal secretions, blood, feces, and

urine. Virus has been recovered from the nasopharynx 7 days before exanthem and 7–8 days after its disappearance. Patients with subclinical disease are also infectious.

Epidemiology. Humans are the only natural host of rubella virus, which is spread by oral droplet or transplacentally through congenital infection. Prior to institution of the rubella vaccine program in 1969, the peak incidence of the disease was in children 5–14 yr of age. Now most cases occur in susceptible teenagers and young adults. Large outbreaks have been reported among college students and in unvaccinated populations, such as Amish communities. Hospital epidemics among employees, with transmission to susceptible patients, have prompted hospitals to require that employees having contact with patients be immune to rubella. Health care personnel in physicians' offices should also be screened for rubella antibody and, if necessary, immunized. Maternal antibody is protective for the first 6 mo of life. Boys and girls are equally affected. In closed populations, such as institutions and military barracks, almost 100 % of susceptible individuals may become infected. In family settings the spread of the virus is less: 50–60 % of susceptible family members acquire the disease. Many infections are subclinical, with a ratio of 2:1 inapparent to overt disease. Rubella usually occurs during the spring. It can be difficult to diagnose clinically because enteroviral and other rashes may produce a similar appearance. A single attack usually confers permanent immunity. Epidemics occurred every 6–9 yr before vaccine was available. Serologic studies prior to the use of rubella vaccine showed that about 80 % of adult populations in the United States and other continents had antibody to rubella. In island populations, such as those of Trinidad and Hawaii, only 20 % of adults screened had detectable antibody.

The epidemiology of the congenital rubella syndrome is discussed in Chapters 96 and 97. Infants with rubella are a source of infection for older children who are not immune and for nonimmune adults, including pregnant women and nursery personnel.

Clinical manifestations. The incubation period is 14–21 days. The prodromal phase of mild catarrhal symptoms is shorter than that of measles and may be so mild as to go unnoticed. The most characteristic sign is retroauricular, posterior cervical, and postoccipital adenopathy. No other disease causes the tender enlargement of these nodes to the extent that rubella does. An enanthem may appear just before the onset of the skin rash. It consists of discrete rose spots on the soft palate that may coalesce into a red blush and extend over the fauces.

Lymphadenopathy is evident at least 24 hr before the rash appears and may remain for 1 wk or more. The exanthem is more variable than that of rubeola. It begins on the face and spreads quickly. Its evolution is so rapid that the rash may be fading on the face by the time it appears on the trunk. Discrete maculopapules are present in large numbers; there are also large areas of flushing which spread rapidly over the entire body, usually within 24 hr. The rash may be confluent, particularly on the face. During the 2nd day the rash may assume a pinpoint appearance, especially over the trunk, resembling that of scarlet fever. Mild itching may occur. The eruption usually

clears by the 3rd day. Desquamation is minimal. Rubella without a rash has been described.

The pharyngeal mucosa and the conjunctivae are slightly inflamed. In contrast to rubeola, there is no photophobia. Fever is slight or absent during the rash and persists for 1, 2, or occasionally 3 days. The temperature seldom exceeds 38.4C. Anorexia, headache, and malaise are not common. The spleen is often slightly enlarged. The white blood cell count is normal or slightly reduced; thrombocytopenia is rare, with or without purpura. Especially in older girls and women, polyarthritis may occur with arthralgia, swelling, tenderness, and effusion but usually without any residuum. Any joint may be involved, but the small joints of the hands are affected most frequently. The duration is usually several days to 2 wk; rarely it persists for months. Paresthesia also has been reported. In one epidemic, orchidalgia was reported in about 8 % of infected college-aged males.

Differential diagnosis. Because similar symptoms and rashes can occur with many other viral infections, rubella is a difficult disease to diagnose clinically except when the patient is seen during an epidemic. A history of having had rubella or rubella vaccine is unreliable; immunity should be determined by testing for antibodies. Particularly in its more severe forms, rubella may be confused with the mild types of scarlet fever and rubeola. Roseola infantum (exanthem subitum) is distinguished from rubella by the severity of the fever and by the appearance of the rash at the end of the febrile episode rather than at the height of the signs and symptoms. Drug rashes may be extremely difficult to differentiate from rubella. The characteristic enlargement of the lymph nodes strongly supports a diagnosis of rubella. In infectious mononucleosis a rash may occur that resembles that of rubella, and enlargement of the lymph nodes in each disease may lead to confusion. The hematologic findings in infectious mononucleosis should be sufficient to distinguish the two diseases. Enteroviral infections accompanied by a rash can be differentiated in some instances by respiratory or gastrointestinal manifestations and the absence of retroauricular adenopathy.

Diagnostic tests include isolation of virus from various tissues and serologic tests. Hemagglutination-inhibition (HI) antibody has been the usual method of determining immunity to rubella. Several newer tests including latex agglutination, enzyme immunoassay, passive hemagglutination, and fluorescent immunoassay appear to be equal or superior to the HI test in sensitivity. Rubella-specific immunoglobulin (Ig) M can be present in the blood of affected newborn infants.

Complications and prognosis. Complications are relatively uncommon in childhood. Neuritis and arthritis occur occasionally. Resistance to secondary bacterial infection is not altered significantly. Encephalitis similar to that seen with rubeola occurs in about 1/6,000 cases. The prognosis of childhood rubella is good; that of congenital rubella varies with the severity of the infection. Only about 30 % of infants with encephalitis appear to escape residual neuromotor deficits, including an autistic syndrome.

Prevention. In a susceptible person, passive protection from or attenuation of the disease may be variably afforded by intramuscular injection of immune serum globulin (ISG) given in large dosage (0.25–0.50 mL/kg or 0.12–0.20 mL/lb) within the first 7–8 days after

exposure. The effectiveness of immune globulin is not predictable. It apparently depends upon the antibody content of the product used and upon unknown factors. The value of ISG has been questioned also because in some instances rash was prevented and clinical manifestations were absent or minimal though viable virus was demonstrable in the blood. This form of prevention of rubella is not indicated, except in nonimmune pregnant women.

Since 1979 live-virus vaccine RA 27/3 (human embryonic lung fibroblasts of the WI-38 line) has been used exclusively for active immunization against rubella in the United States. RA 27/3 vaccine has many advantages over other rubella vaccines used in the past because it produces nasopharyngeal antibody and a wide variety of serum antibodies, provides better protection against reinfection, and more closely resembles the protection provided by natural infection. The vaccine virus is heat and light sensitive; therefore, the vaccine should be stored in the refrigerator at 4 C and used as soon as it is reconstituted. Vaccine is administered as a single subcutaneous injection.

Antibody develops in about 98 % of those vaccinated. Although virus may persist, especially in the nasopharynx, and shedding occurs from 18–25 days after vaccination, communicability does not appear to be a problem.

The duration of persistence of rubella antibody following vaccination with RA 27/3 is uncertain but is probably lifelong. Preventive measures are of the greatest importance for the protection of the fetus. It is especially important that girls have immunity to rubella before reaching child-bearing age, either by contracting the natural disease or by active immunization. The immune status can be evaluated by appropriate serologic tests.

The rubella vaccine program in the United States calls for immunization of all boys and girls between the ages of 12 and 15 mo and puberty and of nonpregnant postpubertal females. Immunization is effective at 12 mo of age but may be delayed until 15 mo and given as measles-mump-rubella (MMR) vaccine. Rubella immunization should be offered to potentially susceptible postpubertal women at any health care visit. For women who say they might be pregnant immunization should be deferred. Pregnancy testing is not routinely necessary, but counseling about the advisability of avoiding pregnancy for 3 mo after immunization should be provided. The current immunization policy has successfully interrupted the usual epidemic cycle of rubella in the United States and decreased the reported incidence of congenital rubella syndrome to only 20 cases in 1994. However, it has not resulted in a decrease in the percentage of women of child-bearing age who are susceptible to rubella.

Pregnant women should not be given live rubella virus vaccine, but inadvertent immunization should not ordinarily be a reason to interrupt the pregnancy. The infants of more than 200 women immunized during pregnancy with RA 27/3 vaccine have been studied; no cases of clinically evident congenital rubella syndrome were found to occur. Other contraindications include immune deficiency states, severe febrile illness, hypersensitivity to vaccine components, and therapy with antimetabolites, corticosteroids, and steroid-like substances.

Clinical manifestations that may follow rubella immunization include fever, typical lymphadenopathy, rash, and arthritis and arthralgia. The last two occur more frequently in older girls

and adult women and may last for weeks. Two unusual syndromes have been reported in association with rubella vaccine: one with paresthesia of the hand or arm that occurs at night lasts for up to 1 hr and may recur frequently during the night; the other is manifested by pain behind the knee and limitation of motion. Symptoms are worst in the morning, diminishing during the day. They may last for up to 5 wk. Both syndromes may recur.

Management of Pregnant Women Exposed to or Acquiring Rubella. Pregnant women, especially early in pregnancy but also during the entire gestational period, should avoid exposure to rubella regardless of history of the disease during childhood or of history of active immunization. Exposure of pregnant women to infants with congenital rubella syndrome should be especially guarded against because of prolonged shedding of virus. Risk of damage to the fetus decreases after the 14th wk of gestation.

Because approximately 80 % of women of child-bearing age are immune to rubella as a result of the natural infection or of immunization, the immune status to rubella of women who may become pregnant should be determined.

If a pregnant woman whose immune status is unknown is exposed to rubella, an antibody test should be performed immediately as an emergency measure. If determined to be immune, she can be reassured that the pregnancy can be continued without added risk. If she is found to be susceptible and therapeutic abortion is unacceptable or unavailable to her, passive immunization with ISG, 20–30 mL intramuscularly, should be attempted immediately. Active immunization of pregnant women is not advised.

If exposure to rubella occurs in a susceptible pregnant woman to whom abortion is available and desirable because of significant potential hazard to the fetus, it is probably advisable to withhold ISG, observe her carefully, and repeat the rubella antibody test. If rubella then develops at a stage of pregnancy at which she feels the risk is greater than she wants to assume or if serial antibody tests show that subclinical infection has occurred, abortion may be induced.

Reinfection. The incidence of reinfection on exposure of individuals who are serologically immune to wild virus is 3–10 % among those demonstrating serologic immunity without a history of immunization and 14–18 % among those immunized with RA 27/3 vaccine. Infection has been demonstrated among the fetuses of reinfected pregnant women as well as among pregnant women who had received rubella vaccine. The relevance of reinfection of serologically immune pregnant women to the production of congenital malformations remains to be determined. Until these questions are answered, all pregnant women should make every effort to avoid exposure to rubella.

Treatment. Unless bacterial complications occur, treatment is symptomatic. Adamantanamine hydrochloride (amantadine) has been reported to be effective in vitro in inhibiting early stages of rubella infection in cultured cells. An attempt to treat a child having congenital rubella with this drug was unsuccessful. Because amantadine is not recommended for pregnant women, its usefulness is very limited. Interferon and isoprinosine have been used with limited success.

PART 6 **EXANTHEMAS (scarlet fever, pseudtuberculosis)**

Streptococci are among the most common causes of bacterial infection in infancy and childhood. Infection during the first 3 mo of life with group B b{beta}-hemolytic streptococci is common and may present as bacteremia, meningitis, osteomyelitis, or septic arthritis.

Etiology. Streptococci are gram-positive cocci that grow in pairs or variable length chains, classified on the basis of their ability to hemolyze red blood cells: those with hemolysins producing complete hemolysis (b{beta}-hemolytic), those producing partial hemolysis (α {alpha}-hemolytic), and those producing no hemolysis (g{gamma}-hemolytic). α{alpha}-Hemolysis produces a green color on sheep erythrocytes (viridans group).

Lancefield further separated the streptococci on the basis of differences in carbohydrate components (C-carbohydrate) within the cell wall; streptococcal groups A through H and K through V have been identified so far. important is M protein Group A b{beta}-hemolytic streptococci can be divided into more than 80 immunologically distinct types that are based on differences in the M protein.

Streptococci elaborate toxins, enzymes, and hemolysins. More than 20 extracellular antigens released by group A hemolytic streptococci growing in human tissues have been identified. The extracellular products of greatest clinical significance are pyrogenic (formerly erythrogenic) exotoxins (A, B, and C), streptolysin O, streptolysin S, NADase, streptokinases, DNase, hyaluronidase, proteinase, amylase, and esterase. Pyogenic exotoxins are responsible for the rash of scarlet fever and for shock in toxic shocklike illness. Generally, the elaboration of pyogenic exotoxins depends on bacteriophage infection (lysogeny) of the streptococcus. Extracellular digestive enzymes liquefy pus and, together with hyaluronidase, facilitate rapid spreading of streptococci through tissue planes. The proteinase, in particular, is associated with tissue destruction of severe invasive streptococcal disease. Antibodies to streptolysin O (ASO), DNase B, hyaluronidase, NADase, and streptokinase are useful in the serodiagnosis of group A streptococcal disease. M-type specific antibodies are detectable 4-8 wk after infection; antibiotic therapy ablates this response.

Epidemiology. Generally, incidence is lowest among infants, who may be protected by transplacental acquisition of type-specific antibodies and a lack of pharyngeal receptors for streptococcal binding. Streptococcal infection of the skin is most common in children younger than 6 yr; streptococcal pharyngitis is most common between 5 and 15 yr of age. Streptococcal disease, including scarlet fever, is uncommon in children less than 3 yr of age, The incidence of streptococcal pharyngitis is higher in temperate climates; incidence and severity appear to increase in cold weather. Streptococcal skin disease is more prevalent in tropical climates and in warmer weather in temperate climates.

Group A b{beta}-hemolytic streptococci are spread from person to person. Infection may be spread by droplets; nasal and pharyngeal carriers are effective disseminators. Infection also may be spread by contact with skin lesions or transmitted by food, milk, and water. The sources of infection in scarlet fever are patients and carriers. The

patient is infective from the first hours of the disease. The most important forms in the epidemiology of scarlet fever are the so-called formes frustes, healthy carriers. These forms often escape diagnosis; the patients are not isolated and therefore serve as sources of infection. The main way of transmission is aerial-droplet. Infection can also occur through infected articles, or through an intermediary. The last depends on the known stability of the causative agent, i.e. on its ability to removable for some time.

Susceptibility. The portal of entry of scarlet-fever infection is i the mucous^membranes of the fauces and pharynx, and the primary |focus of infection develops there; but the causative agent can some-times penetrate the organism through damaged is kin or the mucous / membrane of the genital organs (the extrabuccal or extrapharyngeal form).

Susceptibility to scarlet fever varies considerably with age. Children between two and six or seven years of age are mostly affected; the disease is rare among adolescents over 15 and in adults. The well known, almost absolute immunity of babies under three months to scarlet fever cannot be explained by specific immunity acquired through mother's placenta. Even being in a constant and close contact with the nursing mother with scarlatina, infants of this age do not develop scarlet fever, thus showing complete insusceptibility to this disease, which is probably the result of the specific reactivity of the neonates.

Pathogenesis. After inhalation or ingestion, streptococci attach themselves to respiratory epithelial cells by their surface fibrils and cell wall lipoteichoic acid. Fibrils contain antiphagocytic epitopes of type-specific M proteins, which with capsular hyaluronic acid resist phagocytosis. Extracellular digestive enzymes facilitate the spread of infection by interfering with local thrombosis (streptolysins) and pus formation (DNase) and enhancing connective tissue digestion (hyaluronidase, proteinase). Suppurative complications follow local inflammation (peritonsillar abscess, retropharyngeal abscess), direct extension (otitis media, sinusitis), lymphangitic spread (lymphadenitis), or bacteremia (sepsis, osteomyelitis, pneumonia).

According to A. Koltypin, three principal components can be schematically distinguished in the pathogenesis of scarlet fever: toxic, infectious (septic), and allergic. They are closely interrelated, their distinction is, of course, rather artificial, and they are manifested in a different degree. In some cases toxic phenomena, and in others septic, predominate; in some cases there may be allergic waves and in others none.

The toxaemia caused by the scarlatinal toxin is expressed by a complex of characteristic symptoms (central and vegetative disorders, hyperthermia, exanthema, and cardiovascular disturbances).

The action of the streptococcus itself is thought to condition the development of the infectious (septic) component of scarlet fever, which is expressed in an inflammatory-necrotic process at the portal of entry, a septic condition, and complications of a septic order (purulent lymphadenitis, purulent otitis, sinusitis, septic metastases, etc.).

Given preliminary sensitization of the organism, signs of allergy begin to develop from the very onset of the disease. Moreover, sensitization during the first stage resulting from the action of various allergens (streptococci and their breakdown products)

creates favourable conditions for the development of late complications if there is re-infection.

Clinical manifestations.The most common infections caused by group A b{beta}-hemolytic streptococci involve the respiratory tract, skin, soft tissues, and blood.

Scarlet Fever is the result of infection by streptococci that elaborate one of three pyrogenic (erythrogenic) exotoxins. The incubation period ranges from 1–7 days, with an average of 3 days. The onset is acute and is characterized by fever, vomiting, headache, toxicity, pharyngitis, and chills. Within 12-48 hr the typical rash appears.

Generally, temperature increases abruptly and may peak at 39.6on the 2nd day and gradually returns to normal within 5-7 days in the untreated patient; it is usually normal within 12-24 hr after initiation of penicillin therapy. The tonsils are hyperemic and edematous and may be covered with a gray-white exudate. The pharynx is inflamed and covered by a membrane in severe cases. The tongue may be edematous and reddened. During the early days of illness the dorsum of the tongue has a white coat through which the red and edematous papillae project (i.e., white strawberry tongue). After several days the white coat desquamates; the red tongue studded with prominent papillae persists (i.e., red strawberry tongue, raspberry tongue). The palate and uvula may be edematous, reddened, and covered with petechiae.

The exanthem is red, is punctate or finely papular, and blanches on pressure. In some individuals, it may be palpated more readily than it is seen, having the texture of gooseflesh or coarse sandpaper. The rash appears initially in the axillae, groin, and neck but within 24 hr becomes generalized. Punctate lesions generally are not present on the face. The forehead and cheeks appear flushed, and the area around the mouth is pale (i.e., circumoral pallor). The rash is most intense in the axillae and groin and at pressure sites. Petechiae may occur owing to capillary fragility. Areas of hyperpigmentation that do not blanch with pressure may appear in the deep creases, particularly in the antecubital fossae (i.e., pastia lines). In severe disease, small vesicular lesions (miliary sudamina) may appear over the abdomen, hands, and feet.

Desquamation begins on the face in fine flakes toward the end of the 1st wk and proceeds over the trunk and finally to the hands and feet. The duration and extent of desquamation vary with the intensity of the rash; it may continue for as long as 6 wk.

Scarlet fever may follow infection of wounds (i.e., surgical scarlet fever), burns, or streptococcal skin infection. Clinical manifestations are similar to those just described, but the tonsils and pharynx generally are not involved. A similar picture may be observed with certain strains of staphylococci that produce an exfoliative toxin.

Clinical Forms. The clinical picture of scarlet fever varies considerably in severity and in the character of its symptoms. Along with very mild rudimentary cases, hypertoxic forms with a fulminant course are encountered. But apart from these extreme forms, there are many-clinical variants. A number of authors (V. Molchanov, A. Koltypin, M. Danilevich) distinguish the following forms of scarlet fever, according to the severity of its course: mild, moderately severe, and severe. Depending on the predominance of toxic or septic phenom-

ena, the severe form is distinguished as toxic or septic. If both components are present, the scarlet fever is defined as mixed or toxicoseptic. In addition to the principal forms, there are also atypical ones: hypertoxic, abortive, and extrapharyngeal (extrabuccal). In mild scarlet fever the toxaemia is weak. The temperature is within the range of 38-38.5°C. The patients' general condition is little disturbed. There may sometimes be no vomiting at the onset. The angina has a catarrhal character. Rash is typical, but sometimes pale and sparse. Fever and all acute manifestations disappear toward the fourth or fifth day. This is the commonest form of scarlet fever, which lately occurs in 80 or even 90 per cent of cases revealed. Complications are rare, but are possible, mainly during the second period (lymphadenitis, otitis, nephritis). Moderately severe scarlet fever has an acute onset, with a complete set of symptoms. Toxaemia is marked; the temperature rises to 39°C, and even to 40°C on individual days. There are headache, lassitude, malaise, and sometimes delirium at night. Vomiting is frequent during the first days and may recur. Tachycardia: pulse rate is up to 140-160 per min. There is no depression of cardiac activity. Angina is catarrhal and there are sometimes films on lacunae and slight necroses. The rash is bright and abundant. The onset of the severe toxic form is violent. It is characterized by repeated vomiting, which may continue during the second and third day. Diarrhoea is not infrequent. Fever is high, up to 40-41°C. The patient is in a state of strong excitation or, on the contrary, of depression. Consciousness is clouded, and there is delirium; there may be convulsions and meningeal symptoms. Rash is abundant and bright. The lips are dry, the sclera of the eyes injected, and the pupils contracted. In the severe septic form toxaemia is not of primary importance. The disease is chiefly characterized by severe lesions in the fauces (necrotic angina), an exceptionally marked inflammatory reaction in the regional lymph nodes and extremely frequent septic complications. Severe toxicoseptic scarlet fever has a combination of the symptoms of the two forms described above. It usually begins as a toxic form, but on the third to fifth day signs of a septic character aggravate it.. In the hypertoxic or fulminant form the symptoms of severe toxaemia described above progress with extreme rapidity; the patient lapses into a comatose state and dies in the first days, sometimes even during the first 24 hours.

A rare variety of toxic form—haemorrhagic scarlet fever—lias been described, in which severe nervous and cardiovascular phenomena are accompanied with extensive haemorrhages into the skin and mucous membranes. This form is usually fatal.

The rudimentary form is the mildest form of scarlet fever and lias very weakly expressed symptoms.

In extrabuccal or extrapharyngeal forms of scarlet fever the portal of entry of infection is not the fauces, but damaged skin or mucosa in various regions. The following variants can be distinguished according to the portal of entry and the mechanism of infection: (a) burn (in burns of the 2nd and 3rd degree); (b) wound, or traumatic; (c) surgical; (d) puerperal; (e) complicating various exposed purulent foci on the skin.

Diagnosis. Although 30 % of children with sore throat have a positive throat culture for group A streptococci,. Streptococcal pharyngitis is suggested by age greater than 5 yr, high fever, exudates, tender anterior cervical lymphadenopathy, scarlatiniform rash, and a history of exposure. A positive result for a throat culture may indicate streptococcal pharyngitis, but hemolytic streptococci are common inhabitants of the nasopharynx in well children. Isolation of a group A streptococcus from the pharynx of a child with pharyngeal infection does not necessarily indicate that the disease is caused by this organism. Treatment is, however, recommended for all children with pharyngitis and a positive throat culture or rapid antigen test for group A streptococci, even though in some cases the streptococci represent colonization.

The immunologic response of the host after exposure to streptococcal antigen can be assessed by measuring antistreptolysin O (ASO) titers. ASO titers may be very high in patients with rheumatic fever; in contrast, they are weakly positive or not elevated at all in patients with streptococcal pyoderma; responses in patients with glomerulonephritis are variable who develop an antibody response to this organism, indicating that subclinical infection. Anti-DNase (deoxyribonuclease) B provides the best serologic test for streptococcal pyoderma; responses to hyaluronidase, but antihyaluronidase (AH) titers are elevated with less regularity than are ASO titers.

Differential diagnosis. As a result of its deviations from the classic symptom complex, the clinical picture of scarlet fever can resemble other diseases accompanied with rash: viz. rubeola scarlatinosa, measles, German measles, the prodromal rash of chickenpox and smallpox, miliaria, drug and toxic eruptions (toxicodermia), pseudotuberculosis or Far-East scarlatina-like fever, etc.

Measles differs from scarlet fever in the presence of an initial catarrhal period with fever, catarrhal phenomena, enanthema, and Belsky-Filatov spots on the oral mucous membrane. The rash, which appears in stages, usually breaks out on the fourth day. Its elements are small at first, but later change to large maculopapules of irregular shape with a marked tendency to confluence. The skin between the individual elements remains unaffected. After fading of the rash a spotty pigmentation is apparent, followed by fine, branny desquamation. Leucopenia, neutropenia, eosinopenia, or aneosinophilia are revealed in the blood.

German measles (rubeola) are characterized by low fever in the absence of constitutional disturbances. Rash elements are small and pink, with only a slight tendency to fuse, and are localized chiefly on the trunk and the extensor surfaces of the limbs; the area around the mouth and nose is also affected. There are no petechial haemorrhages on the skin or subsequent desquamation. There is a swelling of the lymph nodes (micropolyadenitis), particularly of the occipital and posteriorly located cervical nodes. Blood findings are leucocytosis, neutropenia, and the presence of plasma cells.

Pseudotuberculosis.

Pseudotuberculosis - infection due to Y. pseudotuberculosis is most often seen as a Far-East scarlatina-like fever and pseudoappendicitis syndrome without diarrhea.

Far-East scarlatina-like fever. This is anthropozoonotic disease classified as yersiniasis caused by the pseudotuberculous microbe Yersinia pseudotuberculosis (V. Znamensky et all). Like scarlatina, it is characterized by an acute onset of the disease, elevated temperature (sometimes to 39-40°C) that persists for 3-5 days, fine (scarlatina-like) rash with subsequent peeling of the skin on the hands and soles. Vomiting occurs as well. Changes in the blood are the same: leucocytosis, neutrophilosis, insignificant eosinophilia. As distinct from scarlatina, true angina is absent, and only hyperaemia of the faucial mucosa occurs; the tonsils are unaffected. Almost all patients complain of pain in the joints and muscles of the extremities and in the lumbar region; gastrointestinal disorders are frequent, and some patients complain of acute pain in the iliac region (mesenteric adenitis).

The disease affects mostly adults. The diagnosis is verified by the agglutination test with the pseudotuberculosis bacillus; other laboratory tests, such as immunofluorescence and indirect haemagglutition tests are also recommended for differential diagnosis.

Pseudoappendicitis syndrome (mesenteric adenitis) Children usually present with fever and abdominal pain that is diffuse or localized to the right lower quadrant. Frequently, there is tenderness over the McBurney point and strong clinical suspicion of appendicitis. At surgery, the terminal ileum is thickened and shiny with enlarged mesenteric nodes, which may appear necrotic. The appendix is normal or only mildy inflammed. The pathology is similar to that described for Y. enterocolitica, with ileal and colonic mucosal ulceration and mesenteric adenitis. Necrotizing, epithelioid granulomas are seen in the mesenteric nodes. The appendix is frequently grossly and microscopically normal. Mesenteric nodes are frequently the only source of positive cultures. Y. pseudotuberculosis antigens bind directly to HLA class II molecules and function as superantigens, which may partly explain the clinical syndromes resembling Kawasaki syndrom.

Mesenteric adenitis should be suspected in children with unexplained fever and abdominal pain. A characteristic picture of enlarged mesenteric lymph nodes, thickening of the terminal ileum, and no image of the appendix may appear on ultrasound. Y. pseudotuberculosis is rarely isolated.

Appendicitis is the most common diagnosis. Inflammatory bowel disease and nonspecific intra-abdominal infections are also considered.

The disease affects mostly adults. The diagnosis is verified by the agglutination test with the pseudotuberculosis bacillus; other laboratory tests, such as immunofluorescence and indirect haemagglutition tests are also recommended for differential diagnosis.

Scarlet fever may be differentiated from Kawasaki disease by an older age at onset, absence of conjunctival involvement, and recovery of group A streptococci. Streptococcal toxic shock like syndrome, associated with the pyrogenic toxins, produces toxicity, fever, shock, tissue injury (necrotizing fasciitis, myositis), pneumonia, rash (local or diffuse erythema, maculopapular, petechial, desquamation), and multiorgan dysfunction (kidney,

lung, central nervous system). The shock, local tissue injury, older age, and nonscarlatiniform rash differentiate this syndrome from scarlet fever.

Arcanobacterium haemolyticum (formerly Corynebacterium haemolyticum) also produces tonsillitis, pharyngitis, and a scarlatiniform rash in adolescents and young adults.

Severe sunburn can also be confused with scarlet fever.

Acute pharyngitis or tonsilitis that is indistinguishable clinically from that caused by group A b{beta}-hemolytic streptococci may be caused by many viruses, including Epstein-Barr virus (infectious mononucleosis). A viral cause may be suggested by failure to isolate streptococci and can be identified specifically by viral culture and serologic studies. Infectious mononucleosis may be suggested by the clinical manifestations, the presence of atypical lymphocytes in the peripheral blood, and a rise in heterophil and Epstein-Barr viral antibody titers.

Acute pharyngitis similar to that caused by b{beta}-hemolytic streptococci may occur in patients with diphtheria, tularemia, toxoplasmosis, infection with Mycoplasma or A. haemolyticum, and, rarely, in individuals with tonsillar tuberculosis, salmonellosis, and brucellosis or infections caused by Neisseria gonorrhoeae, Neisseria meningitidis, and Yersinia enterocolitica. These diseases can be differentiated by appropriate cultures and serologic tests.

Patients with infectious mononucleosis, have pharyngitis, tonsilitis, rash, lymphadenopathy, and splenomegaly as well as atypical lymphocytes.

The exanthems produced by several enteroviruses can be confused with scarlet fever, but differentiation can be established by the course of the disease, the associated symptoms, and the results of culture. Roseola is characterized by the cessation of fever with the onset of rash and the transient nature of the exanthema.

Complications. Complications are very frequent and varied in scarlet fever, and are distinguished as early and late according to when they occur.

Early complications develop in the initial period of the disease, and are the result of the toxemia in streptococcal infection (otitis, Cervical lymphadenitis, mastoiditis, sinusitis, Adenophlegmon or hard phlegmon, pneumonia). Hematogenous dissemination of streptococci may cause meningitis, osteomyelitis, or septic arthritis.

Late complications are generally encountered during the third or fourth week, and are apparently allergic in origin; streptococci play an important role in most of them (nephritis, myocarditis, and synovitis, rheumatism - rheumatic polyarthritis, endocarditis).

Treatment. Diet. During the initial feverish period, when there are difficulty in swallowing, disturbance of metabolism, and reduced secretory function of the digestive glands, food should be fluid or semifluid, mainly carbohydrates with an adequate vitamin content, vitamin C in particular.

Antibacterial (antistreptococcal) therapy. Antibiotics markedly accelerate the removal of the streptococcus from the fauces, preclude complications.

The penicillin dose depends on the age of the patient and gravity of the disease; it varies from 50 000 to 100 000 U/kg a day (for 2-4 intakes). The treatment should continue for 7 -10 days. The goals of therapy are to decrease symptoms and prevent sep-

tic, suppurative, and nonsuppurative complications. Penicillin is the drug of choice for the treatment of streptococcal infections. All strains of group A b{beta}-hemolytic streptococci isolated to date have been sensitive to concentrations of penicillin achievable in vivo.

Children with streptococcal pharyngitis and tonsilitis should be treated with penicillin (125–250 mg/dose three times a day) for 10 days. satisfactory blood levels are achieved even when the stomach is not empty. A single intramuscular injection of a long-acting benzathine penicillin G (600,000 U for children <60 lb and 1,200,000 U for children >60 lb) may be more effective for treatment or prevention of relapse and is indicated for all noncompliant patients or those having nausea, vomiting, or diarrhea.

Erythromycin (40 mg/kg/24 hr), clindamycin (30 mg/kg/24 hr), or cefadroxil monohydrate (15 mg/kg/24 hr) may be used for treating streptococcal pharyngitis in patients who are allergic to penicillinr. Generally, relapse rates a e lower with regimens other than penicillin.

Treatment failure, defined as persistence of streptococci after a complete course of penicillin, occurs in 5–20 % of children and is more common with oral than with intramuscular therapy. It may be due to poor compliance, reinfection, the presence of b{beta}-lactamase–producing oral flora, tolerant streptococci, or presence of a carrier state. Persistent carriage of streptococci predisposes a small number of patients to symptomatic relapse

Intoxication should be controlled by intravenous administration of the Ringer solution, and a glucose solution.

Antiallergenic therapy are used. Corticosteroids (in combination with antibiotics) are recommended to treat grave toxic and toxicoseptic forms of scarlet fever. Prednisolone should be given in a dose of 1-1.2 mg/kg daily; the dose should be gradually decreased in 2-3 days. The treatment should continue for 5-7 days. Disintoxication therapy is also necessary: intravenous infusion of colloidal solutions (polyglucin, neocompensan), glucose solution with strophanthin and vitamins, and other measures. These methods should be used in various combinations depending on each particular case.

Prophylaxis. The isolation continues for at least ten days from the day of the onset of the disease, provided all signs of the acute period subside. Recovering children and adults who attend preschool children's institutions (and schoolchildren of the first two years) may be admitted to these institutions in 12 days after suspension of the isolation.

Treatment of contacts. When a patient is found to have scarlet fever all close contacts (members of the family and fellow-tenants) are given a thorough medical examination for abortive forms of the disease.

A quarantine of seven days from the moment of isolation of the patient is imposed on contacts who attend children's institutions or are in the first two years at school. Regular concurrent disinfection should be carried out in premises where a patient has been home-treated.

Management of carriers of group A b{beta}-hemolytic streptococci is controversial. It has been suggested that treatment of the carrier precludes the development of type-specific immunity, thereby leaving the individual susceptible to reinfection later in life. Children thought to have recurrent streptococcal infections may be carriers who have frequent viral respiratory infections masquerading as streptococcal infections. Treatment with a non-penicillin antibiotic (e.g., cephalosporin, erythromycin, clindamycin) may be useful in eradicating the carrier state but should be reserved for the rare problem case. No streptococcal vaccines are available for clinical use.

Prognosis.The prognosis for adequately treated streptococcal infections is excellent; most suppurative complications are prevented or readily treated. When therapy is provided promptly, nonsuppurative complications are prevented and complete recovery is the rule. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

PART 7 **EXANTHEMAS (chickenpox, herpes zoster virus, herpes simplex virus)**

Primary infection with varicella-zoster virus (VZV) causes varicella (chickenpox). The virus establishes latent infection in dorsal root ganglia; its reactivation causes herpes zoster (shingles).

Etiology. VZV is a human herpesvirus; it is classified as an alpha herpesvirus because of its similarities to the prototype for this group, which is herpes simplex virus (HSV). VZV is an enveloped, double-stranded DNA virus; the viral genome encodes more than 70 proteins, including proteins that are targets of immunity and a viral thymidine kinase, which makes the virus sensitive to inhibition by acyclovir and related antiviral agents.

Pathology. Varicella begins with mucosal inoculation of virus transferred in respiratory secretions or by direct contact with skin lesions of varicella or herpes zoster. Inoculation is followed by an incubation period of 10 -21 days, during which subclinical viral spread occurs. Widespread cutaneous lesions result when the infection enters a viremic phase; peripheral blood mononuclear cells carry infectious virus, generating new crops of vesicles for 3-7 days. VZV is also transported back to respiratory mucosal sites during the late incubation period, permitting spread to susceptible contacts before the appearance of rash he transmission of infectious virus by respiratory droplets distinguishes VZV from other human herpes viruses. Visceral dissemination of the virus follows the failure of host responses to terminate viremia, which results in infection of lungs, liver, brain, and other organs. VZV becomes latent in dorsal root ganglia cells in all individuals who experience primary infection. Its reactivation causes a localized vesicular rash that usually involves the dermatomal distribution of a single sensory nerve; necrotic changes are produced in the associated ganglia, sometimes extending into the posterior horn.

The histopathology of varicella and herpes zoster lesions is identical; infectious VZV is present in herpes zoster lesions, as it is in varicella lesions, but is not released into respiratory secretions. Varicella elicits humoral and cell-mediated immunity that is highly protective

against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk of VZV reactivation as herpes zoster.

Epidemiology. Annual varicella epidemics occur in winter and spring. Wild-type VZV strains that cause the annual epidemics of varicella do not exhibit changes in virulence as judged by the clinical severity of primary VZV infections from year to year. Household transmission rates are 80-90 %; more casual contact, such as school classroom exposure, is associated with attack rates of 30 % or less.

Varicella is contagious from 24–48 hr before the rash appears and while uncrusted vesicles are present, which is usually 3-7 days. Susceptible children acquire varicella after close, direct contact with adults who have herpes zoster; this route of transmission maintains the circulation of the virus in the population. For unexplained reasons, varicella is much less common in tropical areas, so that susceptibility rates among adults are as high as 20-30 %.

Herpes zoster shows no seasonal variation in incidence because it is due to the reactivation of endogenous, latent virus. Despite anecdotal reports, epidemiologic studies demonstrate that exposure to varicella does not cause herpes zoster.

Herpes zoster is very rare in children younger than 10 yr except among those given immunosuppressive therapy for malignancy or other diseases, those who have human immunodeficiency virus (HIV) infection, and those who have been infected in utero or during the first year of life. The risk of severe or life-threatening primary or recurrent VZV infection is related primarily to host factors rather than variations in the pathogenicity of VZV strains.

Clinical manifestations of varicella or chickenpox. Although the incubation period of varicella ranges from 10-21 days, the illness usually begins from 14-16 days after exposure. Almost all exposed, susceptible children experience a rash, but it may be limited to fewer than 10 lesions.

Prodromal symptoms are common, particularly in older children; fever, malaise, anorexia, headache, and occasionally mild abdominal pain occur 24–48 hr before the rash appears. Temperature elevation is usually moderate, but may be as high ; fever and other systemic symptoms persist during the first 2-4 days after the onset of the rash. Varicella lesions appear first on the scalp, face, or trunk.

The initial exanthem consists of intensely pruritic erythematous macules that evolve to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24–48 hr. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella.Ulcerative lesions involving the oropharynx and vagina are common; many children have vesicular lesions on the eyelids and conjunctivae, but serious ocular disease is rare.

The average number of varicella lesions is about 300, but healthy children may have from fewer than 10 to more than 1,500 lesions. In secondary household cases and cases involving older children, more days of new lesion formation and more lesions are likely. The exanthem is more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation of lesion sites persists for days to weeks in some children, but scarring is unusual.

The differential diagnosis of varicella includes vesicular rashes caused by other infectious agents, such as enterovirus or Staphylococcus aureus, drug reactions, contact dermatitis, and insect bites.

Complications of varicella. Secondary bacterial infections, usually resulting from S. aureus or Streptococcus pyogenes b-hemolytic streptococcus, are the most common complication of varicella. Cellulitis, lymphadenitis, and subcutaneous abscesses also occur. Varicella gangrenosa, usually resulting from S. pyogenes, is a rare but potentially life-threatening consequence of secondary infection. Acute bacterial sepsis is uncommon, but transient bacteremia may cause focal infections, including staphylococcal or streptococcal pneumonia, arthritis, or osteomyelitis. Encephalitis and cerebellar ataxia are well-described neurologic complications of varicella; the incidence of central nervous system morbidity is highest among patients younger than 5 yr and older than 20 yr. Meningoencephalitis is characterized by seizures, altered consciousness, and nuchal rigidity; patients with cerebellar ataxia have a more gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin from 2–6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. VZV-related encephalitis and cerebellar ataxia may be immune mediated; the severe hemorrhagic encephalitis caused by HSV is very rare in children with varicella. Clinical recovery is typically rapid, occurring within 24 - 72 hr, and is usually complete. Before the association of salicylates was documented, some children with varicella had neurologic symptoms caused by the encephalopathy associated with Reye syndrome. Varicella hepatitis is relatively common and is usually subclinical, but some children have severe vomiting, which must be differentiated from that associated with Reye syndrome. Acute thrombocytopenia, accompanied by petechiae, purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding, is a rare complication that is usually self-limited. Other rare complications of varicella include nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, and orchitis.

Progressive disease caused by primary VZV infection occurs in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborn infants. Varicella pneumonia is very rare in children, but this complication accounts for most of the increased morbidity and mortality in high-risk populations. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1–6 days (average, 3 days) after the onset of the rash. Hypoxemia is often much more severe than is suggested by the physical findings; the chest radiograph may be normal or may show diffuse bilateral infiltrates. Varicella pneumonia is often transient, resolving completely within 24–72 hr, but in severe cases, the interstitial pneumonitis progresses rapidly to cause respiratory failure. Hemorrhage into the cutaneous lesions is a sign of severe varicella in high-risk patients, as is severe abdominal or back pain, although its pathogenesis is uncertain.

The risk of progressive varicella is highest in children with malignancy if chemotherapy was given during the incubation period and the absolute lymphocyte count is less than 500 cells. In one large series, the mortality rate without antiviral therapy was

7 %, and all varicella-related deaths occurred within 3 days after the diagnosis of varicella pneumonia. Hepatitis, encephalitis, and disseminated intravascular coagulopathy are other frequent complications.

The syndrome of inappropriate antidiuretic hormone secretion may accompany disseminated varicella with or without clinical encephalitis. Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children on long-term, low-dose steroid therapy usually have no complications, but fatal varicella has occurred in patients receiving high-dose steroids. Untreated varicella is severe or fatal in children with congenital immunodeficiency disorders, especially involving cell-mediated immunity. Unusual clinical findings of varicella, including lesions that develop a unique hyperkeratotic appearance and chronic new lesion formation for weeks or months, have been described in children with HIV infection.

In rare instances, maternal varicella results in the congenital varicella syndrome, associated with unusual cutaneous defects, atrophy of an extremity, microcephaly, ocular defects, and damage to the autonomic nervous system. Infants who are born within 4 days after or 2 days before the onset of maternal varicella may acquire progressive varicella.

Clinical manifestations of herpes zoster. VZV reactivation is rare in childhood. When it occurs, it causes vesicular lesions clustered unilaterally in the dermatomal distribution of one or more adjacent sensory nerves, which are preceded or accompanied by localized pain, hyperesthesias, pruritus, and low-grade fever. The rash is mild, with new lesions appearing for a few days, symptoms of acute neuritis are minimal, and complete resolution usually occurs within 1–2 wk. Immunocompromised children have more severe dermatomal disease and may experience viremia, causing pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with HIV infection, may have unusual, chronic, or relapsing cutaneous disease, retinitis, or central nervous system disease without rash. Transverse myelitis with transient paralysis is a rare complication of herpes zoster. In contrast to adults, postherpetic neuralgia is very unusual in children.

Laboratory findings and diagnosis. Laboratory evaluation is not necessary for appropriate management of healthy children with varicella or herpes zoster. Abnormal laboratory values are common during varicella. Leukopenia is typical during the first 72 hr; it is followed by a relative and absolute lymphocytosis. Liver function tests are also often moderately elevated. Patients with neurologic complications of varicella or uncomplicated herpes zoster have a mild lymphocytic pleocytosis and a slight to moderate increase in protein; the cerebrospinal fluid glucose is usually normal. Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be accomplished by direct immunohistochemical staining of cells from cutaneous lesions. Multinucleated giant cells can be detected with nonspecific stains, but false-negative results are common, and these methods do not differentiate VZV and HSV infections. The definitive diagnosis of VZV infection requires the recovery of infectious virus using tissue culture. VZV immunoglobulin G (IgG) antibodies can be detected by several methods, but serologic diagnosis is retrospective; testing for VZV IgM anti-

bodies is not useful for clinical diagnosis because commercially available methods are unreliable. VZV IgG antibody tests are valuable to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal.

Treatment. Acyclovir is the drug of choice for varicella and herpes zoster when specific therapy is indicated. Any patient who has signs of disseminated VZV including pneumonia, hepatitis, thrombocytopenia, or encephalitis should receive immediate treatment with intravenous acyclovir. Acyclovir therapy given within 72 hr prevents progressive varicella and visceral dissemination in high-risk patients; the dosage is 10mg/kg every 8 hr, administered intravenously for 7 days or until no new lesions have appeared for 48 hr. Delaying antiviral treatment until prolonged new lesion formation is evident is not an option because visceral dissemination occurs during the same time period. Recent large, placebo-controlled clinical studies have shown that oral acyclovir diminishes the clinical symptoms of varicella in otherwise healthy children, adolescents, and adults when it is administered within 24 hr after the appearance of the initial cutaneous lesions. Drug efficacy was established for all groups, but the clinical benefit may be considered more significant in older children and in secondary household cases. Acyclovir therapy does not interfere with the induction of VZV immunity.

Acyclovir is also effective for treatment of herpes zoster in healthy and immunocompromised patients. Patients at high risk for disseminated disease should receive 500 mg/m2 or 10 mg/kg every 8 hr intravenously. Onset of VZV reactivation reduces the duration of new lesion formation to only about 3 days. Oral acyclovir is an option for immunocompromised patients who are considered at low risk for visceral dissemination. Antiviral drug resistance is rare but has occurred in children with HIV infection; foscarnet is the only drug now available for the treatment of acyclovir-resistant VZV infections.

Prevention. VZV transmission is difficult to prevent because the infection is contagious for 24–48 hr before the rash appears. Infection control practices, including caring for infected patients in isolation rooms with filtered air systems, are essential in hospitals that treat immunocompromised children. Susceptible health care workers who have had a close exposure to varicella should not care for high-risk patients during the incubation period.

Varicella-zoster immune globulin (VZIG) prophylaxis is recommended for immunocompromised children, pregnant women, and newborn infants exposed to maternal varicella. VZIG is distributed by the American Red Cross Blood Services; the dosage is one vial per 10 kg intramuscularly given within 96 hr or, if possible, within 48 hr after exposure. Adults should be tested for VZV IgG antibodies before VZIG administration because many adults with no clinical history of varicella are immune. Because VZIG prophylaxis does not eliminate the possibility of progressive disease, patients should be monitored and treated with acyclovir if necessary. Immunocompromised patients who have received high-dose intravenous immune globulin (100–400 mg/kg) for other indications within 2–3 wk before the exposure can be expected to have serum antibodies to VZV. Close contact between a susceptible high-risk pa-

tient and a patient with herpes zoster is also an indication for VZIG prophylaxis. Passive antibody prophylaxis does not reduce the risk of herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

The live, attenuated varicella vaccine, made from the Oka strain, is the first human herpesvirus vaccine. The live, attenuated varicella vaccine (Oka-Merck strain) has been given to more than 8,500 healthy children and adults in clinical trials in the United States. The vaccine induced seroconversion rates of more than 95 %, with complete protection against disease in 85–95 % of exposures. Persistence of humoral and cell-mediated immunity has been documented in 94–100 % of vaccine recipients monitored for 1–6 yr. The Oka-Merck varicella vaccine can be given to children with acute leukemia in remission, with careful attention to the status of their underlying disease and immunosuppressive therapy regimens. VZV reactivation has been described in a few healthy vaccine recipients, but the incidence of herpes zoster resulting from vaccine virus in children with leukemia was significantly lower than reactivation of naturally acquired VZV. Licensure of the Oka-Merck vaccine was approved in 1995 in the United States; live, attenuated varicella vaccines have been approved for clinical use in Japan, Korea, and some European countries.

Herpes simplex virus

Herpes Simplex Virus (HSV) is common among humans, and has a variety of clinical manifestations involving the skin, mucous membranes, eye, central nervous system, and genital tract. It also causes generalized systemic disease. Disease manifestations are in large part determined by the immune competence of the host. Two strains of the virus are identified: HSV-1 commonly infects skin and mucous membranes above the waist. HSV-2 primarily infects the genitalia and the neonate.

Two types of infection are recognized:

1. Primary infection is the susceptible host's first experience with the virus, which in most instances is a subclinical infection; otherwise there are usually local superficial lesions (see later discussion) accompanied by varying degrees of systemic reaction. In newborn infants and severely malnourished infants, a serious systemic infection, often without superficial lesions, may occur. Circulating antibodies and a cell-mediated response develop in nonfatal cases.

2. Recurrent herpetic lesions represent reactivation of a latent infection in an immune host with circulating antibodies. Reactivation follows such nonspecific stimuli as changes in the external milieu (e.g., cold, ultraviolet light) or in the internal milieu (e.g., menstruation, fever, or emotional stress). The lesions tend to be localized and, generally, are not associated with systemic reactions. Viral reactivation may take place in the absence of clinical recurrence, leading to asymptomatic viral shedding.

Etiology. HSV is a double-stranded DNA containing enveloped virus. The icosahedral protein core is surrounded by a lipid envelope in which is embedded a number of viral glycoproteins (e.g., glycoproteins B, C, D) responsible for viral–target cell interaction and infection. These glycoproteins are also key targets for the host humoral and cellular immune response. HSV grows rapidly in human and nonhuman cell lines

and produces characteristic cytopathic changes. HSV-1 and HSV-2 may be differentiated by DNA analysis (endonuclease restriction analysis) and commercially by reactivity with type-specific monoclonal antibodies in a variety of fluorescent and enzyme-linked immunosorbent (ELISA) assays. Several enzymes important for viral DNA synthesis, such as thymidine kinase and DNA polymerase, are useful targets for antiviral agents.

Epidemiology. The virus develops an extremely compatible relationship with its host. In about 85 % of instances the infection is subclinical. Even when clinical manifestations are present, the host is only rarely seriously disabled. Occasionally, the primary or recurrent infection may lead to institutional or family outbreaks of stomatitis. This has been reported in orphanages and day-care center settings. HSV may also be transmitted by infection of digits (whitlows), during contact sports such as rugby or wrestling (herpes gladiatorum), and rarely in the hospital setting. The incubation period is 2–12 days (average, 6 days). The spread of infection appears to be determined by two factors: close bodily contact and trauma such as teething or a break in the skin.

The higher incidence of HSV antibodies in lower socioeconomic groups correlates with crowded living conditions. The epidemiology differs for the two types of HSV. Detailed serologic studies have been done primarily in low-income groups, in which most infants have transplacental antibody for about the first 6 mo of life. From 1–4 yr, there is a sharp rise in antibodies to HSV-1 and then a much slower rate of acquisition up to 14 yr. At this time, there is a second sharp rise in antibodies, mostly to HSV-2. By adult life HSV antibodies are seen in by far the majority of persons in the lower socioeconomic groups. HSV-1 antibodies are found in 30 % of university students. HSV-2 antibodies are found in up to 60 % of the lower socioeconomic status adults. The incidence of type 2 antibody in higher socioeconomic groups is about 10–30 % and in nuns about 3 %.

Once infected, the majority of people continue to carry the virus in a latent state and maintain an almost constant level of circulating antibodies. The initial level of antibodies reached after a primary infection may fall, and several subclinical reinfections may occur before a stable antibody level is established. Carriers may distribute the virus without having any manifest lesion. Herpes simplex virus can be isolated from the pharynx of about 5 % of asymptomatic adults.

Pathology. The pathologic changes vary with the tissue infected. In general, a specific lesion is characterized by the presence of intranuclear inclusion bodies, homogeneous masses lying in the midst of a severely disorganized nucleus in which the basic chromatin has marginated to the nuclear membrane. Around the specific lesion there is always evidence of an acute inflammatory reaction. In the skin and mucous membranes the typical lesion is a unilocular vesicle. In the skin the vesicle is tense. Ballooned epithelial cells containing intranuclear inclusions can best be seen at the margins of the vesicle. The vesicular fluid contains infected epithelial cells, including multinucleated giant cells and leukocytes. In the corium there is no necrosis, but capillaries are dilated, and there is infiltration with mononuclear and polymorphonuclear cells. In the mucous membrane, because of maceration, there is early leakage of the vesicular fluid resulting in a col-

lapsed vesicle, mainly filled with fibrin. The edematous roof cells form a gray membrane over the lesion.

In otherwise healthy persons, the lesions are confined to the skin and mucous membranes; viremia has rarely been described. Bloodstream spread of the virus with resultant widely disseminated disease is seen mainly in the newborn, in severely malnourished children, in persons with skin diseases such as eczema, and in those with defects in cell-mediated immunity. In these patients the virus spreads hematogenously from the portal of entry to susceptible organs. Virus increases within these organs, and secondary viremia occurs with evidence of extensive cell destruction. It is probable, however, that most cases of HSV-1 encephalitis other than in the newborn are caused by neurogenic transmission of the virus to the brain. Healing begins with clearing of the viremia and a decrease in the production of virus within the cells.

Clinical manifestations. HSV characteristically produces a vesicular lesion. Only rarely is there a viremic distribution that results in widespread systemic disease or neurogenic transmission that leads to meningoencephalitis. Furthermore, although the occurrence of primary and recurrent lesions is an accepted characteristic of herpetic infection, their distinction clinically is often not possible without knowledge of the presence or absence of serum antibodies in the patient.

Lesions of the Skin and Mucous Membranes. On the skin the lesion consists of aggregates of thin-walled vesicles on an erythematous base. These rupture, scab, and heal within 7{endash}–10 days without leaving a scar except after repeated attacks or secondary bacterial infections; temporary depigmentation may occur in blacks. The local lesions may be preceded by mild irritation or burning at the local site or by severe neuralgic pain in the region. In children the vesicles often become secondarily infected, introducing impetigo contagiosa into the differential diagnosis. The lesions tend to recur at the same site, particularly at mucocutaneous junctions, but may occur anywhere.

Primary infection, especially in the immunocompromised patient, may, uncommonly, result in a generalized vesicular eruption in which the lesions are small and may continue to appear over a period of 2–3 wk. If the systemic manifestations are mild, the infection must be differentiated from varicella.

Traumatic lesions of the skin can be infected by HSV. Primary lesions can also occur on apparently unbroken skin, as, for example, on the chin of a drooling infant with herpetic stomatitis, in whom scattered isolated vesicles appear, in contrast to the grouped vesicles of recurrent attacks. When the skin of a limb is infected, vesicles appear in 2–3 days at the site of trauma. There is often centripetal spread along lymph channels, causing enlargement of regional lymph nodes and scattered vesicles on the intervening undamaged skin.

The final clinical picture may be mistaken for that of herpes zoster, especially if accompanied by neuralgic pain, unless the lesions are recognized as not being confined to a dermatome. The lesions heal slowly, often taking 3 wk; recurrences at the site of local trauma are common and may assume a bullous pattern. Wrestlers and medical personnel are prone to herpetic infections of superficial abrasions (herpes gladiatorum and herpetic whitlow). In the latter, infection of minor trauma about the

nails leads to extremely painful, deep-seated spreading lesions with vesicles that resolve spontaneously in 2–3 wk. Similar lesions occur on the fingers of thumb suckers who are suffering from herpetic gingivostomatitis. The lesions should not be incised.

Acute Herpetic Gingivostomatitis (Catarrhal Stomatitis; Ulcerative Stomatitis; Vincent Stomatitis). This primary infection, probably the most common cause of stomatitis in children 1–3 yr of age, can also occur in older children and adults. The symptoms may appear abruptly, with pain in the mouth, salivation, fetor oris, refusal to eat, and fever, often as high as 40–40.6 ^{0}C.

The onset may be insidious, with fever and irritability preceding the oral lesions by 1–2 days. The initial lesion is a vesicle, which is seldom seen because of its early rupture. The residual lesion is 2–10 mm in diameter and is covered with a yellow-gray membrane. When this membrane sloughs, a true ulcer remains. Although the tongue and cheeks are most commonly involved, no part of the oral lining is exempt. Except in edentulous infants, acute gingivitis is characteristic of the disease and may precede the appearance of mucosal vesicles. Submaxillary lymphadenitis is common.

The acute phase lasts 4–9 days and is self-limited. Pain tends to disappear 2–4 days before healing of the ulcers is complete. In some instances the tonsillar regions are involved early and appear exudative, and acute tonsillitis of bacterial origin or enterovirus-induced herpangina may be suspected. Negative cultures for Streptococcus and other bacterial pathogens and failure of the lesion to respond to antibiotic therapy differentiate a bacterial infection. The spread of the vesiculation to the buccal mucosa and anterior portion of the mouth is atypical for herpangina.

Recurrent Stomatitis and Herpes Labialis. The typical oral recurrence of HSV is one or a few vesicles grouped at the mucocutaneous junction. Lesions are usually accompanied by local pain, tingling, or itching and lasts 3–7 days. Systemic symptoms are unusual. Less commonly, localized lesions may occur on the palate in association with a febrile illness or on the mucosa adjacent to a lesion on the lip. Recurrent aphthous ulcers, however, are not caused by HSV. In some persons a generalized stomatitis recurs consistently 7–10 days after a recurrent herpetic lesion of the lip or elsewhere and is often accompanied by skin lesions of erythema multiforme. Indeed, recurrent HSV infection is one of the most common causes of recurrent erythema multiforme.

Eczema Herpeticum (Kaposi Varicelliform Eruption; Juliusberg Pustulosis Vacciniformis Acuta). This, the most serious manifestation of "traumatic herpes," results from a widespread and usually primary infection of the eczematous skin with HSV. The severity of this complication varies; the lesion may be so mild as to be overlooked, or it may be fatal. In a typical severe primary attack, vesicles develop abruptly in large numbers over the area of eczematous skin. They continue to appear in crops for as long as 7–9 days. Isolated at first, they later become grouped and may occur on adjoining areas of normal skin. Wide denudation of the epidermis may occur. Scabs eventually form, and epithelialization occurs.

The systemic reaction varies, but temperatures of 39.4–40.6 for 7–10 days are not uncommon. Recurrent attacks develop on chronic atopic skin lesions. Death may result from

profound physiologic disturbances from loss of fluid, electrolytes, and protein through the skin, from dissemination of the virus to the brain and other organs, or from secondary bacterial invasion. A differentiation from eczema vaccinatum can usually be made by determining with reasonable certainty that the child has not been exposed to vaccinia and by the occurrence of crops of vesicles in herpes. The diagnosis can be accurately established by examination of vesicular fluid with rapid viral diagnostic techniques (see later discussion, Diagnosis).

Ocular Lesions. Conjunctivitis and keratoconjunctivitis may occur as manifestations of either a primary or recurrent infection. The conjunctiva appears congested and swollen, but there is little, if any, purulent discharge. In primary infection the preauricular node is usually enlarged and tender. Cataracts, uveitis, and chorioretinitis have been described in newborn infants and in the immunocompromised.

Corneal lesions may be superficial, in the form of a dendritic ulcer, or deep, as a disciform keratitis. Dendritic keratitis is unique to HSV eye involvement. The diagnosis is suggested by the presence of herpetic vesicles on the lids; it is established by the isolation of the virus. The highly contagious epidemic keratoconjunctivitis (shipyard conjunctivitis) caused by any of several serotypes of adenovirus must be considered in the differential diagnosis. Recurrent herpetic corneal infection may result in scarring of the cornea and vision impairment.

Genital Herpes. Genital infections with herpesvirus occur most commonly in adolescents and young adults, are usually due to HSV-2, and are usually spread by sexual activity. Although hand to genital infection and autoinoculation are possible, genital or rectal herpes in a young child warrants a sensitive and careful appraisal of the possibility of child abuse. Ten to 25 % of cases of primary genital herpes are caused by HSV-1. Almost all cases of recurrent genital herpes are due to HSV-2. In primary genital infection, when the patient has no antibody to either type of herpes (approximately 30 % of cases), systemic symptoms such as fever, regional adenopathy, and dysuria are more likely to occur. In adult women, the vulva and vagina may be involved with vesicles and ulcers, but the cervix is the primary site of infection. Recurrence is common. Both primary and recurrent disease are frequently subclinical, but virus shed during this time may infect a sex partner or an infant during passage through the birth canal.

In males herpetic vesicles or ulcers are usually seen on the glans penis, prepuce, or shaft of the penis. The scrotum is less frequently involved. Genital HSV is a risk factor for human immunodeficiency virus (HIV) infection.

In the immunocompromised host. Unusually severe HSV infection may occur in a variety of hosts including the newborn ; the severely malnourished; and children with malignancies or other conditions necessitating immunosuppressive therapy, with acquired immunodeficiency virus (AIDS), with burns, or with primary immunodeficiency diseases that particularly impair cell-mediated immunity. In children receiving therapy for cancer or organ transplantation, the risk of severe HSV infection coincides with the time of maximum immunosuppression. The most common syndrome is local and chronic mucocutaneous disease. The lesions may resemble typical vesicles and

ulcers or progress to large necrotic painful erosions or atypical exophytic, wartlike lesions. Mucositis, esophagitis, proctitis and pneumonitis are less common. The most severe manifestation, usually a result of primary infection in the immunocompromised child, is widespread disseminated disease involving the liver, lungs, adrenal gland, and central nervous system. These patients have a sepsis-like syndrome with leukopenia, disseminated intravascular coagulopathy, fever, or hypothermia and progression to death. Skin lesions may be localized to mucous membranes, widely disseminated, resembling varicella infection, or absent. This form of HSV infection has a high mortality rate even with therapy.

Central Nervous System Infection. HSV has a predilection to infect the nervous system. Both types 1 and 2 may cause a meningoencephalitis as part of neonatal HSV infection. In patients with primary genital herpes, usually resulting from HSV-2, an aseptic meningitis syndrome may complicate the course. The cerebrospinal fluid reveals a lymphocytic pleocytosis, and the virus may be cultured from it in patients with this self-limited syndrome. HSV-1 is the most common cause of fatal sporadic encephalitis. It has a striking predilection to involve the frontal and parietal areas.

Typical signs and symptoms include fever, altered consciousness, headache, personality changes, seizures, dysphasia, and focal neurologic signs. If untreated, the mortality rate is apparently 75 %, with severe sequelae in survivors. HSV is the cause of some cases of recurrent aseptic meningitis (Mollaret meningitis), on the basis of demonstration of HSV DNA in the cerebrospinal fluid by polymerase chain reaction (PCR).

Laboratory data. Microscopic examination of scrapings from lesions (Tzanck stain) reveals multinuclear giant cells and intranuclear inclusions approximately 50 % of the time. Specific antigen detection methods such as ELISA and immunofluorescent techniques applied to these specimens can be useful in rapidly diagnosing herpes infection and in differentiating the two types of herpes. Virus can be readily isolated from vesicles and from conjunctival swabs in 1–4 days. Cerebrospinal fluid is positive for virus in about one third of infected neonates but is rarely positive in older children with encephalitis. Brain biopsy is required for a definitive diagnosis and exclusion of other treatable entities. PCR permits detection of viral DNA in cerebrospinal fluid and, if positive, will make brain biopsy unnecessary. At this writing, PCR for HSV is available through specialized research laboratories only.

Moderate polymorphonuclear leukocytosis occurs in acute herpetic gingivostomatitis, eczema herpeticum, and meningoencephalitis. In meningoencephalitis there are frequently red cells in the cerebrospinal fluid and an increase in lymphocytes, usually fewer than 100 but occasionally up to 1,000/mm3; the protein level is elevated, and the sugar is usually within the normal range. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) may demonstrate a temporal lobe lesion in early encephalitis. The computed tomographic (CT) scan may be normal in early encephalitis but becomes abnormal as the disease progresses. Thrombocytopenia and elevated liver function tests often occur with systemic infection.

Diagnosis. The diagnosis is based on any two of the following: (1) a compatible clinical pattern; (2) isolation of the virus; (3) development of specific antibodies; (4) demonstration of characteristic cells, histologic changes, viral antigen, or HSV DNA

in scrapings or biopsy material. A rise in cerebrospinal fluid HSV antibody occurs in HSV encephalitis, but it is late in the illness and is useful only for retrospective diagnosis. HSV serologic changes (fourfold rise or seroconversion from negative to positive) usually occur after the critical period for diagnosis and therapy. Illnesses resulting from HSV recurrence may not demonstrate a diagnostic serologic rise, and neonates or severely immunocompromised individuals may fail to produce antibody during primary infection. Reliable antibody tests to differentiate HSV-1 from HSV-2 are not commercially available. HSV-1 and HSV-2 viral isolates may be typed by a variety of readily available antigen (ELISA, fluorescent antibody) and molecular techniques. HSV isolates that are unrelated epidemiologically are all slightly different at the nucleic acid level, as discerned by DNA endonuclease restriction analysis. Using this technique, it is possible to confirm infection of one individual by another and to demonstrate that apparent nosocomial outbreaks or viral transmission represent a chance collection of unrelated cases, which may be extremely important for counseling and medicolegal reasons.

Course and prognosis. Primary localized infections with HSV in the normal host are self-limited, usually lasting 1–2 wk. Mortality rates are high in newborn infants who also have systemic infection and in older infants who are severely immunocompromised or malnourished. In patients with meningoencephalitis the prognosis for survival or for recovery without serious permanent residuals is guarded. Outcome is improved with early diagnosis and therapy.

Attacks may frequently recur, but they seldom cause more than temporary inconvenience except in the eye, where they may eventually cause scarring of the cornea and blindness. Recurrent herpes lesions can be a significant problem in immunocompromised patients. Recurrent genital disease may be associated with significant discomfort and psychologic morbidity. The major complication of any form of genital HSV infection in a woman is infection of her newborn.

Treatment. Acyclovir (9-[-2-hydroxyethoxymethyl] guanine, a purine nucleoside analog) is the mainstay of therapy for HSV. Viral thymidine kinase will phosphorylate acyclovir, which is then triphosphorylated by cellular enzymes to act as an HSV DNA polymerase inhibitor and DNA chain terminator. Thymidine kinase{endash}–negative HSV isolates are resistant to acyclovir. Topical acyclovir may decrease the period of viral shedding but has little effect on symptoms of oral or genital herpes.

Topical trifluorothymidine, vidarabine, and idoxuridine are all usually effective in treating herpetic keratitis but do not reduce the recurrence rate. Topical corticosteroids may increase ocular involvement, if used alone, and should only be utilized with antiviral therapy.

Patients with primary genital infection who are treated with oral acyclovir (200 mg five times daily for 5 days) have significantly less pain, itching, and time to crusting; a shorter duration of viral shedding; and fewer new lesions compared with control patients. A dose of 800 mg twice a day appears to be just as effective and well tolerated and is easier to administer. Those with recurrent genital infections who are treated similarly with oral acyclovir have a shorter duration of viral shedding and heal faster.

Therapy of primary attacks does not prevent recurrences. However, daily prophylactic administration of oral acyclovir can diminish the number of recurrences and may be prescribed if recurrences are frequent or severe. In small studies, oral acyclovir has modest effects in children with primary gingivostomatitis by decreasing drooling, gum swelling, pain, and new lesion formation compared with placebo. Therapy of recurrent oral herpes with oral acyclovir has limited effects. Acyclovir has no effect on HSV-associated erythema multiform. Suppression of the HSV infection by prophylactic therapy as for genital disease prevents the erythema multiforme recurrences. Oral acyclovir therapy is useful for treating recurrent herpes whitlow and rectal herpes.

Intravenously administered acyclovir (10 mg/kg/dose given over 1 hr every 8 hr for 14–21 days) is the treatment of choice for herpes encephalitis. The drug is well tolerated. The best results are obtained when treatment is started early. Patients younger than 30 yr and those who are only lethargic compared with those who have progressed to coma have a better prognosis. Supportive care to minimize increased intracranial pressure, seizure activity, and respiratory compromise requires an intensive care setting and a team of experts. Intravenous acyclovir (5–10 mg/kg/dose given over 1 hr every 8 hr [duration depending on clinical response]) is therapeutic for HSV infection in the immunocompromised host. The larger doses are used for severe and systemic infections. The lower dose may be used for localized mucocutaneous disease. As the patient responds, therapy may be switched to the oral route. Oral acyclovir, as used in genital disease, may be used to suppress HSV recurrences in seropositive patients during periods of maximum immunosuppression after organ or marrow transplantation or during induction therapy for leukemia, lymphoma, or solid tumors. Immunosuppressed patients with frequently recurring HSV infection, such as those with AIDS or primary immunodeficiencies, benefit from chronic suppressive oral therapy. In the neonate, all forms of HSV are treated with high doses (10–20 mg/kg/dose every 8 hr) of acyclovir for 14–21 days.

Acyclovir-resistant HSV is rare in the normal host but occurs in the immunocompromised host treated with multiple, intermittent courses of acyclovir. When immunocompromised patients have unresponsive or worsening HSV infection despite acyclovir therapy, the virus should be forwarded to reference laboratories for drug susceptibility testing. The drug of choice for acyclovir-resistant HSV is intravenous foscarnet (phosphonoformic acid), 40 mg/kg/dose every 8 hr. This drug has serious side effects (azotemia, electrolyte disturbance, anemia, granulocytopenia). Acyclovir and foscarnet dosages must be modified in patients with renal impairment.

Symptomatic and supportive therapy is of great importance. In infants especially, eczema herpeticum and stomatitis may lead to severe dehydration, shock, and hypoproteinemia, requiring replacement of fluids, electrolytes, and proteins.

Oral lavage should be used for mouth care; Ceepryn 1:4,000 or Zephiran 1:1,000 may be useful. Local analgesics, such as viscous lidocaine or benzocaine lozenges, are not advocated because they may cause the child to damage friable and anesthesized parts of the mouth. Genital lesions may be made less painful by using sitz baths. Local drying agents prolong healing and may increase secondary infection. Analgesics

should be used systemically as required. Antibiotics are useful only in treating secondary bacterial infections.

Food and fluid intake will be facilitated by acquiescing to the child's whims. Ice-cold fluids, ice slush, or semisolids are often accepted when other food is refused.

The child or adolescent with recurrent oral or genital herpes may have severe psychologic problems and may benefit from anticipatory guidance or formal counseling. Genital disease should be destigmatized and safer sex practices emphasized. Parents of children with most types of HSV infection, such as gingivostomatitis or skin infection, should be reassured that common childhood HSV infections are not related to sexual activity or abuse.

Prevention. Acyclovir administered during periods of high risk in immunocompromised hosts and chronically in individuals with frequently recurrent genital or oral disease markedly decreases the rate of recurrence. Acyclovir administered before a known trigger factor, such as intense sunlight, usually prevents recurrences.

HSV spread can be limited by standard methods of infection control. Open lesions on skin, hands, and mucous membranes should be well covered. Wrestlers with possible HSV cutaneous lesions should be excluded from practice and competition until they are healed. Wrestling mats should be cleansed with a bleach solution at least daily. Children with immunodeficiencies or chronic skin diseases that predispose to severe HSV infection should not be cared for by persons with herpetic whitlow or active uncovered fever blisters. Active herpes lesions that can be covered are not a reason to exclude children from day-care or school activities.

There is active research to develop a vaccine to prevent HSV infection. HSV may be prevented in some animal models by live, attenuated or subunit viral particle vaccines. Several purified HSV glycoprotein vaccines are antigenic in humans, but whether these vaccines will prevent disease or ameliorate recurrences is not known.

PART 8 **DIPHTHERIA**

The causative agent of diphtheria is Corynebacterium diphtheriae discovered in 1883-4 by Klebs and Loeffler. Corynebacterium species are aerobic, nonencapsulated, non-spore-forming, mostly nonmotile, pleomorphic, gram-positive bacilli. The bacillus produces an exotoxin during growth that is the principal factor in its virulence. The disease is caused only by toxigenic strains of diphtheria bacillus. Avirulent strains are nonpathogenic. Three biotypes (i.e., mitis, gravis, and intermedius), each capable of causing diphtheria, are differentiated by colonial morphology, hemolysis, and fermentation reactions.

Epidemiology. Spread is primarily by airborne respiratory droplets or direct contact with respiratory secretions of symptomatic individuals or exudate from infected skin lesions. Asymptomatic respiratory carriers are important in transmission. A patient may prove to be contagious from the last days of the incubation period, and remains so throughout the whole course of the disease, even after the-disappearance of

all its clinical manifestations. Transmission through contaminated milk and an infected food handler have been proved or suspected.

Portal of entry. C. diphtheria is an exclusive inhabitant of human mucous membranes and skin. But the disease develops only when the infected subject is susceptible. Unsusceptibility depends on the presence of diphtheria antitoxin in the organism and on the state of nonspecific protective mechanisms. Outbreaks are associated with homelessness, crowding, poverty, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources.

Pathogenesis and pathological anatomy. Diphtheria bacilli invading the human organism settle on the mucous membranes of the fauces, nose, or respiratory passages, where they find favorable conditions for multiplication and production of toxin. The organism usually remains in the superficial layers of skin lesions or respiratory mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in its ability to produce the potent polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis. A pathomorphological sign of the interaction between the macro-and the microorganism is fibrinous inflammation. Within the first few days of respiratory tract infection, a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown adherent pseudomembrane. Removal is difficult and reveals a bleeding edematous submucosa. There are dilatation and congestion of the blood vessels of the mucous membranes. Paralysis of palate and hypopharynx are early local effects of the toxin. Toxin absorption can lead to necrosis of kidney tubules, adrenal glands, thrombocytopenia, mycocardiopathy, and demyelination of nerves. The regional lymph nodes are usually also involved.

When the pathological process develops in a mucous membrane lined with single-layer columnar epithelium forms croupous inflammation. When the pathological process develops in a mucous membrane lined stratified squamous epithelium, not only the epithelium, but also the connective tissue (tunica propria mucosae) forms diphtheritic inflammation. The most important protective reaction of the organism in response to diphtheria toxin is the production of antitoxin.

Clinical picture. The incubation period of diphtheria is from two to ten days. Depending on the localization of the pathological process and its severity, there is a great variety of clinical forms of the disease: diphtheria of the fauces, nose, larynx, trachea and bronchi, eyes, external genitalia, skin, etc., is distinguished according to its localization. Simultaneous affection of the fauces and nose or of the fauces and larynx is not infrequent. These forms are known as combined.

Faucial Diphtheria. Diphtheria of the fauces is the most common form of the disease. Three principal forms are distinguished:

a) localized faucial diphtheria with membranous films coating the tonsils only, including atypical insular (because the diphtheritic membrane on the tonsils resembles separate islands) and catarrhal forms (without membrane);

b) diffuse form with the membrane spreading beyond the tonsils to the palatine arches, uvula, and throat;

c) toxic form characterized by extensive lesions in the fauces, a marked reaction in the regional lymph nodes with toxic oedema of the tissues of the neck, and marked general toxaemia. Subtoxic diphtheria is a subtype that is a kind of transition between the diffuse and toxic forms. Variants of toxic diphtheria with a particularly malignant course—hypertoxic and haemorrhagic— should be distinguished (as atypical forms).

The localized form of faucial diphtheria is the most common. Its onset is characterized by general malaise, loss of appetite, headache and a moderate rise in temperature. Slight pain on swallowing is usually noted. These phenomena are often mild, and there may be no pain in the throat at all. On examination of the fauces a mild or moderate hyperaemia of the mucous membrane of the tonsils, palatine arches, and uvula is usually seen on the first day, more rarely on the second. The tonsils are enlarged and covered with a typical film, which has the appearance of a superimposition with smooth or wavy surface, with well-defined edges. The membrane may be white, yellowish-white, or greish-white in colour; it adheres closely to the underlying tissues, and cannot be separated with a swab. At the same time the regional lymph nodes enlarge moderately; on palpation they are hard, with well-defined borders, and slightly or moderately tender.

The diffuse form of faucial diphtheria is characterized the film, wich covers not only the swollen tonsils but also, to a greater or less extent, the mucous membrane of the palatine arches, the uvula, and sometimes the whole of the soft palate and the walls of the throat. There are more pronounced general malaise, lassitude, weakness, anorexia, headache, and disturbed sleep. The temperature rises to 38-39°C.

The toxic form of faucial diphtheria usually begins suddenly, the temperature rapidly rises to 39-40°C, the patient turns pale sharply, and there are headache, general malaise, marked lassitude, sleeplessness, anorexia and, at times, vomiting and abdominal pain. Excitation, but more commonly, marked apathy and adynamia develop. Underlying soft tissue edema and enlarged lymph nodes can cause a "bull-neck" appearance.

The mucous membrane of the soft palate and pharynx is edematous and slightly hyperemic. The tonsils are covered with a thick uneven membrane of a dirty white or brownish-grey colour that extends to soft palate and even to I lie hard. The patient's face is pale, the tongue is coated, while or brownish. The lips are parched. An unpleasant odour is smelt when examining the fauces. The process often spreads to the nasopharynx and nasal cavity. Quite characteristic changes appear in the superior cervical lymph nodes and the soft tissues around them. A painful infiltrate of a dense consistency and blurred outline is found in the area of the lymph nodes, while there is more or less extensive oedema of the soft, tissues above and around, the affected nodes (subcutaneous cellular tissue). The colour of the skin over the oedumatous tissue remains normal. Pressure on the area is painless and does not leave pits and when the tissue is percussed with the finger it shakes like a jelly. The oedema is usually bilateral occupying the whole submaxillary area; it can the ability to spread. Its intensity in the subcutaneous tissue depends on the degree of toxaemia, and it is therefore taken as the basis for the following classification of toxic diphtheria into three degrees:

Degree Extent of oedema: I) to the middle of the neck; II) to the clavicles; III) below the clavicles

The subtoxic form of faucial diphtheria: the oedema of the faucial mucosa is less pronounced and the false membrane less extensive, oedema of the tissues of the neck is usually seen only in the direct vicinity of the affected regional lymph nodes, and as a rule is unilateral. In the hypertoxic form, apart from the rapidly developing local process characteristic of toxic diphtheria, there is grave toxaemia with a catastrophically progressing fall in cardiovascular activity. The patient usually dies within the first five days of the disease. The haemorrhagic form has a symptom complex of second or third degree toxic diphtheria combined with haemorrhagic diathesis. The affected mucosa tends to bleed and copious bleeding from the nose and haemorrhages into the skin are frequent. There is marked thrombopenia and increased blood coagulation time. The skin is pale or greyish and there is a rapidly progressing cardiovascular failure. This form has a very high death rate.

Laryngeal Diphtheria or Diphtheritic Croup is still often encountered in young children (between a year and three or four years of age. Laryngeal diphtheria begins with a rise in temperature and general malaise. Hoarseness quickly develops and is followed by complete aphonia. Cough appears simultaneously, at first dry, hard and 'barking', but as dysphonia develops it loses its resonant quality and becomes hoarse.

Rare Clinical Forms of Diphtheria are Nasal Diphtheria, Conjunctival diphtheria, Diphtheria of the external genitalia, Diphtheria of the skin and wounds. Nasal diphtheria occurs with faucial diphtheria (mixed form).

Complications. Complications associated with specific toxaemia are distinctive of diphtheria, viz. cardiovascular disturbances, neuritis and polyneuritis, and nephrosis.

Complications in the cardiovascular system. Early and late cardiovascular disturbances are distinguished. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease and delay in administration of antitoxin. Characteristically, the first evidence of cardiac toxicity occurs in the 2nd to 3rd wk of illness as pharyngeal disease improves but can appear acutely as early as the 1st wk when a fatal outcome is likely, or insidiously as late as the 6th wk of illness. There are unfavorable sings of diphtheritic myocarditis by Molchanov – gallop rhythm, abdominal pains and vomiting.

Complications affecting the nervous system. Neurologic complications parallel the extent of primary infection and are multiphasic in onset. Acutely or 2–3 wk after onset of oropharyngeal inflammation, hypesthesia, and local paralysis of soft palate occur commonly. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty in swallowing, and risk of death from aspiration. Cranial neuropathies characteristically occur in the 5th wk and lead to oculomotor and ciliary paralysis, which manifest as strabismus, blurred vision, or difficulty with accommodation. Symmetric polyneuropathy has its onset 10 days to 3 mo after oropharyngeal infection and causes principally motor deficit with diminished deep tendon reflexes. Proximal muscle weakness of the extremities progressing distally and,

more commonly, distal weakness progressing proximally are described. Clinical and cerebrospinal fluid findings in the latter are indistinguishable from those of polyneuropathy of Landry syndrome. Paralysis of the diaphragm can ensue. Complete recovery is likely. The forms presenting the greatest danger are paralysis and paresis of the laryngeal muscles, respiratory intercostal muscles, the diaphragm, and those resulting from lesions to the innervation mechanism of the heart (n. vagus). Renal complications-toxic nephrosis (proteinuria and a slight cylindruria). Pneumonia is a common complication of diphtheritic croup.

Diagnosis. Thorough clinical examination, case history, bacteriological tests are most important for early diagnosis. The morphological properties of the isolated microbe are determined in 24 hours and the laboratory can give a tentative conclusion. The final result of the investigation can be obtained in 48-72 hours after isolation of the pure microbe culture and determination of its cultural, biochemical, toxicogenic, and serological properties. The agglutination test with the patient's serum has been suggested as an aid to diagnosis. This method can be used for retrospective diagnosis. Protective titre is 1:80 and higher in reaction of passiv agglutinaion or 0,03 AU/ml.

Differential diagnosis. Follicular angina is distinguished by greyish-white or yellowish-white round, purulent follicles, translucent through the mucous membrane of the tonsils, while lacunar angina is characterized by marked, crumbly, quite easily removed films in the lacunae of enlarged and loose tonsils. Both forms have a marked temperature reaction, much pain on swallowing, bright widespread hyperaemia of the fauces, and a considerable tenderness of the regional lymph nodes. They can be mistaken for the atypical form of insular faucial diphtheria particularly common in the immunized. But in the latter form of diphtheria the patient's general condition does not suffer much, the temperature reaction is mild, there is little or no pain on swallowing, the submaxillary lymph nodes are less painful or even painless, and faucial inflammation is not marked. The diphtheritic membrane is not only localized in the follicles and lacunae, but also outside them, is rather dense and can only be removed with difficulty.

Fusospirillar angina (angina caused by 'bacilli and spirillae with tapering ends) was described by Simonovsky -Vincent. It differs from diphtheria in the unilateral affection of the tonsils and the presence of a deep ulcer with an uneven, dirty-grey or yellow necrotic floor. Bacterioscopy revealing a fusospirillar flora clears up the diagnosis.

Infectious mononucleosis or mononuclear angina (Filatov's glandular fever) can easily be mistaken for faucial diphtheria. Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness.

EBV infects up to 95 % of the world's population. It is transmitted in oral secretions by close contact such as kissing or exchange of saliva from child to child. EBV is shed in oral secretions for 6 mo or longer after acute infection and then intermittently for life. Healthy individuals with serologic evidence of past EBV infection excrete virus 10–20 % of the time. Immunosuppression may permit reactivation of latent EBV. After acquisition in the

oral cavity, EBV initially infects oral epithelial cells; this may contribute to the symptoms of pharyngitis. After intracellular viral replication and cell lysis with release of new virions, virus spreads to contiguous structures such as the salivary glands with eventual viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system including the liver and spleen. The atypical lymphocytes that are characteristic of infectious mononucleosis are CD8+ T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes. This relative as well as absolute increase in CD8+ lymphocytes results in a transient reversal of the normal 2:1 CD4+/CD8+ (helper-suppressor) T-lymphocyte ratio. Many of the clinical manifestations of infectious mononucleosis may result, at least in part, from the host immune response, which is effective in reducing the number of EBV-infected B lymphocytes to less than one per 106 of circulating B lymphocytes. EBV, like the other herpesviruses, establishes life-long latent infection after the primary illness. The latent virus is carried in oropharyngeal epithelial cells and systemic B-lymphocytes as multiple episomes in the nucleus. Reactivation is apparently asymptomatic and not recognized to be accompanied by distinctive clinical symptoms. Oncogenesis: EBV was the first human virus to be associated with malignancy and, therefore, was the first virus to be identified as a human tumor virus. Malignant EBV-associated proliferations include nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, and lymphoproliferative disorders and leiomyosarcoma in immunodeficient states including AIDS.

The incubation period of infectious mononucleosis in adolescents is 30–50 days. In children it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1–2 wk. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint. The physical examination is characterized by generalized lymphadenopathy (90 % of cases), splenomegaly (50 % of cases), and hepatomegaly (10 % of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes, and submandibular lymph nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Symptomatic hepatitis or jaundice is uncommon. Splenomegaly to 2–3 cm below the costal margin is typical; massive enlargement is uncommon. The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates. Petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis resembles that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids. Rashes are usually maculopapular and have been reported in 3–15 % of patients. Eighty per cent of patients with infectious mononucleosis will experience a rash if treated with ampicillin or amoxicillin; the reason for this phenomenon is unknown.

Routine Laboratory Tests. In more than 90 % of cases, there is leukocytosis of 10,000–20,000 cells/mm3, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40 % of the total number. Compared with regular lymphocytes microscopically, atypical lymphocytes are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-cytoplasm ratio.

Heterophile Antibody Test. Heterophile antibodies agglutinate cells from species different from those in the source serum. The transient heterophile antibodies seen in infectious mononucleosis, also known as Paul-Bunnell antibodies, are IgM antibodies detected by the Paul-Bunnell–Davidsohn test for sheep red cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep or, for greater sensitivity, horse red cells.

Outcome and prognosis. The prognosis for a patient with diphtheria depends on the virulence of the organism (subspecies gravis has the highest fatality), age, immunization status, site of infection, and speed of administration of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths.

Treatment. Bed rest is essential during the acute phase of disease, with a return to physical activity guided by the degree of toxicity and cardiac involvement. The complications of airway obstruction and aspiration should be aggressively avoided at patients with oropharyngeal and laryngeal diphtheria, with an artificial airway established pre-emptively. But in toxic diphtheria, even when there are no complications, patients are kept in hospital and strictly confined to bed for the following minimum periods: in subtoxic and toxic diphtheria of the first degree for 21 to 28 days; in toxic diphtheria of the second degree for 40 days; and in toxic diphtheria of the third degree for 50 days from the beginning of the disease. The complications of diphtheria like myocarditis and polyneuritis also call for prolonged absolute bed rest. A special diet is not necessary in diphtheria; only during the first days are fluids and semi-fluids prescribed when there are marked lesions in the fauces.

1. Treatment of diphtheria with antitoxic serum. Specific antitoxin is the mainstay of therapy and should be administered on the basis of clinical diagnosis, because it neutralizes only free toxin. Efficacy diminishes with elapsing time after the onset of mucocutaneous symptoms. In doubtful cases the physician can choose the expectant tactics only on the condition that the localized form of the disease can be suspected. The dose of antitoxin depends on the severity (clinical form) of the disease and the time lapse from its onset; the more severe the forms and the later treatment are started, the greater the dose should be. Age is only of relative significance in determining the required dose. Serum should be given by the modified Bezredka method - 0,1 ml is first given subcutaneously. Followed by 0,2ml dose in 30 minutes, and finally the remaining dose in 60 minutes. The intradermal test uses 0.02 mL of 1:100 saline-diluted antitoxin or 1:1,000 saline-diluted antitoxin if the individual has a history of animal allergy or prior exposure to animal serum. An immediate reaction is defined as a wheal with surrounding erythema at least 3 mm larger than the negative control test result, read at 15 to 20 min. Desensitization is performed in those showing immediate

reactions according to protocol recommended by the American Academy of Pediatrics with successive doses every 15 min. For those with negative test results, a preliminary dose of 0.5 mL of antitoxin diluted in 10 mL of physiologic saline or 5 % glucose solution is given as slowly as possible with 30 min of observation; the remainder is then diluted 1:20 and given at a rate not to exceed 1 mL/min. Most authorities prefer the intravenous route with infusion over 30–60 min. The effect of antitoxin treatment begins to show within eight to twelve hours, or in 24 hours. In 24 to 36 hours the diphtheritic membrane begins to shrink, and disappears in most cases toward the third or fourth day. In the toxic form it takes longer, from five to seven days, and even more.

2. Antimicrobial therapy is indicated to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. Only penicillin or erythromycin is recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin given orally or parenterally (40–50 mg/kg/24 hr; maximum, 2 g/24 hr), aqueous crystalline penicillin G given intramuscularly or intravenously (100,000–150,000 U/kg/24 hr divided in four doses), or procaine penicillin (25,000–50,000 U/kg/24 hr divided in two doses) given intramuscularly. Antibiotic therapy is not a substitute for antitoxin therapy. Therapy is given for 14 days.

3. Infusion of rheopolyglucin and other salt solutions in combination with a 10 % solution of glucose (1:1) is prescribed in toxic diphtheria. This treatment favours disintoxication.

4. Some clinicians have had success in treating toxic diphtheria with glucocorticoids (hydrocortisone, prednisolone). The course of treatment takes from seven to twelve days. The effect of countering the toxaemia is more rapid and there is reduction of the incidence of grave complications.

5.Vitamin therapy is widely employed in diphtheria, especially in its toxic forms. Nicotinic acid (Ac. nicotinicum) is widely used to treat toxic diphtheria as it improves metabolism in the tissues. Bed rest, strychnine, vitamin B6, nicotinic acid, cyanocobalamine (vitamin B_{12}), glutamic acid, dibazol and proserine are indicated if diphtheritic paralysis supervenes.

Prophylaxis. Active immunization. Universal immunization with diphtheria toxoid throughout life to provide constant protective antitoxin levels and to reduce indigenous C. diphtheriae is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic C.diphtheriae, it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 70–80 % of a population is immunized. Serum antitoxin concentration of 0.01 IU/mL is conventionally accepted as the minimum protective level, and 0.1 IU/mL provides the certain protective level.

Immunization against diphtheria is now compulsory for all children. Adsorbed pertussis-diphtheria-tetanus vaccine (APDT) and diphtheria-tetanus toxoids (ADT) are used for immunization. The pediatric preparation (i.e., DTP, DT, DTaP) contains 6.7–12.5 Lf units of diphtheria toxoid per 0.5-mL dose; the adult preparation (i.e., Td) contains no more than 2 Lf units of toxoid per 0.5-mL dose. Three doses (of 0.5 ml)

are given at intervals of 30 to 40 days in the primary immunization of babies. Children are reimmunized with the same dose (0.5 ml) 18 months. A third reimmunization is given with adsorbed diphtheria-tetanus toxoid at the age of 6, than – 11, 18 and adult. In USA, India and many other countries for children from 6 wk to the seventh birthday, give five 0.5-mL doses of diphtheria-containing (D) vaccine. The primary series includes doses at approximately 2, 4, and 6 mos of age. The fourth dose is an integral part of the primary series and is given approximately 6–12 mo after the third dose. A booster dose is given at 4–6 yr (unless the fourth primary dose was administered after the fourth birthday). For persons 7 yr of age or older, use three 0.5-mL doses of diphtheria-containing (D) vaccine. The primary series includes two doses 4–8 wk apart and a third dose 6–12 mo after the second dose.

Control of diphtheria carriers. When an asymptomatic carrier is identified, several steps are taken. First, antimicrobial prophylaxis is given for 7-10 days. Second, age-appropriate preparation of diphtheria toxoid is administered immediately if there has not been a booster within 1 yr. Third, individuals are placed in strict isolation (respiratory tract colonization) or contact isolation (cutaneous colonization only) until at least two subsequent cultures taken 24 hr apart after cessation of therapy are negative. Fourth, repeat cultures are performed at a minimum of 2 wks after completion of therapy for cases and carriers, and if positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed.

The measures to be taken in an epidemic focus are as follows. (1) Patients with pharyngeal diphtheria are placed in strict isolation, and patients with cutaneous diphtheria are placed in contact isolation until the cultures taken after cessation of therapy are negative. Elimination of the organism should be documented by at least two successive cultures from the nose and throat (or skin) taken 24 hr apart after completion of therapy. But before they are re-admitted to a children's institution two negative supplementary checks for carrier state are required. Carriers of nonvirulent bacilli are allowed to attend children's institutions, but carriers of virulent diphtheria bacilli are not given permission to attend children's institutions where all children are immunized until 30 days after detection of their carrier state. A commission, the epidemiologist including, decides it. (2) Prompt identification and investigation of close contacts are the highest priorities. Several steps are taken. First, these individuals are closely monitored for illness through the 7-day incubation period. Second, cultures of the nose, throat, and any cutaneous lesions are performed. Third, antimicrobial prophylaxis is given, regardless of immunization status, using oral erythromycin (40–50 mg/kg/24 hr for 7–10 days) or, using intramuscular benzathine penicillin (600,000 U for those <30 kg or 1,200,000 U for those >30 kg). The efficacy of antimicrobial prophylaxis is presumed but not proved. Fourth, diphtheria toxoid vaccine, in age-appropriate concentration, is given to immunized individuals who have not received a booster dose within 5 yr. Some experts suggest that the longevity of protective antibody is variable enough that a booster should be given to close contacts if 1 yr has elapsed since immunization. Children who have not received their fourth dose should be vaccinated. Those who have received fewer than three doses of diphtheria toxoid or who lack

knowledge of immunization status are immunized with age-appropriate preparation on a primary schedule. (3) Terminal disinfection is carried out in the patient's home.

PART 9 **MUMPS (Epidemic Parotitis)**

Mumps is an acute, generalized viral disease in which painful enlargement of the salivary glands, chiefly the parotids, is the usual presenting sign.

Etiology. The causative agent in mumps is a filterable virus from the group of myxoviruses (Paramyxovirus parotitidis) that varies in size, averaging 100-200 nm. Only one serotype is known. Primary cultures of human or monkey kidney cells are used for viral isolation. As seen by electron microscopy, it has a flat It contains ribo-nucleic acid (RNA). The virus is of low stability and is rapidly inactivated by high temperatures, ultraviolet rays, weak formalin solutions, lyzol, and alcohol. It is grown on developing chick embryos. The mumps virus is pathogenic for monkeys, in which it produces a characteristic inflammation of the parotid glands.

Virus has been isolated from saliva, cerebrospinal fluid, blood, urine, brain, and other infected tissues.

Epidemiology. The source of infection is a patient. The research of recent years has shown that the virus is discharged only during the last days of incubation and the first days after onset of the illness. Patients cease to be contagious by the ninth day.

Mumps is endemic in most urban populations; the virus is spread from a human reservoir by direct contact, airborne droplets, fomites contaminated by saliva, and possibly by urine. It is distributed worldwide and affects both sexes equally; 85 % of infections occurred in children younger than 15 yr prior to widespread immunization. Susceptibility to mumps is lower than to other infections spread by an aerial-droplet route (like measles and chickenpox), and is the greatest between the ages of five and fifteen. The index of susceptibility is 0.5-0.7. Its incidence is relatively low in small children, and babies under 12 months are 'remarkably insusceptible to parotitis' (N. Filatov). The disease is not uncommon in adults, particularly under the age of 25, and there are many reports of epidemic outbreaks in military units.

Now disease often occurs in young adults, producing epidemics in colleges or in the work place. Epidemics appear to be primarily related to lack of immunization rather than to waning of immunity.

Epidemics occur at all seasons but are slightly more frequent in late winter and spring. Sources of infection may be difficult to trace because 30-40 % of infections are subclinical. There has been a decrease in the incidence since the introduction of mumps vaccine in 1968.

Virus has been isolated from saliva as long as 6 days before and up to 9 days after appearance of salivary gland swelling. Transmission does not seem to occur longer than 24 hr before appearance of the swelling or later than 3 days after it has subsided. Virus has been isolated from urine from the 1st-14th day after the onset of salivary gland swelling.

Lifelong immunity usually follows clinical or subclinical infection, although second infections have been documented. Transplacental antibodies seem to be effective in protecting infants during their first 6-8 mo. Infants born to mothers who have mumps in the week prior to delivery may have clinically apparent mumps at birth or experience illness in the neonatal period. Severity ranges from mild parotitis to severe pancreatitis. The serum neutralization test is the most reliable method for determining immunity but is cumbersome and expensive. A complement-fixing antibody test is available (see Diagnosis). The presence of V antibodies alone suggests previous mumps infection.

Pathogenesis. The pathogenesis and pathological anatomy of mumps have not yet been adequately studied. It is a general infection in which the virus develops not only in the salivary glands, but also in the blood and other organs. The possibility of primary infection in the menin-ges or testes has been established. All the data point to the view expressed long ago by N. Filatov that the virus invades the parotid glands not through Stensen's duct, but by way of the blood circulation.

The portal of entry is apparently the mucous membrane of the mouth, nose, and pharynx from which the virus penetrates into the blood and is carried secondarily to the salivary glands and other organs where it predominantly affects the interstitial tissue. The parotid gland is apparently the site of accumulation of the virus from which it is discharged into the environment with saliva.

The antibodies, whose titre attains its maximum in 2-4 weeks, appear during the first days of the disease.

Clinical manifestations.The incubation period of mumps lasts on average for 18 to 20 days, but extremes of 11 and 23 days occur. In children, prodromal manifestations are rare but may be manifest by fever, muscular pain (especially in the neck), headache, and malaise.

Its onset is characterized by elevation of temperature (up to 38° or 39°C) and swelling of the parotid gland (usually on one side, but sometimes on both). The swelling obliterates the fossa retromaxil laris and may spread downwards anteriorly and posteriorly to the neck (Fig. 36). When the swelling is considerable the auricle is lifted upward. The centre of the swelling is elastic-solid on palpation and painful when pressed; the thickness and the tenderness of the swelling fall off toward the periphery. A painless or slightly tender inflammatory oedema is seen on the periphery. At times it spreads to the face and far to the neck. The skin over the inflamed gland is tense and lustrous, but remains usually of normal colour. Swelling of the parotid gland is accompanied with pain irradiating to the ear or neck, that becomes more intense during chewing or swallowing.

In one or two days the parotid gland on the opposite side may become involved; and in about half the cases the submaxillary, and sometimes the sublingual, glands are affected. In submaxillitis palpation directly inward from the margin of the lower jaw displays a swollen, solid, and painful submaxillary gland, oval or round in shape (Fig. 37). Submaxillitis is sometimes accompanied with extensive oedema of the cervical cellular tissue; cases of isolated inflammation of the submaxillary gland and of its

primary affection with subsequent supervention of parotitis have been observed.The swelling of the affected gland increases for the first three to five days, then begins to regress and subsides by the eighth to tenth day. Resolution of the inflammatory infiltrate may be prolonged to several weeks, but as a rule the glands do not suppurate. Simultaneously with subsidence of inflammation the temperature falls, the pain declines, and the patient's general condition improves. If several glands are affected one after the other the disease may last for two and more weeks.

Mumps is sometimes attended, with bradycardia and enlargement of the spleen. Leucopenia or normocytosis, a relative lymphocytosis, and frequently monocytosis, are chief blood findings. The ESR usually falls or deviates a little from the normal.

A variety of mumps that must be mentioned is the abortive forms expressed in mild swelling of the parotid gland with little or no rise of temperature.

Pathological involvement of the nervous system and of various glandular organs is a typical feature of mumps. The lesions of these organs are more correctly considered a symptom rather than a complication of the disease, whose causative agent has a definite tropism.

Orchitis, which occurs in 10 to 35 per cent of young men and boys at puberty, usually develops on the sixth to eighth day of the disease. Rise of temperature, often accompanied with chill, malaise, and adynamia, and sometimes with delirium, excitation, and symptoms of circulatory failure are noted. More or less strong pain developing in one of the testes irradiates to the inguinal and lumbar regions. The testis enlarges, becomes tender and painful; the scrotum is oedematous and its skin is ofteq tense and red. A bilateral process is rare. The symptoms begin to subside in two or three days, and usually disappear completely by the end of the first week or the beginning of the second. Primary orchitis without previous affection of the salivary glands has been reported.

Oophoritis, mastitis and bartholinitis are rare manifestations of mumps in older girls and young women.

Pancreatitis normally manifests by strong epigastric pains and pains in the region of the left hypochondrium. Girdle pain occurs sometimes. Palpation is markedly painful. Nausea, anorexia, sometimes vomiting and diarrhoea occur. The diastase of the blood and urine increases highly. The pancreas may be affected in the presence of only part of these symptoms, or the symptoms may be nonmanifest. Mumps dacryocystitis have been described.

Acute serous meningitis is not infrequent in mumps, and mostly arises when the affection of the salivary glands is mild or moderate.

It usually develops at the height of the disease, and is characterized by symptoms of meningeal irritation (headache, frequent vomiting, rigidity of the occipital muscles, Kernig's and Brudzinsky's signs). The transparent or opalescent cerebrospinal fluid flowing in lumbar puncture is at normal or elevated pressure. Its protein content is normal or slightly increased, the cytosis is increased at the expense of lymphocytes (30-700 cells per mm^3). The sugar and chloride content is normal. The mumps virus is often discovered in the cerebrospinal fluid. All these symptoms persist for 5-10 days

and then subside gradually leaving no traces. Residual phenomena remain however in some patients'for long periods of time. Primary serous meningitis with or without subsequent affection of salivary glands has been encountered. The true nature of such meningitis is proved by the presence of characteristic epidemiological links, and by serological tests.

Complications. Viremia early in the infection probably accounts for the widespread complications.

Meningoencephalomyelitis. This is the most frequent complication in childhood. The true incidence is hard to estimate because subclinical infection of the central nervous system, as evidenced by cerebrospinal fluid pleocytosis, has been reported in more than 65 % of patients with parotitis. Clinical manifestations occur in over 10 % of patients. The incidence of mumps meningoencephalitis is approximately 250/100,000 cases; 10 % of these cases occurred in patients older than 20 yr. The mortality rate is about 2 %. Males are affected three to five times as frequently as females. Mumps is one of the most common causes of aseptic meningitis

The pathogenesis of mumps meningoencephalitis has been described as (1) a primary infection of neurons and (2) a postinfectious encephalitis with demyelination. Injecting mumps virus into suckling hamsters has produced similar lesions.

Mumps meningoencephalitis is clinically indistinguishable from meningoencephalitis of other origins.Moderate stiffness of the neck is seen, but the remainder of the neurologic examination is usually normal. The cerebrospinal fluid (CSF) usually contains fewer than 500 cells/mm^3, although occasionally the count may exceed 2,000. The cells are almost exclusively lymphocytes, in contrast to enteroviral aseptic meningitis, in which polymorphonuclear leukocytes often predominate early in the disease. Mumps virus can be isolated from cerebrospinal fluid early in the illness.

Atrophy of the optic nerve is encountered even more rarely.

Orchitis, Epididymitis. Approximately 30–40 % of affected testes atrophy. Impairment of fertility is estimated to be about 13 %, but absolute infertility is probably rare.

Oophoritis. There is no evidence of impairment of fertility.

Nephritis. Viruria has been reported frequently. In one study of adults, abnormal renal function occurred at some time in every patient, and viruria was detected in 75 %. The frequency of renal involvement in children is unknown. Fatal nephritis, occurring 10–14 days after parotitis, has been reported.

Thyroiditis. Although uncommon in children, a diffuse, tender swelling of the thyroid may occur about 1 wk after the onset of parotitis with subsequent development of antithyroid antibodies.

Myocarditis. Serious cardiac manifestations are extremely rare, but mild infection of the myocardium may be more common than is recognized. Electrocardiographic tracings revealed changes, mostly depression of the ST segment, in 13 % of adults in one series. Such involvement may explain the precordial pain, bradycardia, and fatigue sometimes noted among adolescents and adults with mumps.

Mastitis. This is uncommon in each sex.

Deafness. Unilateral, rarely bilateral, nerve deafness may occur; although the incidence is low (1:15,000), mumps is a leading cause of unilateral nerve deafness. The hearing loss may be transient or permanent.

Ocular Complications. These include dacryoadenitis, painful swelling, usually bilateral, of the lacrimal glands; optic neuritis (papillitis) with symptoms varying from loss of vision to mild blurring with recovery in 10–20 days; uveokeratitis, usually unilateral, with photophobia, tearing, rapid loss of vision, and recovery within 20 days; scleritis; tenonitis, with resultant exophthalmos; and central vein thrombosis.

Arthritis. Arthralgia associated with swelling and redness of the joints is an infrequent complication; complete recovery is the rule.

Thrombocytopenic Purpura. This sign is infrequent.

Mumps Embryopathy. There is no firm evidence that maternal infection is damaging to the fetus; a possible relationship to endocardial fibroelastosis has not been established. Mumps in early pregnancy does increase the chance of abortion.

Diagnosis.The diagnosis of mumps parotitis is usually apparent from the symptoms and physical examination. When the clinical manifestations are limited to those of one of the less common lesions, the diagnosis is not so clear but may be suspected, especially during an epidemic. The routine laboratory tests are nonspecific; there is usually leukopenia with relative lymphocytosis, but complications often result in polymorphonuclear leukocytosis of moderate degree. An elevation of serum amylase is common; the rise tends to parallel the parotid swelling and then to return to normal within 2 wk or so. The etiologic diagnosis depends on isolation of the virus from the saliva, urine, spinal fluid, or blood or the demonstration of a significant rise in circulating complement fixation antibodies during convalescence. Serum antibodies to the S antigen reach their peak early in about 75 % of patients and are detectable at the time of the presenting symptoms. They gradually disappear within 6–12 mo; antibodies against the V or viral antigen usually reach a peak titer in about 1 mo, remain stationary for about 6 mo, and then slowly decline during the ensuing 2 yr to a low level, at which they persist. The presence of a high anti-S titer and a low anti-V titer during the acute stage of an otherwise undiagnosed meningoencephalitis, for example, strongly suggests a mumps infection, which would be confirmed if a convalescent serum (taken 14–21 days later) revealed a fourfold rise of anti-V antibodies accompanied by little change in the titer of anti-S antibodies.

Differential diagnosis. Difficulties in diagnosing mumps occur in mild and abortive forms, and when only submaxillary glands are affected, or the meningitis or orchitis is its first manifestation. Diagnosis is established from the features of the clinical course described above and the epidemiological data.

The secondary parotitis developing in the course of severe acute infections (typhoid fever and typhus, sepsis, pneumonia, etc.) is usually unilateral and, as a rule, suppurative.

Toxic parotitis is met mainly in adults suffering from acute or chronic mercury, lead, or iodine poisoning; it develops slowly, does not run a cyclic course, and is often accompanied with changes in the buccal mucous membrane.

Cervical lymphadenitis is differentiated from mumps by an inflammatory focus in the fauces with localization of the swelling in the region of superior cervical lymph nodes. In mumps the swelling first obliterates the sulcus between the mandible and the mastoid process (directly under the auricle). Determination of diastase in the urine may be useful in diagnostication of pancreatitis.

Primary meningitis of mumps aetiology can be confused with tuberculous meningitis. The latter develops slowly and gradually, the pressure of the cerebrospinal fluid is increased and its sugar content lowered; it may contain Mycobacterium tuberculosis. It is more difficult to differentiate primary meningitis of mumps aetiology from acute serous meningitis caused, for instance, by an enteroviris. Diagnosis is established either on the basis of subsequent inflammation of the salivary glands, or when there is a history of exposure to mumps. An accurate diagnosis is made with the help of virological and serological methods.

The complement-fixation and haemagglutination inhibition tests (isolation of the causative agent in the culture of cells) have been suggested as auxiliary methods for early diagnosis of mumps. Both reactions can be made with a standard antigen, a diagnostic culture, consisting of the virus grown on the membranes of a developing chick embryo. Both these tests should be made twice, once during the first week, and again at the end of the second week or during the third. Thus, elevation of antibody titre, which has special diagnostic value, is revealed.

This includes parotitis of other origin, as in viral infections including human immunodeficiency virus (HIV) infection, influenza, parainfluenza 1 and 3, cytomegalovirus, or the rare instances of coxsackievirus A and lymphocytic choriomeningitis infections. These infections can be distinguished by specific laboratory tests; suppurative parotitis, in which pus can often be expressed from the duct; recurrent parotitis, a condition of unknown origin, but possibly allergic in nature, which has frequent recurrences and a characteristic sialogram; salivary calculus, obstructing either a parotid or, more commonly, a submandibular duct, in which the swelling is intermittent; preauricular or anterior cervical lymphadenitis from any cause; lymphosarcoma or other rare tumors of the parotid; orchitis resulting from infections other than mumps, for example, the rare infections by coxsackievirus A or lymphocytic choriomeningitis viruses; and parotitis caused by cytomegalovirus in immunocompromised children.

Prognosis is favourable. Mortality of mumps is remarkably low. Affection of the internal ear may lead to permanent deafness. Atrophy of the testes with subsequent aspermia can follow bilateral orchitis.

Treatment. Treatment of parotitis is entirely symptomatic. Diet is restricted to fluids or semi-fluids to spare the affected glands. Heat is applied to the glands by means of cotton or wool bandages, Sollux lamp, etc. Ultra-high frequency therapy and ultra-violet irradiation are also recommended.

The mouth should be rinsed with weak disinfecting solutions. In severe mumps some investigators recommend gamma-globulin (3-6 ml). Strict confinement to bed is called for in orchitis; the testis should be supported and cold applied. Corticosteroid preparations produce considerable alleviation of pain and subjective improvement. To

relieve the severe headache and other meningeal symptoms in concomitant meningitis lumbar puncture, which is also recommended when complications develop in the inner ear. Dehydration therapy is carried out.

Mumps arthritis may respond to a 2-wk course of corticosteroids or a nonsteroidal anti-inflammatory agent. Salicylates do not appear to be effective.

Prophylaxis. Passive. Hyperimmune mumps gamma globulin is not effective in preventing mumps or decreasing complications.

Active. Vaccinated children usually do not experience fever or other detectable clinical reactions, do not excrete virus, and are not contagious to susceptible contacts. Rarely, parotitis can develop 7–10 days after vaccination. The vaccine induces antibody in about 96 % of seronegative recipients and has a protective efficacy of about 97 % against natural mumps infection. The protection appears to be long lasting. In one outbreak of mumps, several children who had been immunized with mumps vaccine in the past experienced an illness characterized by fever, malaise, nausea, and a red papular rash involving the trunk and extremities but sparing the palms and soles. The rash lasted about 24 hr. No virus was isolated from these children, but increases in the titer of mumps antibody were demonstrated

PART 10 **MENINGOCOCCAL INFECTION**

The causative agent of epidemic meningitis is Weichselbaum's meningococcus (Neisseria meningitidis). This microorganism has the form of a diplococcus 0.6-0.8 mm in size, and is gram-negative, its growth is facilitated in a moist environment at 35–37 ^{0}C. The meningococci have been divided into serogroups based on antigenic differences in their capsular polysaccharides. At least 13 serogroups have been identified, but groups A, B, C, W, and Y account for most meningococcal disease. The other serogroups often colonize the nasopharynx but rarely disseminate. Lipooligosaccharides (e.g., endotoxin) and proteins that found in the outer membrane complex are also used to serotype meningococcal strains.

Epidemiology. The sources of infection are sick persons and carriers who expel the causative agent with the secretions of the nasopharynx and upper respiratory passages. Since there are a great many more carriers than patients, the epidemiological role of the former is very great.

The aerial-droplet route transmits infection. Children are mostly susceptible to the disease: about 70 % of incidence are infants under 5. The proportion of adults increases in epidemics. Those who suffer from meningitis or meningococcal carrier state, develop immunity, and recurrent epidemic meningitis is rarity.

The meningococcal infection is characterized by periodic rises of the incidence at 10-15 or longer year intervals. Meningococcal disease, particularly group A, remains a major health problem in much of the developing world. Many areas, such as China and Africa, have an endemic rate of disease of 10–25 per 100,000 persons and major periodic epidemics (100–500 cases/100,000). Epidemic disease typically involves individuals who are older than those with endemic disease.

Seasonal variations in the incidence are also observed; it increases in winter and early spring months. The incidence depends on the specific immunity of the population. High density of population, the absence of proper hygiene, and improper sanitation favour the spreading of the disease.

Pathogenesis and pathological anatomy. The portal of the infection entry is the nasopharyngeal mucosa. Colonization of the nasopharynx with meningococci usually leads to asymptomatic carriage, and only rarely does dissemination occur. Colonization can persist for weeks to months. Carriage rates vary from 2–30 % in a normal population during nonepidemic periods.

The carrier-state develops frequently then nasopharyngitis. For colonization to take place, meningococci must evade mucosal IgA and adhere to epithelial cells in the nasopharynx due to the secretion of proteases. The bacteria enter nonciliated epithelial cells by a parasite-directed endocytotic process and are carried across the cell in membrane-bound vacuoles.

Meningococci disseminate from the upper respiratory tract through the bloodstream. Serum antibody leading to complement-mediated bacterial lysis has been shown to block this dissemination, and a deficiency of antimeningococcal antibody is associated with the development of meningococcemia. Individuals with primary or acquired complement deficiency have an increased risk of developing meningococcal disease and 50–60 % of individuals with properdin, factor D, or terminal-component deficiencies develop bacterial infections that are caused almost solely by N. meningitidis. Bactericidal antibody is directed against the capsular polysaccharide, subcapsular protein, and lipooligosaccharide antigens. Newborn infants have protective antibody that is primarily IgG of maternal origin. As this antibody wanes, infants 3–24 mo of age experience the highest incidence of meningococcal disease.

The generalized form of infection occurs only in 0.5-1 % of cases. Meningococcal bacteraemia or meningococcaemia manifests sometimes as sepsis.

The important role in meningococcaemia belongs to marked intoxication with the endotoxin released during decomposition of the microbial bodies. The concentration of circulating endotoxin is directly correlated with activation of the fibrinolytic system; development of disseminated intravascular coagulopathy, multiple organ system failure, septic shock, and death. Various organs are affected, in the first instance fine vessels.

Cutaneous hemorrhages, ranging from petechiae to purpura, occur in most fatal infections and are associated with acute vasculitis with fibrin deposition in arterioles and capillaries. Diffuse adrenal hemorrhage may occur at patients with fulminant meningococcaemia (i.e., Waterhouse-Friderichsen syndrome). Acute inflammatory cells in the leptomeninges and perivascular spaces characterize meningitis.

Clinical classification by V.Pokrovsky:

1. Local forms
    - nasopharyngitis
    - healthy carrier

2. Generalized forms
    - meningitis
    - meningococcemia
    - meningoencephalitis
    - meningitis+meningococcemia
3. Rare forms
    - arthritis
    - iridocyclitis
    - chorioiditis
    - pneumonia

Clinical picture. The incubation period lasts for 3-5 days on average (maximum 10 days).

The most frequent form of the manifest meningococcal infection is nasopharyngitis. Its symptoms are headache, painful swallowing, subfebrile temperature in some patients, hyperemia of the nasopharyngeal mucosa and hyperplasia of lymphoid follicles, rhinitis with scanty discharge, and difficult nasal breathing. The clinical signs persist for 5-7 days.

Meningitis. The onset of the disease is usually violent, and a considerable elevation of temperature accompanied by chill is noted; severe headache, vertigo, and vomiting also occur. Catarrh of the nasopharynx is common. Characteristic is hyperaesthesia of the skin and increased sensitivity to light and sound. Disturbances of consciousness are also frequent. In young children clonic and tonic convulsions are often.

Rigidity of the occipital muscles develops very early (usually during the first 24 or 48 hours), and Kernig's and Brudzinsky's signs become positive. The abdomen is retracted. Anisocoria, strabismus, and paresis of the facial nerve are occasional. The patient's posture is usually typical: he is lying on his side with head tossed back and legs flexed to the abdomen.

Red dermographism is very common and herpes often occurs on the lips. The pulse is initially rapid, but slows down later. Respiration is usually accelerated. Constipation is common in older children, but diarrhea is often seen in infants. The blood shows marked hyperleucocytosis, neutrophilosis with a shift to the left, aneosinophilia; the ESR is considerably increased.

In lumbar puncture spinal fluid flows under increased pressure (300-500 mm H_2O). During the first day of illness it may be transparent or slightly opalescent, but later becomes turbid and purulent. It displays marked neutrophilosis (from several hundreds to several thousands of cells per mm^3) and a considerable protein content (up to 1-2 g/1 and more), sugar content is lowered.

The meningococcaemia (septic form) occurs at patients of all ages. The onset is acute and violent, with intermittent fever. This infection is usually attended by skin rash, which is the most frequent symptom. The rash is haemorrhagic, often with macular (measles-like) lesions. The haemorrhagic lesions are stellar formations varying in size; they are hard to palpation and are often elevated over the skin level. They are usually localized on the but-

tocks and lower extremities, less frequently on the arms, the trunk, and the face. Meningococci are found in blood smears taken from the periphery of the lesions.

Significant haemorrhage into the skin is often followed by necrosis of the tissues with subsequent rejection of the necrotized tissue; scars remain on the skin.

Arthritis in meningococcaemia is less frequent (5 % of cases). Several joints would be usually affected, with a purulent or a seropurulent exudate in the joint capsule. Inflammation of the chorioidea (iridocyclochorioiditis) is a less common, but very typical, complication of meningococcaemia; its first sign is a change in the colour, which becomes sort of rusty.

The hypertoxic (fulminating) form of meningococcal infection has a sudden turbulent onset and is characterized by grave toxemia (uncontrollable vomiting, convulsions, clouded consciousness, and cardiovascular weakness). The patient soon becomes comatose. Meningeal symptoms are sharply pronounced or, on the contrary, rudimentary. Death usually ensues within 12 to 24 hours after the onset. Swelling of the brain and protrusion into the great foramen is one of the frequent causes of death.

The fulminating form may develop as the Waterhouse-Friderichsen syndrome. Multiple petechiae and hemorrhage into the skin are characteristic. The arterial pressure falls progressively; the pulse is rapid and hardly palpable. Cyanosis, vomiting (often with blood) and convulsions are other signs. The patient is prostrated and loses his consciousness. The patient dies in 16-30 hours after the onset of the disease unless an urgent and effective therapy is given.

Next form is the meningoencephalitic form is seen mainly in infants and has a prevalence of cortical symptoms, namely disturbances of consciousness, convulsions, focal phenomena paresis, paralysis. The meningeal symptoms may be trivial.

In the rudimentary (abortive) form all the symptoms are weakly expressed, including the meningeal. The changes in the cerebrospinal fluid may be insignificant and transitory.

Features peculiar to meningitis in nursing babies. Onset of the disease is accompanied with high temperature, general restlessness, vomiting, and refusal to suckle. There is marked hyperaesthesia and frequent dyspeptic disturbances. Infants scream loudly. Meningeal symptoms and red dermographism are often mild or absent. Tension and protrusion of the unossified anterior fontanelle are apparent at the beginning of the disease. In the newly born the course of meningitis as a rule is atypical. High temperature, convulsions or tremor, and general muscular hypertension develop. Meningeal symptoms are absent or become apparent only with further progress of the disease. Even with modern methods of treatment mortality remains high among the newly born and babies less than three months old.

Complications. Some patients develop complications associated with the bacterial superinfection. Pneumonia develops mainly in grave meningococcaemia with disordered consciousness: the patient runs a risk of aspiration of his vomit, and mucus from the pharynx and the upper airways.

Chronic hydrocephalus, motor disorders (paralyses, pareses), retardation of mental growth are now rare. Asthenia, headache, and various functional disorders are observed.

Diagnosis. Diagnosis of epidemic meningitis is established from the distinctive features of the clinical symptomatology and course (acute onset and rapid development of meningeal symptoms). The most important diagnostic aid is lumbar puncture and examination of the cerebrospinal fluid. The diagnosis is indisputable when meningococcus is detected by bacterioscopy or is found in a cerebrospinal fluid culture.

Errors in recognizing epidemic meningitis in children are not infrequent: epidemic meningitis can be confused with other forms of meningitis, with various diseases accompanied with meningism syndrome.

Meningeal symptoms are usually mild in meningism and the cerebrospinal fluid unchanged.

Tuberculous meningitis starts gradually and is accompanied with moderate pyrexia; it is recognized from the anamnesis and the results of tuberculin tests. Miliary tuberculosis often shows up on X-ray pictures of the lungs. Cerebrospinal fluid is transparent or slightly opalescent; cell count is moderately increased through an increase in the number of lymphocytes. When cerebrospinal fluid is allowed to stand a delicate web-like pellicle of fibrin forms on its surface. Mycobacterium tuberculosis is often found in the cerebrospinal fluid.

Acute serous meningitis differs in the cerebrospinal fluid findings (complete transparency; moderately increased cell count through a higher number of lymphocytes; normal sugar content). Acute serous meningitis is not infrequent in mumps, and mostly arises when the affection of the salivary glands is mild or moderate.

It usually develops at the height of the disease, and is characterized by symptoms of meningeal irritation. The transparent or opalescent cerebrospinal fluid flowing in lumbar puncture is at normal or elevated pressure. Its protein content is normal, there are 30-700 cells per mm^3. The sugar and chloride content is normal. The mumps virus is often discovered in the cerebrospinal fluid. All these symptoms persist for 5-10 days and then subside gradually leaving no traces. Primary serous meningitis with or without subsequent affection of salivary glands has been encountered. The true nature of such meningitis is proved by the presence of characteristic epidemiological links, and by serological tests.

In the meningeal form of poliomyelitis the cerebrospinal fluid is transparent. A slight or moderately increased cell count and normal or slightly increased protein content (cellular-protein dissociation) is noted during the first five days; later the cell count drops, and a protein-cellular dissociation is observed from the tenth day. Lymphocytes predominate among the cells. Diagnosis is facilitated if tendon reflexes disappear, and even more so if flaccid paralysis or paresis develops.

In contrast to primary meningococcus meningitis, purulent meningitis caused by staphylococcus, pneumococcus, Afanasyev-Pfeiffer bacillus, and streptococcus usually develops secondarily to purulent otitis, pneumonia, sepsis, etc. Gram-positive cocci and diplococci are found in the cerebrospinal fluid, which is purulent.

Staphylococcal meningitis. This occurs usually in the newborn baby who often has associated umbilical sepsis, pyoderma or septicemia. In older children it follows otitis media, mastoiditis, sinus thrombosis and septic lesions of the scalp.

Hemophilus influenzae meningitis. Usually the type B organisms are responsible. It is frequent in children between the age of 3 and 12 months. Subdural effusions follow the initial illness. This complication should always be suspected in infants in whom focal neurological signs and fever persist. Convulsions are common. Residual auditory deficit is a common complication.

Subarachnoid hemorrhage. Sudden headache and sensorial alteration occur without preceding fever. The course of illness is rapid and signs of meningeal irritation are marked. A CT scan and cerebrospinal fluid may reveal the diagnosis. Death occurs early if unrecognized and not treated.

Difficulties in differential diagnosis of meningococcaemia arise in cases where it has no symptoms of meningitis, and may be mistaken for septicaemia of other etiology, thrombopenic purpura, and haemorrhagic vasculitis. It should be remembered that meningococcaemia is characterized by high temperature, pronounced intoxication, marked changes in the blood (hyperleucocytosis with the shift to the left); a stellar pattern of haemorrhagic eruption is typical. Accurate diagnosis is established bacteriologically. Meningococcus can be detected not only in the blood but also in the skin lesions.

Prognosis. Despite the use of appropriate antibiotics, the mortality rate for disseminated meningococcal disease remains at 8–12 % and more. Poor prognostic factors include hypothermia, hypotension, purpura fulminans, seizures or shock on presentation, leukopenia, thrombocytopenia, and high circulating levels of endotoxin and tumor necrosis factor. Some studies have included the development of petechiae within 12 hr of admission, hyperpyrexia, and the absence of meningitis.

Treatment. Aqueous penicillin G is the drug of choice to treat meningitis and should be given in doses of 300000 - 400000 units per kg of body weight daily at intervals of three to four hours (infants under 3 months of age are given 400 000 - 500 000 U/kg). The treatment should be continued for 7-10 days without reducing the dose.

Cefotaxime (200/mg/24 hr) and ceftriaxone (100 mg/kg/24 hr) are effective empirical therapy for meningococcal disease and may be useful in patients who are allergic to penicillin. A marked therapeutic effect can already be seen during the first two days.

When to stop antibiotics therapy:

- No fever for 5 days
- Cerebrospinal fluid protein and sugar return to normal lev els
- Cell count in the cerebrospinal fluid is less then 30/mm3 and 70 % of than are lymphocytes.

Children with meningococcemia can be given antibiotics of bacteriostatic action - laevomycetin sodium succinate (50-100 mg/kg for 6-8 days) during first day of disease, simultaneously with big dozes of hormones.

In addition to etiolotropic preparations, pathogenic and symptomatic therapies are also important. Toxicosis can be controlled by administration of large amounts of liquids (ample drinking, intravenous infusion of physiological solution, glucose solution, plasma substitutes, and plasma); electrolyte balance and osmotic pressure should be taken into consideration. Dehydration therapy should be especially intensive in the presence of brain swelling (respiratory ar-

rhythmia, convulsions, cyanosis, and arterial hypertension). Corticosteroids should be given simultaneously. Osmotic diuresis – 0.5 gm/kg of 20 % mannitol is administered every 4 hours.

Seduxen, aminazine, phenobarbital, sodium oxybutyrate are given in the presence of convulsions. Vitamins should also be given. To correct metabolic acidosis, a 4 per cent sodium bicarbonate solution should be given to the patient; hypokalaemia can be corrected by potassium preparations (7.5 % potassium chloride solution, panangin). To improve the cardiovascular function ATP, and cocarboxylase are indicated.

The patient needs adequate care and supervision, and good nutrition. Grave forms of meningococcal infection require urgent aid and should be treated at resuscitation and intensive therapy departments.

Prophylaxis. The following measures are carried out in an epidemic focus. The patient is hospitalized and isolated; he is discharged after the clinical manifestations of the disease subside and two negative results of bacteriological studies of the pharyngeal mucus.

Child contacts and exposed adults are quarantined (isolated at home). Only after a negative bacteriological report (examination of nasopharyngeal discharge) or after 7 days of separation from the patient they admitted to children's institutions.

It is advisable that contacts should be treated with sulphonamides or antibiotics (Rifampin) for 5 days as a prophylactic measure, the standard dose being given.

A quadrivalent vaccine composed of capsular polysaccharide of meningococcal groups A, C, Y, and W-135 is licensed in the United States. The vaccine is immunogenic in adults but is unreliable in children under 2 yr of age. The group B polysaccharide is poorly immunogenic in children and adults, and no vaccine is available against this serogroup.

Immunization is useful to control outbreaks of meningococcal disease of the serogroups represented in the quadravalent vaccine. It is also recommended for travelers to countries with a high incidence of meningococcal disease. Individuals with anatomic or functional asplenia and those with complement component deficiencies should be immunized.

PART 11 WHOOPING-COUGH (pertussis)

The causative agent of whooping cough is the Bordet-Gengou bacillus Haemophilus (Bordetelld) pertussis, discovered in 1906, a small, ovoid, non-motile rod 0.5 to 2.0 urn long, gram-negative, strictly aerobic, and haemoglobinophilic. It grows best on a potato-glycerol blood agar (Bordet-Gengou culture medium). Other nutrients, however, particularly casein-carbon agar medium, are now widely used. When cultured, the bacillus forms small, round, lustrous colonies resembling drops of mercury. Its resistance is very low. B. pertussis and B. parapertussis are exclusive pathogens of humans (and some primates). B. bronchiseptica is a common animal pathogen.

Sydenham first used the term pertussis (intense cough) in 1670; it is preferable to "whooping cough" since most infected individuals do not whoop. The most closely studied factors of the microbial cell evoking a response in the organism are agglutinogen (allergen), toxin, and haemagglutinin.

Epidemiology. During the prevaccine era of 1922 - 1948, pertussis was the leading cause of death from communicable disease among children under 14 yr of age.

The source of infection in whooping-cough is a sick person. The disease is particularly infective in the initial stage, but gradually becomes less contagious. Patients continue to discharge H. pertussis up to the 28-30th day, and very rarely a little longer. Treatment with antibiotics shortens the period of infectivity.

Susceptibility to whooping cough is high, but not as high as to measles (in non-immune group the index of susceptibility is 0.7). Its heaviest incidence is in children between one and five, but unlike other infections it very often affects very young children not sparing babies of a few months or even a few days old. Pertussis is extremely contagious, with attack rates as high as 100 % in susceptible individuals exposed to aerosol droplets at close range. B. Pertussis does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented.

Neither natural disease nor vaccinations provide complete or lifelong immunity against reinfection or disease. Protection against typical disease begins to wane 3–5 yr after vaccination and is unmeasurable after 12 yr. Subclinical reinfection undoubtedly contributes significantly to immunity against disease ascribed to both vaccine and prior infection.

Patients with abortive forms and patients with asymptomatic forms of whooping-cough (actually carriers) can also be sources of infection. It must be supposed that the absence of cough in carriers sharply reduces their infectivity.

Infection is transmitted by the aerial-droplet route, but is possible only by direct, more or less lengthy, contact with a patient. Isolation of patient in separate wards or semicubicles, therefore, prevents dissemination of infection. Transmission via objects or intermediaries occurs only in exceptional cases owing to low viability of the causative agent.

The high susceptibility of children and unfavourable housing and living conditions (overcrowding, for example) are conducive to epidemic spread of the infection. Regular and constant seasonal variations in its incidence are not characteristic, but either a spring-summer or a winter peak in the epidemic wave may occur depending on conditions.

Pathological anatomy. The commonest lesions are in the respiratory organs. Laryngoscopy reveals catarrh of the larynx and trachea during the catarrhal stage. This picture of common catarrh of the larynx, trachea, and bronchi is a postmortem finding at patients dying during the paroxysmal stage, and only in rare, particularly severe, and complicated cases is there superficial epithelial necrosis in the respiratory tract. There is the spastic condition of the bronchial muscles. Atelectases and microfocal and confluent bronchopneumonia are apt to occur, but the pulmonary lesions have no features of any kind specific to whooping-cough. There is marked derangement of the blood and lymph circulation (lymphostasis and haemostasis). Congestion of the pulmonary circulation, dystrophic changes of the myocardium, and dilatation of the right ventricle of the heart with hypertrophy of its walls are not uncommon. A constant postmortem finding is lesions of the nervous system: the disturbance of circulation expressed mainly in marked dilatation of cerebral capillaries and oedema of the brain; haemorrhages into the brain matter are not uncommon.

Pathogenesis. The portal of entry of infection in whooping cough is the upper respiratory tract. H. Pertussis settles in the mucous membrane of the larynx, bronchi, and bronchioles, and also in the pulmonary alveoli, but no bacteriaemia or penetration of the causative agent into the organs and tissues occurs.

Only B. pertussis expresses pertussis toxin (PT), the major virulence protein. Serotyping is dependent upon heat-labile K agglutinogens. Of 14 agglutinogens, 6 are specific to B. pertussis. Serotypes vary geographically and over time.

B. Pertussis produces an array of biologically active substances, many of which are postulated to play a role in disease and immunity. Following aerosol acquisition, filamentous hemagglutinin (FHA), some agglutinogens (especially FIM2 and FIM3), and a 69-kD nonfimbrial surface protein called pertactin (PRN) are important for attachment to ciliated respiratory epithelial cells. Tracheal cytotoxin, adenylate cyclase, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, dermonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptomatology and facilitates absorption of PT. PT has multiple proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction), some of which may account for systemic manifestations of disease.

The principal pathogenic factor is the toxin produced by H. pertussis, which brings the cough reflex into play by its intense irritation of the nervous receptors of the respiratory mucosa. Toxin absorbed into the blood, on the other hand, has general effect (chiefly on the nervous system), expressed in marked tendency to generalized vascular spasm (arterial hypertension), spasm of the small bronchi and vocal cords, and in spasmodic twitching or even attacks of clonicotonic convulsions of the skeletal muscles.

The mechanism of one of the chief symptoms of whooping-cough the paroxysmal bouts of coughing is most fully and convincingly explained by the conception advanced by A. Dobrokhotova, I. Arshavsky, and V. Soboleva. Its essence is as follows. The continuous flow of impulses coming from receptors in the mucosa of the respiratory tract leads to the development of a stable focus of excitation in the central nervous system, characterized by signs of dominance by A. Ukhtomsky. Formation of this focus is apparently aided by the effect of pertussis toxin upon the central nervous system already mentioned. Paroxysms of coughing result, therefore, not only from impulses arriving from the respiratory tract, but also in response to stimulation of receptor regions not connected with the cough reflex; a fit can be provoked, for example, by examination of the throat, injections, or a loud noise, etc. Owing to the inert character of the dominant focus, paroxysms can persist for a long time after recovery from the infection. The dominant focus becomes inhibited when other, stronger centres of excitation arise. This mechanism is probably responsible for the absence of fits of coughing during absorbing, interesting games. The cough, being an unconditioned reflex action, can become established as a conditioned reflex action as the disease develops. A paroxysm may be provoked, for example when the doctor visits the ward or by the sight of a spatula, etc.

As a result of the frequent and prolonged paroxysms of coughing, and of the circulatory disturbances in the lungs, pulmonary ventilation becomes disturbed leading to hypoxaemia and hypoxia. When the latter develops, a major role is probably played by the lesions to the capillary wall (disturbance of its permeability) caused by the pertussis endotoxin. Such symptoms of the nervous system as convulsions are apparently associated with disturbed cerebral circulation and with the hypoxaemia resulting from reduced pulmonary ventilation; but a direct effect of the pertussis toxin on the central nervous system may also be responsible for their development. Inadequate supply of oxygen to the tissues, and disruption of oxidation processes, leads to the development of acidosis, while hypoxia and acidosis in turn aggravate the disturbed function of the nervous system.

Secondary flora (pneumococcus, streptococcus, etc.) plays a major role in the development of complications, which are particularly frequent when whooping-cough is combined with other infections, e.g. influenza, catarrh of the upper respiratory tract, measles or dysentery.

Clinical picture. The incubation period of whooping-cough is 3 to 15 days and averages 5 to 8 days. The course of the disease can be divided into three stages: catarrhal, paroxysmal, and convalescent.

The first, catarrhal stage is attended with a moderate rise in temperature, but the latter may sometimes be subfebrile, or even normal. Significant fever (above 39°C) is rare. A dry cough with no specific features develops in the first days. This symptom intensifies gradually, becoming the leading one in the clinical picture of the disease. By the end of the catarrhal period the cough takes on the character of more or less prolonged paroxysmal bouts, occurring mostly at night. Cold in the nose is also often noted during the catarrhal stage, but the patient's general state is not much disturbed, if at all. Appetite is normal. The catarrhal stage lasts for three to fourteen days, but may sometimes be shorter, especially in nursing babies. In other cases, on the contrary, it may be protracted.

The transition to the second, paroxysmal stage is gradual. Fits of spasmodic or convulsive coughing develop. At the height of the disease paroxysms are unmistakable; they begin suddenly, or after a brief precursor (aura)—a feeling of irritation in the throat, pressure in the chest. The fit consists of a series of short coughs following one another in rapid succession without a break. Then the child makes an inspiration which, owing to laryngeal spasm, is accompanied with a crowing sound (whoop). The paroxysm is then repeated in the form of the same successive spells with a subsequent whoop. There may be several whoops during a bout. The more severe the whooping-cough, the more prolonged are the paroxysms and the greater the number of whoops. A bout often ends in expectoration of viscid, transparent mucus and sometimes vomiting. In severe fits the mucus may be bloodstained. Vomiting, however, is not an absolutely constant sign, but the more severe the whooping-cough, the more often it occurs. In mild forms there may be only occasional or no vomiting. Whoop (forceful inspiratory gasp) infrequently occurs in infants under 3 mo that are exhausted or lack muscular strength to create sudden negative intrathoracic pressure. The outward appearance of the patient during a fit is characteristic. The face becomes red or even takes on a cyanotic hue; the cervical veins

become engorged; the eyes are injected and filled with tears; the tongue is forcibly protruded to the limit, and it's tip curves upward; and in severe bouts urine and faeces may be involuntarily passed.

Adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then the chest heaves and air rushes into the lungs, usually without a whoop. Post-tussive emesis is common in pertussis at all ages and is a major clue to the diagnosis in adolescents and adults. Post-tussive exhaustion is universal.

Various external stimuli (examination of the throat, dressing and undressing, feeding, a loud noise, the crying of children, etc.) can provoke a fit. Many clinicians have noted that bouts occur mostly at night. For diagnostic purposes a fit of coughing can be provoked by pressing against the larynx and or by pressing the root of the tongue with a spatula.

As a result of frequent paroxysms accompanied with disturbed circulation and congestion, the patient's face and eyelids become swollen, and haemorrhages sometimes appear in the skin and conjunctiva. In severe cases the oedema also involves the whole body, particularly the lower limbs.

When the oral cavity is examined a shallow ulcer on the frenulum of the tongue is found, which soon becomes covered by a white protruding film. The ulcer results from mechanical rubbing of the frenulum against the sharp edges of the lower incisors.

In uncomplicated whooping-cough general condition is not disturbed in most patients, even when bouts are frequent, so that children lead their normal life playing between attacks; their appetite is not impaired. Temperature, which rises moderately in the catarrhal stage, usually falls to normal in most patients by the time coughing fits begin; only slight subfebrile elevations occasionally occur. Marked pyrexia during the paroxysmal stage is usually indicative of a complication.

Signs of emphysema are often found during examination of the lungs. Auscultation reveals dry and dull moist rales. Heightened transradiancy of lung tissue, low position and flatness of the diaphragm (signs of emphysema), increased shadow of hili, intensified pulmonary pattern, and reticulations or linear bands are revealed by X-ray examination. Sometimes, mostly in older children, a shadow is distinguished in the form of a triangle, with its base on the diaphragm and the apex in the region of the hilus ('a basal triangle'). In the cardiovascular system an acceleration of pulse is noted during paroxysms, and an elevation of arterial and venous pressure. Capillary resistance is reduced, which encourages haemorrhages into the skin and mucous membranes. Signs of the nervous system involvement are irritability, in severe case inertness, adynamia, disturbed sleep, convulsive twitching of the facial muscles, and sometimes dimmed consciousness.

In the overwhelming majority of patients' blood counts reveals marked leucocytosis and lymphocytosis. The number of leucocytes may reach $20 \cdot 10^9/1$-$70 \cdot 10^9/1$ and over. The leucocytosis to some extent depends on the severity of the disease: as a rule, the more serious the case, the higher the leucocyte count. The ESR is either lowered or

normal. These haematological shifts are already met in the catarrhal stage, and disappear as the infectious process is overcome. The paroxysmal stage lasts from two to eight weeks. The frequency and severity of attacks gradually diminish as the disease passes into the third stage.

During convalescence the cough is no longer paroxysmal and bouts gradually become less frequent. The sputum becomes mucopurulent. As paroxysmal stage fades into convalescence, the number, severity, and duration of episodes diminish. All symptoms of the disease subside gradually. This stage lasts from two to four weeks, so that the overall duration of the disease varies between five and twelve weeks and even more protracted cases have been observed.

Clinical forms. Three principal forms of whooping-cough are distinguished: mild, moderate, and severe. In the mild form the frequency of coughing fits is between five and fifteen a day; they are typical, but short, and only rarely end in vomiting. The patient's condition is undisturbed. In the moderate form the number of fits varies between 15 and 24; they are protracted, with 5-10 whoops, and often end in vomiting. The patient feels unwell, but is not seriously ill. In the severe form, there are numerous bouts of coughing (25 to 30, or more, a day). Paroxysms are severe and last up to 15 minutes, with ten whoops, and almost always terminate in vomiting. Disturbed sleep, loss of appetite, loss of weight, adynamia and often a long febrile state are noted. In young children, even with a moderate frequency and short duration of fits, whooping-cough can take a very serious course.

An abortive form of pertussis, characterized by the absence of typical attacks with coughing relapses, and by a shortened course, often occurs in recent years in addition to the three main forms of the disease. These forms occur mostly in vaccinated children.

The course of whooping-cough in vaccinated children is usually mild or abortive, if compared to the unimmunized; complications are less common, haematological shifts are less pronounced, and the outcome is more favourable. Immunized children have foreshortening of all stages of pertussis. Adults have no distinct stages.

In infants under 3 mo the catarrhal phase is usually a few days or not recognized at all when apnea, choking, or gasping cough herald the onset of disease. Convalescence includes intermittent paroxysmal coughing throughout the 1st yr of life including "recurrences" with subsequent respiratory illnesses; these are not due to recurrent infection or reactivation of B. pertussis.

Diagnosis. The most important condition for effective control of whooping-cough is its recognition at the initial (catarrhal) stage, when it is most infective. But diagnosis at that stage presents considerable difficulties. It is also sometimes difficult to establish the diagnosis when the disease runs an atypical course, especially in babies a few months old.

In diagnosis of whooping-cough the distinctive features of it's clinical course must be considered - it's cyclic character, paroxysmal bouts of coughing with whoops, ending with expectoration of viscid mucus and vomiting, typical appearance of the patient, ulcer on the frenulum of the tongue, etc.; and also typical haematological shifts;

the results of X-ray examination of the chest and analysis of the epidemiological situation are also of value.

Bacteriological tests can also be of great diagnostic aid, particularly during the early stage of whooping-cough. Testing for H. pertussis is usually done by means of 'cough plates': an open Petri dish of nutrient medium is held five to eight centimetres from the patient's mouth during a paroxysm. A sterile cotton tampon is now used to take the material from the nasopharynx for examination for the pertussis bacillus. Microbiological studies are very valuable for diagnosis of pertussis. It should be noted that when pertussis is treated with antibiotic cultivation of the pertussis bacillus for diagnostic purpose is effective only in rare cases. To accelerate diagnosis, an immunofluorescence method is now recommended by which the pertussis microbe can be detected directly in the mucus taken from the nasopharynx. Agglutination and complement-fixation reactions have also been suggested. They are particularly convincing when repeated tests show increasing immunological shifts. But these reactions only become positive from the second week of the paroxysmal stage; they are often negative in nursing babies. The reactions are thus mainly employed for retrospective diagnosis.

The catarrhal stage of whooping-cough has to be differentiated from influenza, viral catarrhs of the upper respiratory tract, and measles. It is distinguished by less pronounced nasal and conjunctival catarrh and by more frequent nocturnal fits of coughing; another distinctive sign is marked by leucocytosis. It diners from measles, in addition, in the absence of enanthema, of Belsky-Filatov-Koplik spots, and of marked pyrexia. The paroxysmal stage of whooping-cough is mistaken at times 1) for tracheobronchitis, which is accompanied with persistent cough, sometimes followed by vomiting; 2) for tuberculous bronchoadenitis, which causes compression of the vagus nerve and of the inferior laryngeal nerves; and 3) for a foreign body in the upper respiratory tract, which can occasionally be responsible for attacks of suffocating cough. In contrast to whooping-cough, however, there is no progressive increase in the strength of paroxysms, no whoops, no ulcer on the frenulum of the tongue, and none of the haematological shifts characteristic of whooping-cough.

Complications. Increased intrathoracic and intra-abdominal pressure during coughing can result in conjunctival and scleral hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias. Laceration of the lingual frenulum is not uncommon. Rectal prolapse, once reported as a frequent complication of pertussis, was probably due to pertussis in malnourished children or missed diagnosis of cystic fibrosis.

Prognosis. The overwhelming majority of deaths occur among children under one year of age. The cause of death is pneumonia and, less frequently, convulsive fits. The outcome of whooping-cough is aggravated by concomitant diseases (tuberculosis, rickets, or dystrophy), and by other acute supervening infections (influenza, measles, dysentery, etc.). Central nervous system abnormalities (absent-minded, backward at school, and even very retarded mentally) occur at a relatively high frequency and are almost always the result of hypoxemia or hemorrhage associated with coughing or apnea in young infants.

Treatment. Properly organized regimen and nursing are very important in the treatment of whooping-cough. Bed rest is called for only when there is fever and severe complications. Cold fresh air has a wonderful effect on patients. Continuous open-air treatment improves pulmonary ventilation and oxygen exchange, and apparently also has a powerful reflex effect on the central nervous system. Paroxysms become fewer and weaker. In summer children should be outdoors for most of the day, and in winter for several hours each day. In winter walks can be made in places protected from the wind, but only if nasal respiration is free. Patients are allowed outdoors at temperatures not lower than minus 10°C. Individual tolerance of fresh air and low temperatures naturally has to be considered, and care must be taken to avoid chilling. It is also necessary to ensure that the sick-room is freely ventilated.

Much attention should be given to educational work among older children; their leisure should be organized, with various lessons and occupations, games, reading of stories, and so on. Coughing is less frequent in children absorbed in games. The fact that paroxysms usually cause vomiting, which greatly interferes with the assimilation of food, must be taken into account in feeding the patients. Calorie-rich digestible, concentrated food, with plenty of vitamins, is prescribed. Patients should be fed small portions shortly after a paroxysm; care must be taken to protect children after feeding from external stimuli that can provoke a paroxysm, such as various diagnostic and therapeutic manipulations, examination of the throat, etc. When vomiting does occur soon after a meal, feeding should be repeated.

The specific, limited goals of hospitalization are to 1) assess progression of disease and likelihood of life-threatening events at peak of disease, 2) prevent or treat complications, and 3) educate parents in the natural history of the disease and in care that will be given at home. For most infants without complications, this is accomplished in 48–72 hr. Heart rate, respiratory rate, and pulse oximetry are continuously monitored, with alarm settings so that every paroxysm is witnessed by health care personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Typical paroxysms that are not life threatening have the following features: duration less than 45 sec; red but not blue color change; tachycardia, bradycardia (not <60 beats/min in infants), or oxygen desaturation that spontaneously resolves at the end of the paroxysm; whooping or strength for self-rescue at the end of the paroxysm; self-expectorated mucus plug; and post-tussive exhaustion but not unresponsiveness. Within 48–72 hr, the direction and severity of disease is usually obvious by analysis of recorded information. Many infants have marked improvement following hospitalization and antibiotic therapy, especially if they are early in the course of disease or have been removed from aggravating environmental smoke, excessive stimulation, or a dry or polluted heat source. Apnea and seizures occur in the incremental phase of illness and in those with complicated disease.

Antibiotics are successfully used today as a specific (aetiotropic) therapy of whooping-cough. Antibiotics are indicated in grave and medium-grave forms of the disease, in the presence of complications, and in infants in whom the complications are especially grave. Erythromycin, ampicillin, tetracyclines given in the catarrhal or early spasmodic period decrease the number and gravity of fits, lessen the course of the disease, and its gravity.

Erythromycin is given per os, 5 000-10 000 U/kg, 3-4 times a day. Ampicillin is given per os or intramuscularly, 25-50 mg/kg, four times a day. The therapy should continue for 8-10 days. Tetracyclines are given 25 000-30 000 U/kg a day, for 10-12 days. They produce a favourable effect on the course of the disease. If the symptoms recur after suspension of the therapy, it should be repeated.

In order to attenuate the pertussis attacks, neuroplegics are recommended: aminazine, propazine. The ampouled solution of aminazine is given intramuscularly, 1-3 mg/kg; propazine is given per os, 2-4 mg/kg a day. The daily dose is given for three intakes; the course continues for 10-12 days. The frequency and gravity of attacks of coughing decrease; vomiting stops or becomes less frequent; the spastic condition of the vessels decreases. Many physiotherapeutic procedures are recommended, such as U-V rays, calcium ionophoresis, diathermia, inhalation of negative aerosols with proteolytic enzymes, etc. Oxygen therapy (oxygen tent) is especially valuable in pertussis, in particular in infants and neonates with marked signs of hypoxia.

Symptomatic therapy and the treatment of complications are on general lines. Intramuscular injections of a 25 per cent solution of magnesium sulphate, and intravenous injections of hypertonic glucose solution (producing dehydration) are prescribed, in addition to oxygen therapy, for convulsions.

Pneumonia is widely treated with antibiotics (antibiotics of tetracycline series, erythromycin, gara-mycin, etc.) and oxygen. Hormonal preparations (prednisolone) with an anti-inflammatory, desensitizing effect are also recommended in severe pneumonia. Respiratory arrest calls for prolonged artificial respiration.

Stimulating therapy (gamma-globulin injections, vitamins, etc.) is prescribed when the course of whooping-cough tends to be sluggish and protracted. It is advisable to send children convalescing from a severe attack to a sanatorium for two to three weeks after they cease to be infectious.

Prophylaxis. Measures to be taken in an epidemic focus. The earliest possible isolation of the patient is imperative. In practice diagnosis of whooping-cough is often established only when whoops appear, so that isolation is delayed, reducing its epidemiological value. Early diagnosis is therefore essential for the success of the anti-epidemic measures. The patient is usually left at home, and put in a separate room or behind a screen. The patient is placed in respiratory isolation for at least 5 days after initiation of erythromycin therapy.

Erythromycin, 40–50 mg/kg/24 hr, orally in four divided doses (maximum 2 g/24 hr) for 14 days should be given promptly to all household contacts and other close contacts, such as those in day care, regardless of age, history of immunization, or symptomatology. Close contacts younger than 7 yr who are underimmunized should be given a pertussis-containing vaccine, with further doses to complete recommended series. Children younger than 7 yr who received a 3rd dose 6 mo or more before exposure, or a 4th dose 3 yr or more before exposure, should receive a booster dose. If infection with B. pertussis is documented at any age, the individual is exempted from routine pertussis immunization

Hospitalization is indicated in severe and complicated forms of whooping-cough, particularly in children under two years of age, children from families living in poor conditions, and from families where there are babies under six months of age that have not had

the disease. Patients are isolated for 30 days from the onset of the disease. The organization of the hospital regimen requires special attention. Patients must be carefully protected against secondary hospital infection, which is often the cause of exacerbations and complications.

The quarantine period for unimmunized contacts under seven years of age that have not had whooping-cough is 14 days from the time of isolation of the patient. If the latter has not been isolated, and contact with him continued during the whole period of the disease, quarantine is imposed until the patient ceases to be infective. There is no need in complete terminal disinfection of the premises after isolation of a patient, because the causative agent is not viable and perishes rapidly; but thorough ventilation of the premises and disinfection of handkerchiefs, towels, and dishes are necessary. Favourable results have been obtained through prophylactic use of gamma-globulin, particularly of specific antipertussis gamma-globulin with a high antibody content (3 to 6 ml twice, at an interval of 48 hours).

Prevention. Universal immunization of children with pertussis vaccine, beginning in infancy, is central to the control of pertussis.

Whole Cell Vaccine. The vaccine currently used for primary immunization recommended by the World Health Organization for use throughout most of the world is a killed whole cell vaccine composed of a suspension of inactivated B. pertussis, combined with diphtheria and tetanus (DT) toxoids and aluminum-containing adjuvants (DTP vaccine). Vaccine potency is translated to opacity units (also a safety standard) or protective units. U.S. preparations contain 4–12 protective units and not more than 16 opacity units per 0.5-mL dose. Efficacy of whole cell vaccine varies by case definition from 64 % for mild cough, to 81 % for paroxysmal cough, and to 95 % for severe clinical illness. Individuals over 7 yr of age are not routinely given pertussis-containing vaccine. When used in adults to control a hospital outbreak, whole cell vaccine was found to be less reactogenic than reported in children.

Acellular Vaccine. Purified component acellular pertussis (aP) vaccines, originally developed in Japan, are immunogenic and associated with fewer adverse events when compared with DTP. Vaccines provided by six manufacturers have been used exclusively in Japan since 1981, and their use has controlled pertussis.

PART 12 ACUTE RESPIRATORY VIRAL INFECTIONS

Influenza

Influenza viruses are classified as Orthomyxoviridae. It contains ribonucleic acid (RNA). The influenza virus perishes rapidly outside the human organism and is very sensitive to the action of disinfectants, heating, ultra-violet rays, and desiccation. Three different types of the virus are known (A, B and C). Each type has several serological varieties. It is especially characteristic of influenza A virus and shows itself in variation of its surface antigens: haemagglutinin (H) and neuraminidase (N). Potentially any of 13 hemagglutinins and 9 neuraminidases residing in animal reservoirs may be introduced into humans. When a virus identified by a novel and serologically distinct hemagglutinin or neuraminidase enters the population, there is potential for a pandemic of influenza with excess morbidity and mortality on a global scale in a largely

nonimmune population. The most dramatic pandemic in recent history occurred in 1918 when influenza was estimated to have killed more than 20 million people. Influenza B has a lesser capacity for major antigenic change and no identified animal reservoir.

Epidemiology. The source of infection is the patient, who is particularly infective. It the height of the disease, during pyrexia. The contagious period lasts for four to seven days. Infection is chiefly conveyed by the aerial-droplet route. The susceptibility of man to influenza is very high, practically universal. Children are very susceptible to influenza from six months of age. Immunity against influenza A is effective in man for about two years, and against influenza B, three years.

Pathological anatomy. Influenza causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion. The pulmonary tissue is readily involved in the inflammatory process and segmental oedema, focal and segmental (sometimes con- fluent) pneumonia with involvement of the interstitial tissue develop. Influenza is attended by pronounced circulatory disorders in various organs, the lungs and the brain included: markedly excessive blood supply, vascular stasis, small haemorrhages. When influenza type B is accompanied by the administration of salicylates, the fatty liver, cerebral edema, and mitochondrial changes that are the hallmarks of Reye syndrome can be seen.

Pathogenesis. The pathogenicity of the influenza virus is mainly expressed in its epitheliotropicity and toxicity. Toxaemia is a typical clinical feature of influenza, and is much more common in this disease.

The virus attaches to sialic acid residues on cells via the hemagglutinin and, via endocytosis, makes its way into vacuoles, where, with progressive acidification, there is fusion to the endosomal membrane and release of the viral RNA into the cytoplasm. The RNA is transported to the nucleus and transcribed. Newly synthesized RNA is returned to the cytoplasm and translated into proteins, which are transported to the cell membrane. This is followed by budding of virus through the cell membrane. The packaging mechanisms for the segmented genome are not well understood. A proteolytic cleavage of the hemagglutinin occurs at some point in the assembly and release of the virus which is essential for successful reinfection and amplification of virus titer.

The places most affected by the toxic action of the virus are the nervous system (central and vegetative) and blood vessels. A central place in the pathogenesis of influenza is taken by circulatory disturbances associated with lesions of the vegetative innervation and vascular system, disturbances that play a cardinal role in causing functional derangement of the nervous system and pulmonary complications. Secondary bacterial flora invading the primary viral lesions can aggravate and prolong the course of the primary viral disease.

The extremely short incubation period of influenza and its growth on the mucosal surface pose particular problems for invoking a protective immune response. Mucosally produced immunoglobulin (Ig) A antibodies are presumably directed at the same

antigenic sites and are thought to be the most effective and immediate response that can be generated to protect against influenza.

Clinical picture. The incubation period of influenza is one or two days, but may sometimes be as short as a few hours. The onset of illness is abrupt and is marked by coryza, conjunctivitis, pharyngitis, and dry cough, with elevation of temperature and chill. The febrile reaction may vary according to the severity of the disease; the temperature may be high (39-40°C and over), but may remain subfebrile when the course of the disease is mild. General toxaemia is characteristic, and is mainly expressed in symptoms of involvement of the central nervous system, namely strong headache, vertigo, hyperaesthesia, adynamia, and sleepiness or, on the contrary, excitation. High fever is often accompanied with dimmed consciousness, delirium, and hallucinations. Muscular and neuralgic pain is frequent. Vomiting, convulsions and loss of consciousness (cerebral syndrome), and a syndrome of meningism are not uncommon in young children. Nursing babies stop gaining weight before the onset of influenza.

Influenza toxaemia also produces marked changes in the cardiovascular system. A brief period of hypertension is followed by a fall of arterial pressure, tachycardia or bradycardia, arrhythmia, diminished heart sounds, and sometimes by cyanosis. Collapse occurs in severe cases. There may be haemorrhage into the conjunctiva and mucous membranes owing to involvement of capillaries. Epistaxis is not uncommon. Catarrhs of the upper respiratory tract are not constant in influenza, they are absent in 20 - 30 % of the cases. But in the majority of patients, they (along with toxaemia) are the leading and appear from the first day. In others they develop on the second or third day. Signs of catarrh of the upper respiratory tract are the following: cold, dryness and irritation in the fauces, a dry cough, and not infrequently hoarseness and dyspnoea. The nasopharyngitis arising in nursing babies disturbs respiration considerably, and inhibits sucking; their appetite is poor, they sleep badly and lose weight. Laryngitis is sometimes encountered, most frequently in children under two years of age. In some cases influenza laryngitis is accompanied with stenosis.

Croup in influenza patients develops mostly in infancy as a result of oedema of the laryngeal mucosa and the spasm of the laryngeal muscles. Its signs and course differ from those of diphtheric croup. In most cases its onset is sudden. Voice is normal or only slightly hoarse, coughing is loud, coarse and barking. Signs characteristic of laryngeal stenosis develop: noisy respiration (especially during the inspiration), depressions in the yielding parts of the chest, tension of the auxiliary respiratory muscles. In contrast to diphtheric croup, the croup attending influenza and also other respiratory viral infections is characterized by mild signs of laryngeal stenosis. Because of the absence of cyclic character, stages of laryngeal stenosis, rather than stages of croup, like in diphtheritis, are differentiated: I and II degrees are characterized by moderate or weak signs and the absence of respiratory insufficiency; III degree is characterized by permanent intense signs of marked stenosis and symptoms of respiratory insufficiency (cyanosis, drop of pulse at the height of the inspiration, restlessness of the patient); IV degree is characterized by a grave respiratory insufficiency, general cyanosis, and cardiovascular insufficiency.

Herpes may develop in some patients. The fauces are often hyperaemic. The granular character of the mucous membrane of the soft palate.

Blood findings are typical for virus infection.

Three main forms of influenza are distinguished according to the principal clinical syndromes reflecting the clinico-pathogenic nature of the disease. They are as follows: (a) toxic (and a subtoxic variant), (b) catarrhal, and (c) toxico-catarrhal. Additional syndromes may supplement the characteristic features of each of these forms (with

Influenza may also be distinguished as mild, moderately severe, and severe according to the gravity of its course. The syndromes of encephalopathy, meningism, hemorrhage accompany severe form.

A variety of mild influenza is the abortive form; patients are ambulant, and it is therefore of great epidemiological significance.

Complications. Pneumonia is a common and dangerous complication that develops either during the first days of the disease or later, when it is the result of mixed viral-bacterial infection. Pleura may become implicated with resultant fibrinous or purulent pleurisy caused by secondary bacterial flora (mostly staphylococcus). Abscesses of the lungs are sometimes the outcome of pneumonia. Various complications involving the nervous system, such as neuralgia, neuritis, or radiculitis, may occur. Clinical syndromes of encephalitis, meningoencephalitis, and purulent meningitis (the latter due to secondary infection) are occasionally met. Catarrhal otitis is not uncommon in children. Other complications (highmoritis, ethmoiditis, sphenoiditis).stomatitis, purulent otitis, pyelitis, cystitis, nephritis, keratitis, phlebitis, etc.) may also occur.

Diagnosis and differential diagnosis. Typical signs of influenza are its acute onset, marked toxaemia, frequent catarrhs of the respiratory tract, and leucopenia following a transitory initial leucocytosis.

Rapid diagnostic tests for influenza A are being introduced that use antigen capture in an enzyme-linked immunosorbent assay format. The diagnosis can be confirmed serologically with acute and convalescent sera drawn around the time of illness and tested by hemagglutination inhibition.

Intoxication in para-influenza and respiratory syncytial and adenoviral infections is less pronounced, whereas the catarrh of the airways is more marked. Adenoviral infection is also characterized by a gradual onset, the presence of symptoms of pharyngitis, conjunctivitis and swelling of the cervical and submandibular lymph nodes. The lower respiratory ducts are often involved in the respiratory syncytial infection (bronchitis, bronchiolitis); the larynx becomes involved in para-influenza.

Epidemiological data can be of great assistance, i.e. whether the same illness has occurred in the child's family or in the institution it attends. Diagnosis is much easier, of course, during an epidemic.

The serological reactions are performed twice. A four-fold (or greater) increase of antibody titre is considered diagnostic. Immunofluorescent method is now being widely employed in clinical practice.

Prognosis. The outcome of influenza depends above all on the resistance of the organism. The course of the disease is most severe and has its highest mortality in infants, in children suffering from hypotrophy and with chronic infections.

Treatment. Strict bed rest should be enjoined for children during the whole period of illness. The sick-room should be regularly and thoroughly ventilated. Warm or hot drinks are prescribed. Human leucocytic interferon is recommended for treatment of influenza. When there is a danger of complications from secondary bacterial infection in severe cases, it is advisable to prescribe antibiotics.

In serious cases hormonal preparations are used. Vikasol, rutin and calcium preparations are given in haemorrhagic syndrome. To bring about dehydration in patients with a cerebral syndrome (racking headache, vomiting, convulsions, loss of consciousness), intramuscular injections of a 25 per cent solution of magnesium sulphate and diuretics are given as well as hypertonic glucose solution.

Prophylaxis. The most important general sanitary-prophylactic measure during an influenza epidemic is the organization of a proper regimen and hygiene of children's institutions.

In the presence of immediate danger of infection with influenza (e.g. in an epidemic focus), prophylactic use of interferon and 0.25 per cent oxolin ointment are recommended intranasal.

The split-virus vaccine is recommended for children younger than 12 yr. Two doses of vaccine are recommended for primary immunization of children younger than 8 yr. The dosage is divided in half to a volume of 0.25 mL for children younger than 3 yr. Live, attenuated intranasally administered vaccines are in clinical trials and have been demonstrated to have an efficacy comparable to that of inactivated vaccine. Their ease of administration could serve to increase their use. The vaccination is carried out 2-3 months before the expected epidemic rise.

Para-influenzal infection

According to the literature para-influenza accounts for between 10 to 30 per cent and over of the total number of viral respiratory illnesses in children. Viruses in the parainfluenza family are common causes of respiratory illness in infants and young children. They cause a spectrum of upper and lower respiratory tract illnesses, but are particularly associated with laryngotracheitis, bronchitis, and croup.

The causative agents are para-influenza or haemadsorbing viruses (Myxouiruses parainfluenzae) They contain ribonucleic acid (RNA) Four serological types (1, 2, 3, and 4) are known. The major antigenic moieties are envelope spike proteins that exhibit hemagglutinating (HN protein) and cell fusion (F protein) properties.

Epidemiology. Infection is conveyed from a sick person by the aerial-droplet route. Type 3 is endemic and can cause disease in the infant younger than 6 mo. Types 1 and 2 are more seasonal. They occur in the summer. Parainfluenza type 4 is more difficult to grow in tissue culture; thus, its epidemiology is less well defined. However, it does not appear to be a major cause of illness.

Clinical picture. Incubation continues for 3-4 days (from 1 to 7 days). The parainfluenza viruses account for 50 % of hospitalizations for croup and 15 % of cases of bronchiolitis and pneumonia. Parainfluenza type 1 causes more cases of croup, whereas parainfluenza type 3 causes a broad spectrum of lower respiratory tract diseases. The onset of the disease is less acute than in influenza. The temperature elevation is moderate and in uncomplicated cases it persists only for 2-5 days. Laryngitis or laryngotrachitis is typical of para-influenzal infection. It shows in dry coarse cough and a slight or moderate coarseness of the voice. It attended by symptoms of the laryngeal stenosis (the picture of croup). Croup develops in para-influenzal infection of any type. Stenotic phenomena (depression of the yielding parts of the chest during inspiration, tension of the respiratory muscles, etc.) are moderate. Para-influenzal rhinitis tends to a protracted course. It can persist for two weeks. Pneumonia is the most frequent complication of para-influenza in infants.

Diagnosis. Direct immunofluorescent staining has been used in some centers to identify infected cells in secretions rapidly.

In contrast to influenza, the onset of para-influenza is less acute. The intoxication symptoms are absent or only slightly pronounced, the catarrhal symptoms are more pronounced, frequent laryngeal affections are typical. The diagnosis becomes less difficult in epidemic outbreaks. Laboratory diagnosis is based on isolation of para-influenza viruses from nasopharyngeal washings and on serological methods.

Epiglottitis is characterized by a fulminating course of high fever, sore throat, dyspnea, rapidly progressive respiratory obstruction, and prostration, although respiratory distress is frequently the first manifestation. Within a matter of hours, it may progress to complete obstruction of the airway and death unless adequate treatment is provided. With adequate treatment, the illness rarely lasts for more than 2–3 days. Often the child, particularly the younger patient, is apparently well at bedtime but awakens later in the evening with high fever, aphonia, drooling, and moderate or severe respiratory distress with stridor. Usually no other family members are ill with acute upper respiratory disease. The older child often complains initially of sore throat and dysphagia. Severe respiratory distress may ensue within minutes or hours of the onset, with inspiratory stridor, hoarseness, brassy coughs (less commonly), irritability, and restlessness. Drooling and dysphagia are common. The neck may be hyperextended, although other signs of meningeal irritation are absent. The older child may prefer a sitting position, leaning forward, with the mouth open and the tongue somewhat protruding. Some children may progress rapidly to a shocklike state characterized by pallor, cyanosis, and impaired consciousness.

Respiratory syncytial infection (RS-viral infection)

It belongs to the family Paramyxoviridae, along with parainfluenza, mumps, and measles viruses but is classified in a separate genus: the pneumoviruses. It contains RNA. Two serotypes of the RS-virus are now distinguished. Respiratory syncytial virus (RSV) is the major cause of bronchiolitis and pneumonia in infants younger than 1 yr. It is the most important respiratory tract pathogen of early childhood.

Epidemiology. The occurrence of annual outbreaks and the high incidence of infection during the first months of life are unique among human viruses. The source of infection is a sick person. The infection is spread by the aerial-droplet route. The patient remains contagious probably for 5-7 days. The susceptibility to the RS infection is very high. Most infants fall ill during their first two or four years of life. Seasonal variations are quite marked: the highest incidence occurs in the cold seasons.

Pathology and pathogenesis. Bronchiolitis is characterized by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucous plugs obstructing bronchioles with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, infiltration is more generalized, and epithelial necrosis may extend to both the bronchi and the alveoli. Infants are particularly apt to experience small airway obstruction because of the small size of the normal bronchioles.

Clinical picture. The incubation period lasts for 3 to 7 days (5 days on the average). The onset is usually gradual, with affections of the upper and lower respiratory tracts. The affection of the upper airways is manifested by rhinitis with scanty serous or seromucous discharge, cough, sometimes hoarse voice. Lower respiratory tracts are very frequently involved in infants (especially in nurslings under one year of age). A picture of diffuse bronchitis and bronchiolitis is observed. Bronchiolitis is characterized by a strong dyspnoea of the mixed type with prevalence of difficult expiration. Marked asthmatic syndrome is not infrequent. The examination of the lungs reveals fine or medium bubbling rales and symptoms of emphysema. The picture of respiratory insufficiency is supplemented by cyanosis. All these symptoms subside completely (or almost completely) in 2-6 days. The X-ray picture of the lung roots is more distinct, and the lungs appear inflated; focal changes are absent. The temperature is subfebrile and increases transiently to 38-39°C only in few patients.

Most frequent complications are pneumonia and catarrhal otitis caused by secondary bacterial flora. Grave pneumonia in infants is the cause of lethal outcomes.

Most infants with lower respiratory tract illness shed virus for 5–12 days after hospital admission. Excretion for 3 wk and longer has been documented.

Diagnosis. During clinical diagnostication of the RS-infection in children, frequent affections of the lower respiratory tract (bronchiolitis), that are characteristic of the disease. In addition to isolation of the RS-virus, serological methods are also used in the laboratory diagnostication.

When bronchiolitis is mild or when infiltrates are absent by roentgenogram, there is little likelihood of a bacterial component. In infants 1–4 mo of age, interstitial pneumonitis may be caused by Chlamydia trachomatis. In this instance there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing is prominent; wheezing is not. There may also be eosinophilia. Fever is usually absent.

Prognosis. The mortality of hospitalized infants with RSV infection of the lower respiratory tract is about 2 %. The prognosis is clearly worse in young, premature infants or those with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system.

Rhinoviral infection (acute contagious viral cold)

There are 111 serologically distinct rhinoviruses, all members of the Picornavirus family of small RNA viruses (15-30 nm).

Epidemiology. Infection is spread from a patient or virus carrier by the aerial-droplet route. Virus persists for several hours in secretions on hands or other surfaces. Transmission probably occurs when infected secretions carried on contaminated fingers are rubbed into the nasal or conjunctival mucosa. More recent evidence also implicates spread through prolonged contact with aerosols produced by talking, coughing, or sneezing. Contagiousness lasts not more than 5 or 7 days. All ages are susceptible, but incidence is greatest in adults. Postinfectious immunity does not last long, its type is specific, and the antibody titre falls in two years.

Clinical picture. There is an incubation period of 2-4 days; then sneezing, nasal obstruction and discharge, and sore throat ensue. Onset is characterized by the appearance of copious watery discharge from the nose and sneezing; later the discharge becomes more viscid, mucous, or mucopurulent as a result of concomitant bacterial flora. Cough and hoarseness occur in 30–40 % of cases. Headache and other systemic symptoms are not as common as in influenza. Fever is neither as frequent nor as high as in primary infections with respiratory syncytial virus, parainfluenza virus, influenza virus, or adenovirus. Symptoms are worse in the first 2–3 days of illness and last for a week in a majority of patients; they persist for over 14 days in 35 % of young children.

Adenoviral infection

Adenoviruses are DNA viruses of intermediate size, which are classified into subgenera A to G. Types 1–39 are in subgenera A to E, type 40 is subgenus F, and type 41 is subgenus G. Adenoviruses are characterized by location inside the cell nucleus, common complement-fixing antigen, and marked stability to environmental effects.

Epidemiology. The source of infection is a sick person or a carrier of the virus. The causative agents are liberated with he secretion of the respiratory mucosa and faeces. Infection is spread through the aerial-droplet route, and also the routes characteristic of intestinal infections. There is evidence that the infection can be transmitted through the eye conjunctiva in swimming pools. Children from six months to three years of age are particularly susceptible to these infections.

Adenoviral infection occurs sporadically, but extensive epidemics have also been reported.

Certain types tend to occur in epidemics, notably types 4 and 7 in epidemics of febrile respiratory disease, types 3, 7, and 21 in severe pneumonia, type 3 in pharyngoconjunctival fever, type 11 in cystitis, and types 8, 19, and 37 in epidemic keratoconjunctivitis.

Pathogenesis and pathological anatomy. Adenoviruses infect the respiratory and intestinal mucosa. They are accumulated in the epithelial cells and lymph nodes. Virusaemia is probably important in the pathogenesis of the disease.

Clinical picture. The incubation period is between four and seven days, sometimes longer. Adenoviruses cause a wide array of syndromes.

The principal clinical forms are pharyngo-conjunctival fever, catarrh of the respiratory tract, and pneumonia, the intestine (intestinal form), and mesenteric nodes (mesadenitis) are less frequent.

The onset of pharyngoconjunctival fever may be either acute or gradual. Temperature rises to 38-39°C, and there is usually moderate general toxaemia. Headache, adynamia, loss of appetite are noted. Constant symptoms are rhinitis with copious serous or seromucous discharge, bronchitis or tracheobronchitis, pharyngitis, and conjunctivitis. The fauces and posterior and lateral walls of the pharynx are hyperaemic; lymphatic follicles are swollen. The tonsils are rather enlarged, and a film sometimes covers the lacunae. Conjunctivitis may appear from the first day, but more often from the second or third. It usually starts on one side and may later spread to the other eye. Catarrhal, follicular, and membranous conjunctivitis are distinguished according to the character of the inflammation. The last-named is most typical of adenoviral infection. The conjunctiva of the eyelids looks hyperaemic, granular, and rather swollen. There is a sparse seromucous and seropurulent discharge. Fine white or greyish-white membranous films appear on the conjunctiva or plica semilunaris in one to three days. Oedema of the eyelids of soft consistency, sometimes sharply pronounced, is a frequent symptom.

Enlargement of the cervical lymph nodes, and in infants liquid stool, sometimes with mucus, are not uncommon. Sometimes there is enlargement of the liver and spleen. The blood picture is approximately the same in all forms of adenoviral infection: a normal leucocyte count or a slight leucocytosis (less frequently-leucopenia), neutrophilosis; the ESR is normal or moderately increased.

With further development of the disease the fever becomes fluctuating; it may last for five or six to nine or ten days (longer in some cases) and terminates by lysis. In some patients the pyrexia is double- or even triple-wave; the second wave follows the first in several days. The catarrhal phenomena, particularly cold in the nose, are usually persistent and protracted. Subsidence of the conjunctivitis is relatively slow; the membranes persist for several days (sometimes up to the tenth or fourteenth day).

Pneumonia is the most severe form of adenoviral infection occurring mostly in infants under 1 year of age. It is often combined with a syndrome of catarrh of the respiratory tract or of pharyngoconjunctival fever. It may be microfocal, macrofocal, or confluent; there are marked auscultatory signs, namely copious varied rales and not infrequently distinct dullness of percussion sound. Dyspnoea, cyanosis, and general toxaemia are noted. The disease, particularly in nursing babies, has a tendency to a protracted relapsing course and can terminate by death. Mortality has been high in some epidemics.

The intestinal form of adenoviral infection occurs mostly in infants under 1; it is characterized by prevalence of symptoms of acute gastrointestinal disorders, viz., liquid medium-frequency dyspeptic stools, sometimes containing mucus, and deranged appetite; some patients develop vomiting.

Mesadenitis (inflammation of mesenteric lymph nodes) is a rare manifestation of adenoviral infection which develops either against the background of another syn-

drome (e. g. pharyngoconjunctival fever) or as a prevailing syndrome, but almost always in combination with at least a slight catarrh of the upper respiratory ducts and the pharynx. Mesadenitis is characterized by an acute onset of fit-like abdominal pain, fever, nausea, and infrequent vomiting. The tongue is coated, stools are retained. The pain is felt predominantly in the lower part of the abdomen, often in the right iliac region. Appendicitis is often misdiagnosed and the patient is operated. Mesadenitis is sometimes complicated by intussusception.

A pertussis-like syndrome has been described in association with adenovirus infections.

Hemorrhagic Cystitis. This syndrome has a sudden onset of bacteriologically sterile hematuria, dysuria, frequency, and urgency lasting 1–2 wk. Infection with adenovirus types 11 and 21 has been found in some affected children and young adults.

Clinical diagnosis of adenoviral infection can only be made with typical pharyngoconjunctival fever and membranous conjunctivitis. Conjunctivitis is an informative sign for differentiation of this infection from other respiratory viral diseases.

For laboratory diagnosis isolation of the virus from garglings and faeces, and serological examination during the first days and after two or three weeks, are used; a fourfold increase of antibody titre at the minimum is considered diagnostic.

The adenoviral nature of the disease can rapidly and conveniently be identified by luminescent microscopy of imprints from the nasal mucosa by which typical intranuclear DNA inclusions can be revealed. Fluorescent antibodies are quite valuable and specific for rapid diagnostic of viral etiology.

Treatment and prophylaxis. The treatment and general prophylaxis of acute respiratory viral infections is largely the same as for influenza and symptomatic. Careful hand washing and avoidance of manual nose and eye manipulation is the best approach to reducing spread. For relief of acute symptoms, a mild analgesic and saline or decongestant nose drops may be used for a short time.

Use of desoxyribonuclease by instillation into the nose or the conjunctival sac (3-4 drops of fluid preparation, 3-4 times a day) has been suggested in adenoviral infection; good results were obtained in the treatment of adenoviral conjunctivitis; but this method has not gained wide popularity.

Antibiotics are not effective against respiratory viral infections. They are only indicated in complications of bacterial aetiology.

Favourable results were obtained during prophylactic use of human leucocytic interferon and interferonogens. Prophylactic administration of gamma-globulin to asthenic and especially vulnerable children in the epidemic foci is recommended.

Measures in the infection focus. There are no official standards for hospitalization terms, but the patient should be isolated until the clinical signs of the disease disappear, not less than for 7 days from the onset.

PART 13 TORCH-INFECTIONS

Despite immunization programs and effective antimicrobial medications for many infectious agents, congenital infections remain an important cause of birth defects among children throughout the world. Because the agents responsible for these infections can damage the brain, eyes, or ears along with other body organs, survivors often have long-term disabilities that influence motor and intellectual performance.

Relatively few infectious agents can cause congenital infections. These agents – viruses, spirochetes, and protozoa – tend to produce similar signs and symptoms and have been categorized historically as TORCH syndrome. The letters of the latter acronym stand for toxoplasmosis, other organisms, rubella, cytomegaloviral (CMV) infection and herpesviral infection.

TORCH agents can affect the fetus by damaging the placenta (which alters the blood supply to the fetus) or by directly injuring the developing fetal organs. The extent of the damage depends upon the infectious agent and the stage of pregnancy at which infection occurs. Infections acquired early in pregnancy tend to result in more serious birth defects, whereas infections later in pregnancy may produce no visible signs of damage.

Congenital infections can cause numerous long-term abnormalities. Some agents produce specific abnormalities, however. Congenital heart defects are usually associated with rubella (German measles), and scarring of the skin can be caused by herpes. The most serious consequences of congenital infections are the damaging effects on the brain, eyes and ears. As a result, infected infants may have shortened life spans or long-term intellectual and perceptual disabilities. Although many of these children can eventually enter regular educational or child care environments, others are so severely affected that they require long-term specialized care.

TOXOPLASMOSIS

Toxoplasmosis, caused by infection with the protozoan Toxoplasma gondii, is the first most common human congenital infection. Rates of toxoplasmosis vary throughout the world and depend on age, geographic location, and dietary practice.

Unlike most other organisms that cause congenital infections, Toxoplasma gondii is acquired from nonhuman sources. This parasite uses cats as its primary host but can infect many different species of birds and mammals. Humans become infected by consuming contaminated meat that is not fully cooked or by directly ingesting infectious particles. Cat feces may contain large quantities of infectious particles, making these animals an important source of infection. In rare, toxoplasmosis is acquired through blood transfusion.

In most people, toxoplasmosis occurs asymptomatically or causes mild disease. In children with normal immune responses, Toxoplasma infection occa-

sionally causes an infectious mononucleosislike illness with fever, swelling of lymphnodes and rash. In persons with impaired immune responses, however, such as persons with AIDS, toxoplasmosis can be severe, life-threatening disease.

If nonimmune pregnant woman ingests infectious Toxoplasma gondii particles, they enter her blood stream and are carried to the placenta. Approximately one third of fetuses of infected mothers are themselves infected with these organisms. Whether the fetus becomes infected depends primarily on the stage of pregnancy at which maternal infection takes place. Most severe fetal infections are the result of toxoplasmosis infection during the second trimester of pregnancy. Approximately 5% of fetal infections with Toxoplasma gondii result in stillbirth or miscarriage. Most infants who survive fetal toxoplasmosis infection have no symptoms at birth, although some infected infants later had abnormalities of eyes (chorioretinitis) or hydrocephaly. 25-30% of infected newborns has symptoms in infancy. The spectrum of abnormalities caused by Toxoplasma gondii resembles that of congenital CMV infection. Both agents damage brain and eyes.

Diagnosis of toxoplasmosis usually can be established by performing blood tests on the infant and mother. These tests measure antibodies to toxoplasma organisms. If the level of antibody is high or shows a fourfold or greater increase soon after birth, toxoplasmosis is likely. These antibody tests detect only about 75% of actual toxoplasma infections. Diagnosis of Toxoplasmosis can be confirmed by identifying Toxoplasma organisms within human cells during autopsy or analysis of pathologic tissues.

Treatment. In certain regions of the world, the diagnosis can be established before the infant's birth, and the mother can be treated with anti-toxoplasma medications.

Table 1.

Treatment of toxoplasmosis

Manifestation of infection	Medication	Dosage	Duration of therapy
Pregnant women with acute toxoplasmosis first 18 weeks of gestation or until term if fetus not infected	Spiramycin	1 g q8h without food	Until fetal infection is documented or excluded at 18 week. If excluded by PCR at 18 weeks, continue spiramycin until term
Fetal infection confirmed after 17th week of ges-	Pyrimethamine	Loading dose: 100 mg/day in 2 divided doses for	Until term (leukovorin is continued 1 week after

tation or if maternal infection acquired in last few weeks of gestation (after amniocentesis and PCR to determine whether Toxoplasma is infecting the fetus)		2 days, then 50 mg/day	pyrimethamine is discontinued)
	Sulfadiazine	100 mg/kg/day in 2 divided doses (max, 3 g/day)	
	Leukovorin (folinic acid)	5–20 mg daily	
Congenital Toxoplasma infection in infants	Pyrimethamine	Loading dose: 2 mg/kg/day for 2 days, then 1 mg/kg/day for 2 or 6 months, then this dose every Monday, Wednesday, and Friday	1 yr (leukovorin is continued 1 week after pyrimethamine is discontinued)
	Sulfadiazine	100 mg/kg/day in 2 divided doses	
	Leucovorin	5–10 mg 3 times weekly	

OTHER AGENTS

Enteroviruses. Fetal enterovirus infection is uncommonly observed, probably because the placenta acts as a barrier to intrauterine infection. However, a well-documented case of fatal disseminated, midgestational congenital enterovirus 71 infection has been published. Neonates are at risk of serious, sometimes fatal disease resulting from enterovirus infections acquired during the perinatal period. This unique susceptibility, which extends to about 10 days of age, may be based on immunologic immaturity and other host factors. Although neonates respond to enterovirus infection with humoral neutralizing antibody, experimental data suggest that macrophage function, which does not mature sufficiently until several weeks of age in humans, is necessary to limit initial enteroviral replication.

The echoviruses and group B coxsackieviruses are responsible for most neonatal infection. Neonates acquire enterovirus infections perinatally as a result of vertical transmission from infected mothers, and symptoms occur within the first week of life. During seasonal outbreaks, approximately 3% of pregnant women excrete enteroviruses at term. Although most transmit virus to their offspring, the outcome of neonatal infection is strongly influenced by the presence or absence of passively acquired maternal antibody specific for the infecting enterovirus serotype. Thus, the timing of maternal infection in relation to the

development of maternal IgG antibody and delivery of the infant is probably the most critical factor in determining the outcome of neonatal enterovirus infection. Other risk factors for severe and fatal infections include premature birth, maternal history of peripartum illness, and early postnatal age of onset.

Nosocomial postnatal infection occurs less frequently than vertically acquired infection. Infant-to-infant spread within nurseries occurs via the hands of personnel engaged in mouth care, gavage feeding, and other activities affording close direct contact.

Although a wide range of clinical disease has been reported to occur in neonates, including nonspecific febrile illnesses, exanthems, and aseptic meningitis, the most severe manifestations include myocarditis with or without encephalitis, hepatitis, and pneumonia.

Myocarditis. Neonatal myocarditis is most frequently caused by group B coxsackievirus serotypes 2 to 5. The onset is often abrupt, with respiratory distress, tachycardia, cyanosis, jaundice, and diarrhea. Initial examination frequently reveals temperature instability, tachycardia, arrhythmia, hepatomegaly, and signs of poor peripheral circulation. The electrocardiogram can show low-voltage and other electrophysiologic abnormalities, and echocardiographic studies often indicate poor left ventricular or biventricular function. Approximately one-third of illnesses are biphasic, with lethargy, poor feeding, or mild respiratory distress preceding the onset of cardiac manifestations by 2 to 5 days.

Infants with group B coxsackievirus myocarditis often have concomitant meningoencephalitis, pneumonia, hepatitis, pancreatitis, or adrenalitis. Although a limited number of organs can be involved pathologically, the degree of involvement is often severe, which has given rise to the use of terms such as disseminated, systemic, or overwhelming group B coxsackievirus disease in the neonatal period. Mortality in infants with myocarditis alone is generally reported to be 30% to 50%, but it is higher when other organs are involved.

Hepatitis. Neonatal hepatitis may be the sole manifestation of neonatal echovirus infection or can occur in the setting of myocarditis and other manifestions of neonatal group B coxsackievirus infection. Echovirus 11 is prominent among the multiple echovirus serotypes reported to cause neonatal enterovirus hepatitis, which is often erroneously referred to as “enterovirus sepsis or sepsis syndrome” because of progressive hypotension, profuse bleeding, jaundice, and secondary multiple organ dysfunction due to fulminant liver failure. The degree of hepatic involvement varies, but a severe form of hepatitis unique to this age group is characterized by extensive necrosis of the liver and fulminant hepatic failure. Initial signs and symptoms of severe hepatitis resemble those of septicemia, with lethargy, poor feeding, apnea, and jaundice. Within 2 to 3 days, evidence of hypocoagulability appears, along with ecchymoses and prolonged bleeding at puncture sites. Anemia, marked prolongation of the prothrombin time and partial thromboplastin time, and extreme elevations of serum transaminase levels occur. The marked hypocoagulability, more attributable to he-

patic failure than to disseminated intravascular coagulation, causes spontaneous hemorrhage into the skin, lungs, gastrointestinal tract, kidneys, and brain. The mortality rate is high. Infants dying of hepatitis have massive hepatic necrosis and extensive hemorrhage into the cerebral ventricles, pericardial sac, renal medulla, and interstitial spaces of many solid organs. Inflammation is commonly limited to the liver and adrenal glands, with sparing of the heart, brain, meninges, and other organs. Cirrhosis and chronic hepatic insufficiency can develop in survivors.

Central nervous system infection. Signs and symptoms such as extreme lethargy, seizures, hemiparesis, flaccid paralysis, and coma define the more serious form of meningoencephalitis that often accompanies myocarditis or hepatitis. Inflammation of the brain or spinal cord is found in approximately two-thirds of infants dying of myocarditis. These patients have diffuse or scattered lesions consisting of perivascular infiltration with mononuclear cells and polymorphonuclear leukocytes in the cerebrum, cerebellum, pons, medulla, and spinal cord; meningoencephalitis in the absence of other organ involvement is rare.

Pneumonia. Echovirus serotypes 6, 9, and 11 have been associated with a small number of reported cases of perinatal pneumonitis. Some cases are characterized by the onset of symptoms within hours of birth, a finding suggestive of prenatal exposure, and these cases are associated with a high mortality rate. Less severe neonatal pneumonitis has been described with echovirus serotypes 7 and 22. Pathologic evidence of pneumonitis can be seen with group B coxsackievirus myocarditis in newborns, but it is generally limited to focal areas of interstitial inflammation.

Varicella-Zoster virus. The varicella-zoster virus can also cause congenital infection. Because chickenpox infections usually take place during childhood and seldom dining pregnancy, however, this type of congenital infection is uncommon.

Congenital varicella-zoster infection of the fetus, like other congenital viral infections, occurs during maternal infection and results from passage of virus across placenta.

Clinical manifestations of congenital varicella syndrome:

1. skin
    - cutaneous defects
    - cicatricial scars
    - hypopigmentation
    - bullous lesions
2. extremities
    - hypoplastic limb
    - muscular atrophy and denervation
    - joint abnormalities

- absent or malformed digits

3. eye
   - chorioretinitis
   - microphthalmia
   - anisocoria
4. central nervous system
   - intrauterine encephalitis with cortical atrophy
   - seizures
   - mental retardation
5. urinary tract
   - hydronephrosis/hydroureter
6. gastrointestinal tract
   - esophageal dilation/reflux

If maternal chickenpox occurs within 4 or 5 days of delivery, the newborn infant can has widespread infection involving liver, lungs, brain and kidneys. As many as 30% of newborns with varicella-zoster infection died before antiviral therapy. Some infants exposed to persons with chickenpox may require intervention with varicella-zoster immunoglobulin.

Infants with varicella-zoster infection can transmit disease when they have active skin vesicles. These infants, like older children with chickenpox, should be isolated from other infants or nonimmune children and adults until the skin lesions are crusted over.

Human Parvovirus B19. Human parvovirus B19 can occasionally infect a nonimmune pregnant woman and damage the fetus. Human parvovirus B19 can cause stillbirth or severe anemia resulting in extreme edema of fetal tissues, or it may produce no adverse effects on fetus. Most pregnant women who become infected with human parvovirus B19 give birth to normal infants.

RUBELLA

Rubella (German measles) is the most common viral cause of birth defects in children. In children and adults rubella produces only mild systemic disease with fever, rash and catarrhal fenomena. If woman is infected during her first trimester of pregnancy, however, there is a high likelihood of damage to developing fetal organs. By contrast, the infant infrequently has signs of rubella infection when maternal infection occurs after the fourth month.

Like other congenital infections, rubella can cause miscarriage or stillbirth. More often, however, the infant survives and has damage to many tissues, including eyes, brain, heart, liver, lungs, kidneys, skin, bones and hormone-secreting organs. The tissues most commonly affected are eyes, brain and heart. The infant may have cataracts, microphthalmia, chorioretinitis, encephalitis, microcephaly and congenital heart defects (usually patent ductus arteriosus).

Rubella-infected infants often have skin rash, feature that reflects a reduced platelet count and bleeding into the skin.

Nearly all infected infants with signs of rubella will have some degree of long-term neurologic impairment. Like CMV, rubella can damage the inner ear and produce nerve deafness. Many asymptomatic infants born to mothers who had rubella infection during pregnancy later develop deafness or psychomotor retardation. In addition, rubella-infected infants occasionally manifest thyroid dysfunction, growth disturbance, or diabetes mellitus.

Table 2.

Clinical features associated with congenital rubella syndrome

Category	Common	Uncommon
Transient	Low birthweight Thrombocytopenic purpura Hepatomegaly Splenomegaly Bone lesions	Cloudy corneas Hepatitis Generalized lymphadenopathy Hemolytic anemia Pneumonitis
Permanent	Sensorineural deafness Peripheral pulmonary stenosis Pulmonary valvular stenosis Patent ductus arteriosus Ventricular septal defect Retinopathy Cataract Microphthalmia Psychomotor retardation Cryptorchidism Inguinal hernia, Diabetes mellitus	Severe myopia Thyroid disorders Dermatoglyphic abnormalities Glaucoma Myocardial abnormalities Sensorineural deafness
Delayed	Peripheral pulmonary artery stenosis Mental retardation Central language defects Diabetes mellitus Immune complex disease Hypogammaglobulinemia	Severe myopia Thyroiditis Hypothyroidism Growth hormone deficiency Chronic rash Pneumonitis Progressive panencephalitis

Although no effective antiviral therapy is available to treat congenital rubella infection in newborns, rubella can be prevented by vaccination. The rubella vaccine should be included in all childhood immunization programs. In addition, women of childbearing age should have their blood tested to ascertain whether they are immune to rubella. If they are not, they should receive the rubella vaccine at time when they are not pregnant.

Children with congenital rubella should be excluded from center-based programs until throat and urine cultures are negative for the rubella virus. Pregnant women who have not had rubella or have not received rubella immunization should avoid contact with infants with congenital rubella. Excretion of the virus diminishes greatly during the first year of life. Thereafter, these children pose little or no risk to nonimmune pregnant women.

CYTOMEGALOVIRAL INFECTION

Human CMV infection occurs throughout the world in people of all ages. manifestations of CMV infection depend on the age and immune status of the infected individual. In healthy children and adults, including pregnant women, CMV infection rarely causes symptoms, although occasionally an infectious mononucleosis-like illness develops with fever, fatigue, and swelling of the lymph nodes. By contrast, people with impaired immune systems can develop servere complications, such as pneumonia, eye infection or encephalitis.

The majority of congenitally infected infants have no symptoms at birth (the infection is recognizable by the excretion of CMV in the urine). 10-15% of these infected but asymptomatic infants later develop hearing loss caused by chronic CMV infection of inner ear and some children may also have subtle behavioral or developmental consequences. Approximately 5-10% of congenitally infected infants have severe and sometimes fatal condition characterized by damage to numerous body organs, including brain, lungs, and liver. CMV also causes jaundice, skin rash, abnormal blood and platelet counts, enlargement of the spleen and chorioretinitis.

By far the most serious consequence of symptomatic CMV infection is damage to the developing brain. The most common abnormality in infants with severe CMV infection is deficient brain growth manifested by a small head size (microcephaly). Survivors of symptomatic CMV infection often have substantial neurologic impairments, including developmental and mental retardation, motor abnormalities, seizures, visual deficits, and nerve deafness.

Treatment. Currently, there is no approved agent for antiviral therapy for congenital CMV infection, but one study suggests a limited role for ganciclovir treatment of neonates with severe infection. A randomized trial compared ganciclovir, 12 mg/kg/day administered intravenously in 2 divided doses daily for 6 weeks, with no treatment in neonates with severe, symptomatic congenital CMV infection. Hearing thresholds declined significantly in 70% of placebo recipients compared with 20% of ganciclovir recipients evaluated at 1 year of age or older. However, treatment was not associated with statistically significant improvement in the course of disease as indicated by laboratory abnormalities (platelet count, alanine-transaminase, bilirubin) or liver and spleen size. Eligibility for this trial required the presence of signs of CNS disease and thus was limited to patients almost certain to have serious CNS sequelae. Treatment was associated with neutropenia that required dosage adjustment or discon-

tinuation of ganciclovir in about half of treated patients. In addition, ganciclovir treatment of neonates with CMV retinitis has been associated with marked worsening of retinitis after discontinuation of the drug. Animal studies indicate the potential for reproductive toxicity and carcinogenicity at levels similar to those achieved in treating humans; although these two problems have not been recognized in humans treated with ganciclovir. Ganciclovir treatment of severe symptomatic congenital CMV infection may deserve consideration in some situations because of the evidence of modest benefit and lack of alternative treatments. Pharmacokinetic studies and clinical trials of oral valganciclovir for congenital CMV are necessary before recommendation can be considered. There is no evidence to support ganciclovir treatment of newborns with asymptomatic or mild abnormalities in whom the potential for benefit would be low in relation to the risks.

Currently, CMV infection can be neither prevented nor effectively treated. None of the available antiviral agents has proved to be effective against congenital CMV infection, although newer antiviral drugs are cur-rently being investigated. There is no vaccine that can prevent birth defects due to congenital CMV infection.

CMV is present in urine, saliva, blood, cervical secretions and semen of infected individuals. Urine and saliva usually contain the largest quantities of viral particles, and virus can be shed for months or even years. Transmission of CMV results from close, personal contact with infected individuals, often children or sexual partners. Mothers can transmit CMV to their nursing children via breast milk and transfused persons can acquire CMV from infected blood products.

Risk of acquiring CMV varies according to nature of contact with CMV-infected children. Persons who work with children in hospitals have low rates of infection, whereas day care workers or parents of CMV-excreting young children have relatively high rates of CMV infection.Pregnant women should avoid daily, hands-on contact with infants or young children with known congenital CMV infection. The risk may be greatest during the child's first year of life, when large quantities of the virus are excreted in urine or saliva. Approximately 50% of children with congenital CMV infection continue to shed virus in their urine for 4 years or more.

Any young child, especially one attending group day care, may be excreting CMV. Consequently, women who have contact with young children and anticipate pregnancy in the future should know their CMV immune status. This can be determined by blood test (CMV serology), which physician can order. Pregnant women who are seronegative and therefore not immune to CMV should limit their exposure to toddler-age children (who are more likely to be excreting CMV) and should practice good hygiene, by washing their hands after contact with children or their secretions, and by avoiding oral contact with the children or their secretions.

HERPES SIMPLEX VIRUS

HSV causes serious illness in 1 in every 10,000 live-born infants. This virus exists in two forms: HSV type 1, which causes cold sores and gingivostomatitis, and HSV type 2, which causes most genital herpetic lesions. Most cases of perinatal HSV infections are caused by HSV type 2.

Unlike CMV and Toxoplasma gaondii, which are acquired prior to birth, HSV infections are usually acquired perinatally; that is, they occur during or shortly after birth. Although HSV can be transmitted to the fetus via the placenta or amniotic fluid, most infections occur when the infant passes through birth canal of mother who has been infected with HSV and has HSV in her cervical or vaginal secretions. Less often, the infant contracts HSV from adult who has active oral herpes.

Symptoms of perinatal HSV infection usually begin during the first 5-7 days of life and vary according to the distribution of the disease. In approximately 40% of cases, infection is localized to skin, mouth or eye, causing vesicles of the skin or mouth, or inflammation of cornea. In another 35% infection is restricted to the brain (herpes encephalitis) with lethargy or irritability and severe neurologic signs, such as seizures or coma. In as many as 25% of cases, the infection is disseminated throughout infant's body, causing fever, vomiting, jaundice, lethargy, skin vesicles and enlargement of liver or spleen.

Table 3

Characteristics of neonatal HSV infections

Feature	Skin/Eye/Mucous membrane infection	Central nervous system infection	Disseminated infection
Usual age at onset (days)	7–14	14–21	5–10
Clinical findings	Vesicles on red base at sites of trauma; conjunctivitis	Lethargy, irritability, fever, seizures	Shock, hepatomegaly, jaundice, bleeding, respiratory distress
Diagnostic testing	Direct fluorescent antibody test and culture of skin lesions	Direct fluorescent antibody test and culture of skin lesions if present; analysis, culture and PCR of CSF; EEG; neuroimaging studies, brain biopsy	Direct fluorescent antibody test and cultures of skin lesions; culture of nasopharynx, rectum, buffy coat, CSF

Mortality if treated (%)	0	15	54
Sequelae if treated (%)	5	54	38

Treatment. Antiviral therapy is beneficial for neonates with HSV infections. Vidarabine was the first agent demonstrated to benefit neonates with HSV infection, reducing mortality for infants with disseminated or central nervous system infection from 70% in placebo recipients to 40% in vidarabine recipients. Acyclovir is at least as effective as vidarabine and is the preferred agent because it has a more favorable safety profile. An open-label evaluation of increasing dosages of intravenous acyclovir support the use of a 21-day course of 60 mg/kg/day to treat neonatal CNS and disseminated infection. Best therapeutic results are obtained when infection is localized to the skin, eyes, and mouth. With treatment before progression of infection, all infants survive, and > 90% appear to be developmentally normal, although almost half have recurrent skin lesions within 6 months of completion of therapy. By contrast, > 50% of infants with disseminated infection die, whether their disease is treated with vidarabine or acyclovir. About 15% of infants with central nervous system disease die despite therapy, and less than half of survivors are normal at 1 year of age. Recurrence of central nervous system symptoms and an abnormal CSF finding are observed in about 8% of survivors of disseminated or central nervous system disease. A controlled trial is being conducted to determine if long-term suppressive therapy with orally administered acyclovir will reduce recurrences of central nervous system infection and improve long-term prognosis.

Neonates with proven HSV infections should receive acyclovir; the role of empiric acyclovir therapy is not clear. Clinical settings in which empiric therapy should be considered include: (1) the appearance of skin lesions typical of HSV while awaiting results of diagnostic tests; (2) fever or other unexplained signs of infection in a neonate known to have been exposed to HSV at delivery; (3) progressive clinical deterioration in an infant initially suspected to have bacterial sepsis for whom bacterial culture results are negative; and (4) unexplained encephalitis in a neonate with unremitting seizures. Whether or not antiviral therapy is initiated under these circumstances, specimens obtained from the nose, eyes, mouth, pharynx, rectum, CSF, and buffy coat should be submitted for viral culture. Specimens of CSF and peripheral blood mononuclear cells also should be tested for HSV DNA by PCR.

Prognosis for HSV-infected infant depends on extent of disease and prompt initiation of anti-HSV therapy. For example, infants with localized infection of skin do well with little mortality or long-term effects. By contrast, half infants with severe disseminated HSV infections die, and 20% to 30% of the survivors have long-term impairments ranging from poor growth to seizures, blindness and mental retardation.

Some instances of perinatal HSV infection can be prevented. If active genital herpes lesions are present at time of mother's labor, infant should be delivered by cesarean section, particularly if amniotic membrane has not ruptured (less than half the mothers who give birth to infants with HSV have either history of genital HSV infection or evidence of this condition, such as genital lesions). All infants younger than 2 months should be isolated from adults who have active oral herpes lesions. Any adult with active oral herpes should wear protective mask when caring for infants younger than 1 month.

GENERAL RECOMMENDATIONS FOR ALL CONGENITAL INFECTIONS

Children who survive congenital infections often have multiple long-term complications that require multidisciplinary approach to treatment guided by developmental pediatrician or pediatric neurologist. Many medical services may be required, including those of ophthalmologist, orthopedist and audiologist.

Children with developmental delay require early intervention programs. Intelligence testing with age-appropriate instruments should be performed as early as reliable results can be obtained. Because visual abnormalities are common complications of congenital infections, affected children should be examined by pediatric ophthalmologist.

Because many congenital infections are associated with nerve deafness (sensorineural deafness), periodic audiologic testing is important. Some children, particularly those infected with CMV or rubella virus, can develop progressive or new-onset hearing loss. Conservative approach is to perform audiometric testing at birth, at 6 months, at 1 year, and annually thereafter until child reaches school age. Many children will benefit from hearing aids. Deafness is sometimes so severe, however, that the child requires special supportive services throughout school years and beyond.

As with nearly all infections, the risk of transmitting infection from certain congenitally infected infants can be greatly diminished by good hygiene. Diapers should be promptly discarded in appropriate containers. Also, personnel should wash their hands well after contact with infected infants. Gloves need not be worn except when one is handling infants with active HSV or varicella zoster skin lesions or changing diapers of infants with CMV infection.

PART 14 PROPHYLACTIC IMMUNIZATION

The widespread use of vaccines led to the global eradication of smallpox, the elimination of poliomyelitis from the Americas, and the virtual elimination of poliomyelitis from the Western Pacific. In the United States, immunization has almost eliminated congenital rubella syndrome, tetanus, and diphtheria and reduced the incidence of pertussis, rubella, measles, mumps, and Haemophilus influenzae type b meningitis dramatically.

Definitions and mechanisms. Vaccination means the administration of any vaccine or toxoid. Immunization describes the process of inducing immunity artificially by administering antigenic substances, such as an immunobiologic agent. Administration of an immunobiologic agent cannot be equated automatically with the development of adequate immunity.

Active immunization consists of inducing the body to develop defenses against disease by the administration of vaccines or toxoids that stimulate the immune system to produce antibodies and cellular immune responses that protect against the infectious agent. Passive immunization consists of providing temporary protection through the administration of exogenously produced antibody. Passive immunization occurs through the transplacental transmission of antibodies to the fetus, which provides protection against several diseases for the first 3–6 mo of life, and the injection of immune globulin for specific preventive purposes.

Immunizing agents include vaccines, toxoids, and antibodies containing preparations from human or animal donors. Most of these agents contain preservatives, stabilizers, antibiotics, adjuvants, and a suspending fluid.

The principal approaches to active immunization are the use of live, usually attenuated, infectious agents and the use of inactivated or detoxified agents or their extracts or specific products of recombination (hepatitis B). Both approaches have been employed for many diseases (influenza, poliomyelitis). Live, attenuated vaccines are thought to induce an immunologic response more like that elicited by natural infection than killed vaccines. Inactivated or killed vaccines consist of inactivated whole organisms (pertussis vaccine), detoxified exotoxins alone (tetanus toxoid), or endotoxins linked to carrier proteins, soluble capsular material (pneumococcal polysaccharide) or conjugated capsular material (Hib conjugate vaccine), or extracts of some component (hepatitis B) or components of the organism (subunit influenza).

The most important protective antibodies include those that inactivate soluble toxic protein products of bacteria (antitoxins), facilitate phagocytosis and intracellular digestion of bacteria (opsonins), interact with components of serum complement to damage the bacterial membrane with resultant bacteriolysis (lysins), prevent proliferation of infectious virus (neutralizing antibodies), or interact with components of the bacterial surface to prevent adhesion to mucosal surfaces (anti-adhesions). Many of the structural constituents of microorganisms and exotoxins are antigenic. Most antigens require the interaction of B cells (thymus independent) and T cells (thymus dependent) to generate an immune response (measles), but some initiate B-cell proliferation and antibody production without the help of T cells (pneumococcal type III polysaccharide.).

The first step in the induction of a thymus-dependent antibody response is the activation of T helper cells by presentation of an antigen to mononuclear phagocytes or dendritic cells, a step that may be facilitated by the use of an adjuvant. Presentation of an antigen triggers the secretion of a cascade of mediators, called cytokines, which are made by or act on elements of the immune system to stimulate the maturation of naive T helper cells and to communicate between leukocytes, using interleukins (IL) to

regulate the immune response. Depending on the stimulus, T lymphocytes are stimulated to differentiate into one of two subsets: T helper 1 cells (TH1), which mediate cell-mediated immune responses, or T helper 2 cells (TH2), which enhance antibody production. TH1 cells produce IL-2 and interferon-g, and TH2 cells produce IL-4, IL-5, and IL-10.

Antibodies formed to vaccine constituents may be of any immunoglobulin class. Antibodies function alone or in conjunction with other components of the immune system (complement, opsonin) by participating directly in the neutralization of a toxin (diphtheria); by opsonization of virus (poliovirus); by initiating or combining with complement and promoting phagocytosis (pneumococcus, cholera); by reacting with nonsensitized lymphocytes to stimulate phagocytosis; or by sensitizing macrophages to stimulate phagocytosis. The primary response to a vaccine antigen requires a latent period of several days before humoral and cell-mediated immunity can be detected. Circulating antibodies do not appear for 7–10 days. The immunoglobulin class of the response changes over time. Early-appearing antibodies are usually IgM; later-appearing antibodies are usually IgG. When the antigen is thymus-dependent, IgM and IgG antibodies are secreted initially by B cells, with IgM appearing first. IgM antibodies fix complement, making lysis and phagocytosis possible. The IgM titer falls as the titer of IgG rises during the 2nd wk (or later) after immunogenic stimulation. The switch from IgM synthesis to predominately IgG synthesis in B cells requires T-cell cooperation. IgG antibodies are produced in high concentrations and function in the neutralization, precipitation, and fixation of complement. IgG titers reach a peak within 2–6 wk.

Heightened humoral or cell-mediated responses are elicited by a second exposure to the same antigen. Secondary responses occur rapidly, usually within 4–5 days. The secondary response depends on immunologic memory mediated by T and B cells and is characterized by a marked proliferation of antibody-producing cells or effector T cells.

Because the organisms in live vaccines multiply in the recipient, antigen production increases until it is checked by the onset of the immune response it is intended to induce. In recipients who develop a response, the live, attenuated viruses (measles, rubella, mumps) are thought to confer lifelong protection with one dose. In contrast, killed vaccines, except for purified polysaccharide antigens, do not induce permanent immunity with one dose. Repeated vaccination and boosters are needed to develop and maintain high levels of antibody (diphtheria, rabies). Although more antigen is introduced initially in inactivated vaccines, the multiplication of organisms in the host results in a greater antigenic stimulus by live vaccines.

The oral poliovirus vaccine is an exception to this general principle because oral feeding does not consistently result in infection ('take') with the vaccine virus. Therefore, multiple doses are necessary.

The major advantage of non-replicating vaccines is the relative stability of the antigens. Fluctuations in temperature of storage and transportation reduce the potency of live vaccines more rapidly than that of killed and toxoid vaccines.

Vaccine-preventable diseases. Diseases against which vaccines are currently available.

1) Diseases preventable by environmental improvement or by immunization - Japanese encephalitis, tuberculosis, yellow fever, typhoid fever, rabies, cholera and hepatitis B (horizontal transmission).

2) Diseases preventable only by immunization - Poliomyelitis, diphtheria, measles, tetanus, rubella, pertussis, mumps, meningococcal meningitis (A and C serotypes), influenza, H.influenzae meningitis, chicken pox, hepatitis B (vertical transmission).

Passive Immunization. Passive immunization is used to provide temporary immunity in an unimmunized person exposed to an infectious disease when active immunization is unavailable (e.g., hepatitis A) or has not been given before exposure (e.g., rabies). Passive immunization is used in the treatment of certain disorders associated with toxins (e.g., diphtheria), in certain bites (e.g., snake and spider bites), and as a specific (e.g., immune globulin) or nonspecific (e.g., antilymphocyte globulin) immunosuppressant.

Three types of preparations are used in passive immunization: standard human immune serum globulin (e.g., intravenous or intramuscular gamma globulin), special immune serum globulins with a known antibody content for specific agents (e.g., hepatitis B or varicella-zoster immune globulin), and animal serums and antitoxins.

In pediatric practice, routine immunization is given to individual children for their personal protection. In public health practice (primary health care) individual as well as community protection is desired. For the latter, the transmission chain of the infectious agent must be broken by protecting an adequate proportion of susceptible individuals. Thus, the risk of disease in the unimmunized children is also reduced. This phenomenon is generally referred to as the herd effect of immunization.

Vaccines which protect against infections as well as disease have better herd effect than those which protect only against disease. Measles and oral poliovirus vaccines have excellent herd effect. Diphtheria vaccine is directed against the toxin, not against the infecting organism. Vaccine-induced protection is incomplete in the case of pertussis and typhoid fever. For these reasons, herd effect is not very prominent with diphtheria, pertussis and typhoid vaccines. For tetanus, there is no herd effect since transmission is not man-to-man. Recent evidence suggests little or no herd effect for BCG vaccine. The herd effect can be maximized by immunizing large numbers of susceptible children in a short span of time. Thus, measles and oral poliovirus vaccines may be used in discontinuous immunization campaigns to achieve rapid and effective control of disease. This strategy is called annual pulse immunization.

Immunization in primary health care. Ideally all susceptible children should be immunized. Therefore, the opportunity of a sick visit should also be utilized to promote immunization. Minor illnesses such as upper respiratory infection or diarrhea are not contraindications for administering any vaccine.

Some practical aspects:

- There is no contraindication to concurrent administration of multiple vaccines such as DPT, OPV or MMR.

- A lapse in the schedule of immunization does not necessitate reinstitution of the total course. If the second or third dose of DPT or OPV was missed or delayed, there is no need of giving all the three doses of primary vaccination schedule.

- If immunization status of a child is unknown, there is no harm in giving appropriate vaccines again.

- It is desirable not to reduce the dose of the vaccine as it may cause inappropriate immunological response. Dose should not be exceeded to avoid side effects.

- Measles, mumps and rubella vaccines should not be given to children, who were given immune globulin within the previous three months, since this may hinder adequate response to active immunization. But concurrent administration of hepatitis B, tetanus or rabies immune globulin and the corresponding vaccine or toxoid is not contraindicated. Likewise immune globulins do not interfere with immune response to OPV and yellow fever vaccine.

- Live-virus vaccines of all types and BCG should not be given to patients with congenital disorders of immune functions. These should also not be used in children treated with large doses of steroids or during illnesses, which are known to suppress immune response. Short-term (less than two weeks) low-dose steroid therapy is not a contraindication to live-virus vaccines.

-Children suffering from neurologic disorders or with previous history of convulsions is at a higher risk of adverse reactions following pertussis vaccine.

- Active immuno-prophylaxis after exposure to disease is recommended for rabies, measles (within three days of exposure), hepatitis and tetanus.

Immunogenic and protective efficacy. Immunogenic efficacy of a vaccine refers to its ability to induce an immune response; protective efficacy refers to actual protection against disease. In the case of live viral and toxoid vaccines, antibody response almost always results in protection. In the case of killed bacterial vaccines and BCG, antibody response or CMI may not necessarily be protective. The breakthrough disease after immunization is indicative of vaccine-failure. When the administration of recommended doses of vaccine does not result in immune response sufficient to protect against disease, the vaccine-failure is primary. When disease occurs in spite of immune response, it is referred to as secondary vaccine-failure. Primary vaccine failure occasionally occurs after three doses of oral poliovirus vaccine; secondary vaccine failure occurs not infrequently after pertussis, typhoid and BCG immunization. Vaccine failure is very rare after measles, diphtheria, and tetanus immunizations.

Immunological adjuvants are substances given along with antigens in order to enhance their immunogenic efficacy. Aluminium salts are used as adjuvants in diphtheria - pertussis -tetanus vaccines.

Diphtheria. Maternal antibodies protect the infant against diphtheria for several weeks to months after birth. The toxoid vaccine, absorbed with aluminium hydroxide is usually combined with pertussis and tetanus toxoid vaccines as a triple antigen (DPT vaccine) or with tetanus toxoid (DT vaccine). Primary immunization requires three doses, at intervals of 4,6 or 8 weeks; the first booster is recommended during the second year of life (18 months) and a second booster at five years. Subsequent boost-

ers are not necessary in countries such as India where C. diphtheriae infection is common. In case primary immunization is to be carried out in an older child or an adult, the adult type of toxoid (Td) containing less quantities of antigen should be employed.

Immunization does not eliminate C. diphtheriae in skin or nasopharynx. Clinically obvious diphtheric infection may not always confer immunity.

Pertussis. The pertussis vaccine is usually given in the form of the DPT vaccine. Each dose contains a required number of killed organisms of B. pertussis. Since protective antibodies against this disease do not cross the placenta, early immunization is desired. Three doses are recommended at 4-8 weeks of interval, commencing at 1-3 months of age so that primary immunization is completed by 4-6 months of age. The protective efficacy is approximately 75 percent. Occasional vaccine failure may be expected.

Common adverse reactions include local pain, swelling, mild to moderate fever and irritability. Prolonged screaming by the infant is an uncommon reaction, the significance of which is not clear. Rarely convulsions may occur either due to the fever or due to an encephalopathy syndrome. An infant who develops prolonged screaming or convulsions following a dose of DPT should not be given any further pertussis vaccine; further doses should be DT vaccine or tetanus toxoid alone. An infant with progressive neurological disease also should not be given pertussis vaccine. However, a static neurological disease (cerebral palsy) and febrile convulsions are not contraindications. The administration of a few doses of an antipyretic (acetaminophen) is a common practice, which may help reduce fever and pain.

Tetanus. Neonatal tetanus is an important cause of mortality in many developing countries. Since there is no natural immunity to C. tetani toxin, unimmunized mothers do not transfer antibodies to the infants. Therefore, immunizing pregnant women or women of child-bearing age against tetanus using tetanus toxoid (TT) is an important public health strategy to reduce the incidence of neonatal tetanus in high risk countries. If children are fully protected with DPT vaccine and TT booster doses are given at 5-10 year intervals, immunization during pregnancy will eventually become unnecessary. This is a better approach since tetanus may occur at any age. It is particularly important in India with its agrarian society and love for cattle, the two factors contributing to the risk of infection with C. tetani.

BCG vaccination. Bacillus Calmette Guerin (BCG) is an attenuated strain of Mycobacterium tuberculosis var. bovis, used as a live vaccine against tuberculosis. In order to maintain its potency, the vaccine is supplied in freeze-dried (lyophilized) form. At 4°C its potency remains satisfactory for several months.

BCG is administered intradermally over the deltoid muscle. The dosage is 0.05 ml (newboms) or 0.1 ml (all other ages). After 2-3 weeks a papule develops at the site (indicating the multiplication of BCG) which gradually heals leaving a scar. Neonates of mothers with bacillary tuberculosis may be given special isoniazid-resistant BCG along with the drug itself to protect from primary tuberculosis. Four to 12 weeks after immunization the tuberculin (PPD) test becomes positive in the majority of infants.

BCG may be given any time from birth since mother's immunity is not transferred to the fetus. In the neonate and young infant, tuberculin testing is unnecessary before giving BCG.

Poliomyelitis. Two types of polio vaccine are licensed in the United States: OPV, a live, attenuated trivalent poliovirus vaccine (Sabin), and IPV, an inactivated (killed) trivalent poliovirus vaccine (Salk). A full course of either vaccine protects the recipient against paralytic poliomyelitis almost without exception. Because rare cases of paralytic poliomyelitis occur in recipients of OPV or in their close contacts, some have advocated returning to IPV for routine immunization of children. However, immunization advisory groups in the United States have continued to recommend OPV for routine immunization of children because of the virtual eradication of poliomyelitis from the United States by OPV and because of the belief that the circulation of wild virus in the community is controlled better by the greater intestinal immunity afforded by OPV.

Primary immunization by IPV requires 3 doses, given intramuscular or subcutaneous, at 4-8 weeks interval. In countries where poliovirus circulation is slow on account of excellent hygiene, periodic booster doses of IPV are necessary to maintain high antibody levels. Where virus circulation is intensive, it is believed that infection will reinforce immunity and booster doses may not be needed.

Immunization should be completed by about six months of age. For individual protection five doses of OPV are recommended for primary immunization. Three doses may be given simultaneously with DPT, two doses either before or after, at intervals of at least four weeks. At subsequent visits for measles immunization and DPT booster, two additional doses of OPV may be given to ensure near 100 percent protection rate.

OPV should not be given to individuals proven or suspected to be immunocompromised, including those with congenital and acquired immunodeficiencies and those whose immune mechanisms are impaired by therapy. OPV should not be given to household contacts of immunocompromised individuals or to subsequent siblings of a child with congenital immunodeficiency until the younger child is shown to be normal.

Both KPV and OPV are very safe vaccines without adverse reactions. Transient diarrhea following OPV has been noted, but no etiologic association has been proven. One in a few million vaccinees in some Western countries develops paralytic poliomyelitis due to vaccine virus infection itself. In India, the risk of paralytic poliomyelitis is 1 in 100 to 300 unimmunized children.

Where an outbreak of poliomyelitis occurs, the rapid administration of OPV to preschool children irrespective of their previous history of immunization will arrest the epidemic. This is due to the displacement of natural, (wild) poliovirus in the community by vaccine viruses.

Although breast milk contains antibodies against polioviruses, they do not appear to inhibit vaccine-virus 'take' and subsequent immune response. However, it is prudent to withhold breast-feeding for 30 minutes before and after giving OPV.

The potency of OPV is stable for 3-4 months at 4-8°C and for 1-2 years at -20°C. Temperature fluctuations, particularly those above 8°C rapidly reduce the potency.

KPV should be used in immune-compromised children, those with AIDS, family members of immunodeficient individual, partially immunized or unimmunized adults and in some tropical countries with poor facilities for cold chain.

Measles. Live attenuated measles virus is used as the vaccine. The minimum recommended potency is 1000 median cell culture infectious doses of virus. It may be given subcutaneous or intramuscular.

Residual maternal antibody in the infant's serum neutralizes the immunogenic property of the vaccine and it should be offered at an age when most infants would have lost this effect. Therefore, in developing countries the recommended minimum age is nine months. Depending upon the strain of vaccine virus, between 10 and 20 percent of vaccinees may develop mild to moderate fever about 6-8 days after receiving measles vaccine. It lasts 1-3 days and is not associated with malaise. Between 1 and 5 percent of children may develop a few red spots on the trunk at this time. Malignancies associated with immunosuppression and therapy with antimetabolites, alkylating agents and corticosteroids are contraindications for measles vaccine. Treatment for primary tuberculosis is not a contraindication.

The Edmonston-Zagreb strain of vaccine grown in human diploid cells has been successfully administered as an aerosol to immunize infants against measles. By utilizing the respiratory route it is hoped to avoid neutralization by any maternal.

Rubella. As the vaccine consists of live attenuated virus, it should be given only after maternal antibodies have disappeared: the recommended minimum age is 12 months.

Three attenuated virus strains are available, namely HPV-77, Cendehill and RA 27/3. All of them induce antibody response in over 95 percent of recipients. Vaccine is often combined with measles and mumps vaccine. Adverse reactions to rubella vaccine include lymphadenopathy, arthralgia and transient skin rash, all of which are self-limiting. Pregnancy and immunosuppression are contraindications.

Mumps. In developing countries, the priority for mumps prophylaxis is low on account of many other more pressing priorities. The vaccine consists of live attenuated mumps virus (Jeryl Lynn strain). It is usually combined with measles and rubella vaccines into one trivalent vaccine (MMR). Mumps vaccine of MMR may be given after 12-15 months of age. Since orchitis and oophritis are occasional complications of mumps in adults, some experts recommend mumps vaccine to all young adults who have not had the disease earlier. Clinical efficacy is 75 to 90 percent.

Rabies. Since transmission of rabies virus is almost exclusively through the bite of an infected animal and since the incubation period is relatively long, post-exposure prophylaxis is possible. Two types of vaccines are available in India and other developing countries. These are the animal (sheep, goat, rabbit or monkey) brain-grown and inactivated rabies virus vaccine (modified Semple's vaccine) and the cell-culture-grown, inactivated and purified vaccine. Both are killed virus vaccines.

As an animal bites virus if present in saliva, is inoculated into the wound. Immediate washing with soap and liberal amounts of water does eliminate a large part of virus particles. The wound should not be stitched or cauterized. The vaccine should be administered

subcutaneously, preferably in the anterior abdominal wall, daily for 7-14 days: some schedules require booster doses.

The modern rabies vaccines may be prepared in cell cultures of human, simian or avian origin. Currently the vaccines prepared from rabies virus grown in human diploid cell strain (HDCS rabies vaccine) or in chick embryo cells (CEC rabies vaccine) are used widely. The two advantages of the vaccines over the conventional vaccine are the absence of neurological complications and better protective efficacy. The main disadvantage is the high cost. A course consists of six doses given intramuscularly or subcutaneously on days 0,3, 7,14, 30 and 90. When using the vaccines, animal contact incidents are not categorized. However, when the bite of an infected animal is on head, neck, hands or genitalia, irrespective of the type of vaccine given, equine antirabies serum must also be given in doses of 40 iu/kg body weight, with due precautions. When available, human anti-rabies immunoglobulin is preferred but is very expensive. The dose is 20 iu/kg given on day 0, half the dose being given by deep intragluteal injection and half of the dose is infiltrated in the wound.

Cell culture rabies vaccine is suitable for pre-exposure prophylaxis. The schedule is 1 ml of vaccine IM or SC or 0.1 ml ID on days 0, 28 and 56 or on days 0, 7 and 28, respectively. Purified chicken cell cultures vaccine is now easily available and is much less expensive.

Typhoid fever. The currently available vaccine consists of a standard suspension of acetone-killed Salmonella typhi. The addition of S. paratyphi A or B does not seem to offer any advantage; therefore monovalent typhoid vaccine is preferred to TAB or TA vaccines. Primary immunization requires two subcutaneous doses given four weeks apart; during an outbreak the interval can be reduced up to 1 week. The dose is 0.5 ml for children 10 years of age and for younger children the dose is 0.25 ml. Booster doses once in three years are recommended in typhoid endemic areas.

Influenza. The conventional vaccine consists of formalin-killed influenza virus. Two doses are given 4-8 weeks apart for primary immunization. Newer vaccines such as subunit (hemagglutinin) vaccine and a live (recombinant) virus vaccine are used. The objective' of immunization is to prevent mortality in individuals at high risk.

Japane encephalitis (JE). A killed virus vaccine prepared from the Nakayama strain of JE virus grown in suckling-mouse-brain has been used widely in Japan, Korea and some SE Asian countries. Three doses are recommended at four weeks or more intervals. The protective efficacy is moderately high.

ChicKenpox (Varicella). A live attenuated virus (Oka strain) vaccine has been developed in Japan and field-tested in many countries. It is safe and effective; it protects against varicella but not against herpes zoster. Its greatest usefulness is in children with malignancies who are at high risk of life-threatening infections with varicella virus. The vaccine is likely to be released for routine use in a year.

Yellow fever. Yellow fever immunization is required only for those living in endemic zones or those who travel to such areas. Two live virus vaccines are available, namely 17D and Dakar; the former is preferred. The virus is grown in chick embryos

and lyophilized before distribution. The vaccine can only be obtained and administered at a Yellow fever vaccination center.

Being a live vaccine, only one dose is sufficient for protection for at least 10 years. Infants below 6 months and pregnant women should not be given the vaccine due to increased risk of neurological side-effects for the immature brain.

Meningococcal, Pneumococcal and Hemophilus mfluenzae infections. The capsular polysaccharide of N. meningitidis (Groups A and C) has been successfully used to immunize against meningococcal menigitis. Monovalent (group A or C) and bivalent vaccines are available. Similarly, capsular polysaccharides of several serotypes of S. pneumoniae have been combined into a polyvalent vaccine. H. mfluenzae type B vaccine consists of its capsular polysaccharide.

As a rule, infants and very young children respond poorly to polysaccharide antigens. Therefore, these vaccines are offered to children above one year (meningococcal vaccine) or above two years (pneumococcal and H. influenzae vaccines). Ordinarily a single dose of these vaccines is sufficient.

The schedule of immunization

VACCINE	DISEASE				
1 day of life		VHepB			
3 day of life	Tuber-culosis				
1 mo		VHep B			
3 mo			Diptheria Pertusis Tetanus (DPT)	Poliomyelitis Hib	
4 mo			DPT	Poliomyelitis Hib	
5 mo			DPT	Poliomyelitis Hib	
6 mo		VHepB			
12-15 mo					Measles, Mumps, Rubella, (MMR)
18 mo			DPT	Poliomyelitis Hib	
3 year				Poliomyelitis	
6 year			Diphtheria Tetanus	Poliomyelitis	MMR
7year	Tuber-culosis				
11 year			Diphthe-ria, Teta-nus		MMR (if it were missed at 6 year)
14 year	Tuber-culosis		Diphtheria Tetanus	Poliomyelitis	
15 year					Rubella (for girls), Mumps (for boys)
18 year			Diphtheria Tetanus		
Adults		VHepB	Diphtheria Tetanus		

Recomended literature

1. Nelson textbook of pediatrics.15th ed. / edited by Richard E. Behrman, Robert M. Kliegman, Ann M. Arvin.; senior editor, Waldo E. Nelson. – 1996.
2. Essential Pediatrics/O.P.Ghai. Firth Edition. -1999.- New Delhi.- 456p.
3. S.D.Nosov Infectious Diseases of Childhood.-English translation, Mir Publishers.-1984.-391p.
4. Учайкин В.Ф. Руководство по инфекционным болезням у детей.- М.:ГЭОТАР-МЕД, 2002.-824с.
5. Вазианова Ж.И. Инфекционные и паразитарные болезни: В 3 т.- Киев.:Здоровье.-2000.

Contents