Case 20

This 2-year-old male child experienced an upper respiratory infection 2 weeks prior to hospital admission. Four days prior to admission, anorexia and lethargy were noted. The patient was seen in the emergency room 3 days prior to admission. At that time he had a fever of 39.9°C. Physical examination revealed a clear chest, exudative pharyngitis, and bilaterally enlarged cervical lymph nodes. A throat culture was taken, and a course of penicillin was begun. The child's course worsened, and he became increasingly lethargic; he developed respiratory distress on the day of admission. It was noted that the throat culture from 3 days prior to admission had not grown any group A streptococci. On examination, the patient was febrile to 38.9°C and had an exudate in the posterior pharynx that was described as a yellowish, thick membrane which bled when scraped and removed. The patient's medical history revealed that he had received no immunizations. The patient was admitted to the hospital and treatment was begun. Figure 1 shows the organism recovered from the patient's throat culture on special isolation medium. Figure 2 shows a Gram stain of this organism.

1. What was the pathogen? Which medium is used to isolate this organism?

2. To cause disease, does this organism invade the bloodstream? If not, in what way does it cause disease? What special test is necessary to prove that this organism has the potential to cause disease?

3. How can this disease be prevented? What can happen if these prophylactic measures are not continued after childhood?

4. How is this infection treated?

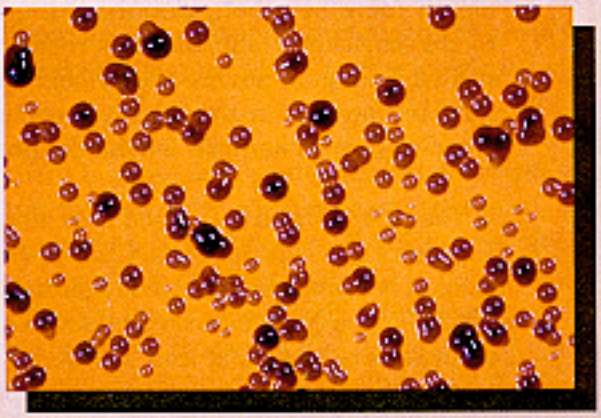

Figure 1

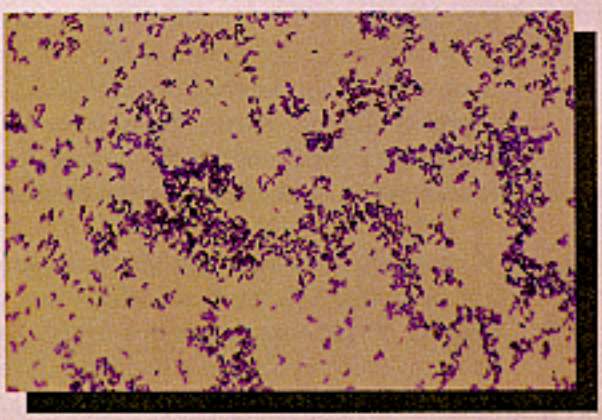

Figure 2

20 Case Discussion

1. The child appeared to have a strep throat that did not get better. On physical examination, the child had the classic pseudomembrane seen in cases of diphtheria. The etiologic agent of diphtheria is *Corynebacterium diphtheriae*, an aerobic, club-shaped, gram-positive rod. The pseudomembrane is composed of bacteria, fibrin, dead epithelial cells, and red and white blood cells. Aspiration of this pseudomembrane can cause death by suffocation.

It is important that the laboratory be notified when the diagnosis of diphtheria is being considered as isolation of *C. diphtheriae* is problematic. Throat cultures are not routinely examined for *C. diphtheriae* because the disease is very rare and because saprophytic *Corynebacterium* spp., also called diphtheroids, are found in abundance in most throat cultures. These diphtheroids, by both colony and Gram stain morphology, are essentially indistinguishable from *C. diphtheriae*. However, a selective medium, cystine tellurite agar, is useful in the isolation of *C. diphtheriae* (Fig. 1). On this medium, *C. diphtheriae* produces black colonies. It should be noted that other diphtheroids, i.e., short, club-shaped, gram-positive bacilli (Fig. 2), and *Staphylococcus aureus* may also turn this medium black. Black colonies should be Gram stained, and gram-positive rods should then be identified biochemically. The potassium tellurite salt in the selective medium also suppresses the growth of many organisms which normally inhabit the pharynx.

2. The pathogenesis of *C. diphtheriae* is one of the best understood among bacteria. The major virulence factor of *C. diphtheriae* is a protein exotoxin called diphtheria toxin. It has been shown to inhibit protein synthesis in a wide variety of mammalian cell types. The gene for toxin production is encoded on a lysogenic phage, and toxin synthesis is regulated, at least in vitro, by the concentration of iron in the environment of the organism. In patients with diphtheria, the organism remains in the pharynx but the toxin can enter the circulation and inhibit protein synthesis in a variety of tissues, with the heart, nerves, and kidneys being particularly targeted. Both myocarditis and neuropathy occur in patients with diphtheria.

Isolates of *C. diphtheriae* which are not lysogenized do not produce diphtheria toxin and are considered nonpathogenic. Since nontoxigenic strains can be isolated from healthy individuals, the isolation of *C. diphtheriae* from the throat does not prove that the patient has the disease. Rather, the pathogenic potential of any clinical isolate must be demonstrated by its ability to produce toxin.

3. Vaccination against diphtheria is mandatory in the United States, and children are not permitted to attend school without proof of vaccination. Because the pathogenicity of this organism is due to its exotoxin, a toxoid vaccine has proven to be protective for this disease. Children receive a series of four vaccinations, with the first three doses given at approximately 2, 4, and 6 months of age and a booster dose given 6 to 12 months later. Children receive another booster dose just before entering school. After that, the individuals should receive booster vaccinations at 10-year

intervals. Diphtheria vaccination is given in conjunction with vaccines for *Clostridium tetani* (tetanus) and *Bordetella pertussis* (pertussis) in a trivalent vaccine known as DTP. The 10-year booster doses are composed of only the diphtheria (D) and tetanus (T) components of this vaccine because of the high rate of adverse reactions to the pertussis (P) component.

The vaccination program for eradicating diphtheria in the United States has been highly effective. Usually fewer than 10 cases are reported per year. The cases that do occur are generally in adults, especially among the homeless, who do not receive routine medical care such as booster vaccinations. Cases are also seen in individuals who refuse vaccination for religious reasons.

An instructive example of what can happen when a population does not maintain protective immunity against diphtheria has occurred in the independent states of the former Soviet Union. In the Russian Federation, the number of reported cases of diphtheria increased from 603 in 1989 (0.4 per 100,000 population) to 39,703 in 1994 (26.6 per 100,000 population). Similar dramatic increases have been observed in the other independent states. Persons aged 15 years of age or older constitute 70% of the cases, which emphasizes the need for continuing the practice of vaccinating adults in order to minimize the number of susceptible individuals in the population.

4. The strategy for treating diphtheria is to use both antibiotics and diphtheria antitoxin. Antitoxin is given to attempt to neutralize circulating diphtheria toxin, since it is responsible for the symptoms caused by this organism. Antibiotics are given to eradicate the organism so that no more toxin can be produced.

The diphtheria antitoxin is prepared in horses, and therefore the development of serum sickness is a distinct possibility. Serum sickness is due to the patient making an antibody response to equine proteins, resulting in the formation of immune complexes. Clinical manifestations of serum sickness include fever, lymphadenopathy, rash, and joint pain. This child was unvaccinated. Because mortality rates of approximately 20% have been reported in unvaccinated individuals, the risk of serum sickness was far outweighed in this case by the potential benefit of giving this antitoxin. Despite appropriate therapy, however, this child died of diphtheria.

References

1. **Centers for Disease Control and Prevention.** Diphtheria epidemic—new independent states of the former Soviet Union, 1990–1994. *Morbid. Mortal. Weekly Rep.* **44:**177–181.
2. **Chen, R. T., C. V. Broome, R. A. Weinstein, R. Weaver, and T. F. Tsai.** 1985. Diphtheria in the United States, 1971–1981. *Am. J. Public Health* **75:**1393–1397.
3. **Pappenheimer, A. M.** 1982. Diphtheria: studies on the biology of an infectious disease. *Harvey Lect.* **76:**45–73.