B subunits enter the cell in an endocytotic vacuole. In the low pH of the vacuole, the toxin unfolds, exposing sites that facilitate translocation of the A subunit from the phagosome to the cytosol. The target is elongation factor 2 (EF-2), which transfers polypeptidyl-transfer RNA from acceptor to donor sites on the ribosome of the host cell. The specific action of the A subunit is to inactivate EF-2, by ADP-ribosylation (ADPR), which shuts off protein synthesis. The details of DT action are illustrated in Chapter 1 as a prototype toxin. *C. diphtheriae* itself is unaffected because it uses a protein other than EF-2 in protein synthesis. (DT, p. 16; ADPR, p. 363)

**DIPHTHERIA**

**CLINICAL CAPSULE**

Diphtheria is a disease caused by the local and systemic effects of diphtheria toxin, a potent inhibitor of protein synthesis. The local disease is a severe pharyngitis typically accompanied by a plaque-like pseudomembrane in the throat and trachea. The life-threatening aspects of diphtheria are due to the absorption of the toxin across the pharyngeal mucosa and its circulation in the bloodstream. Multiple organs are affected, but the most important is the heart, where the toxin produces an acute myocarditis.

**EPIDEMIOLOGY**

*C. diphtheriae* is transmitted by droplet spread, by direct contact with cutaneous infections, and, to a lesser extent, by fomites (Figure 26–1). Some subjects become convalescent pharyngeal or nasal carriers and continue to harbor the organism for weeks, months, or longer. Diphtheria is rare where immunization is widely used. In the United States, for example, fewer than 10 cases are now reported each year. These usually occur as small outbreaks in populations that have not received adequate immunization, such as migrant workers, transients, and those who refuse immunization on religious grounds. It has been more than 25 years since any outbreak exceeded 50 cases.

Diphtheria still occurs in developing countries and in places where public health infrastructure has been disrupted. For example, in the former Soviet Union, where the annual number of diphtheria cases had been below 200, over 47,000 cases and 1700 deaths occurred between 1990 and 1995. This outbreak followed the reintroduction of *C. diphtheriae* into a population where the public health systems had broken down as a result of the political situation. Reinstitution of effective immunization brought diphtheria rates back to base levels.

**PATHOGENESIS**

*C. diphtheriae* has little invasive capacity, and diphtheria is due to the local and systemic effects of DT, a protein exotoxin with potent cytotoxic features (Figure 26–2). It inhibits protein synthesis in cell-free extracts of virtually all eukaryotic cells, from protozoa and yeasts to higher plants and humans. Its toxicity for intact cells varies among mammals and organs, primarily as a result of differences in toxin binding and uptake. In humans, the B subunit binds to one of a common family of eukaryotic receptors that regulate cell growth and differentiation, thus exploiting a normal cell function.

The production of DT has both local and systemic effects. Locally, its action on epithelial cells leads to necrosis and inflammation, forming a pseudomembrane composed of a coagulum of fibrin, leukocytes, and cellular debris. The extent of the pseudomembrane varies from a local plaque to an extensive covering of much of the tracheobronchial tree.

A subunit enters the cytosol from a vacuole

EF-2 is inactivated by ADP-ribosylation

Transfer of tRNA and protein synthesis are stopped

Transmitted by respiratory droplets

Most cases are in unimmunized transients

Outbreaks occur when immunization rates decrease

A subunit inhibits protein synthesis

B-subunit binding determines cell susceptibility

Local effects produce pseudomembrane
Absorption and circulation of DT allow binding throughout the body. Myocardial cells are most affected; eventually, acute myocarditis develops.

**IMMUNITY**

Diphtheria toxin is antigenic, stimulating the production of protective antitoxin antibodies during natural infection. Formalin treatment of toxin produces toxoid, which retains the antigenicity but not the toxicity of native toxin and is used in immunization against the disease. It is clear that this process functionally inactivates fragment B. Whether it also inactivates fragment A or prevents its ability to dissociate from fragment B is not known. Molecular studies of the A-subunit structure and action suggest that another approach to immunization may be by genetic engineering of the A subunit so that it fails to bind EF-2 but retains its antigenicity.

**DIPHTHERIA: CLINICAL ASPECTS**

**MANIFESTATIONS**

After an incubation period of 2 to 4 days, diphtheria usually manifests as pharyngitis or tonsillitis. Typically, malaise, sore throat, and fever occur, and a patch of exudate or membrane develops on the tonsils, uvula, soft palate, or pharyngeal wall. The gray-white pseudomembrane (Figure 26–3) adheres to the mucous membrane and may extend from the oropharyngeal area down to the larynx and into the trachea. Associated cervical