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ANTIBIOTIC PROPHYLAXIS OF CONTACTS OF DIPHTHERIA CASES

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REDUCING COMMUNICABLE DISEASE

By the year 2000, there should be no indigenous cases of poliomyelitis, diphtheria, neonatal tetanus, measles, mumps and congenital rubella in the Region and there should be a sustained and continuing reduction in the incidence and adverse consequences of other communicable diseases, notably HIV infection.

ABSTRACT

The WHO/UNICEF Strategy for diphtheria control includes three main recommendations:

- mass immunization;
- early diagnosis and proper treatment of cases;
- management of close contacts by the use of antibiotics.

Whereas the first two recommendations have been implemented in all NIS having epidemic diphtheria, in some countries there is a controversial discussion regarding the use of antibiotics for close contacts. Therefore WHO, with assistance of CDC and USAID/BASICS has drafted guidelines regarding the antibiotic prophylaxis of contacts of diphtheria cases based on international experience. The guidelines include reprints of publications demonstrating the success of this strategy.

Keywords

DIPHTHERIA – prevention & control
ANTIBIOTIC PROPHYLAXIS
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World Health Organization Regional Office for Europe (WHO/EURO)
Centers for Disease Control and Prevention (CDC)
Basic Support for Institutionalizing Child Survival (BASICS)

ANTIBIOTIC PROPHYLAXIS OF CONTACTS OF DIPHTHERIA CASES

The WHO/UNICEF Strategy for Diphtheria Control in the New Independent States recommends antibiotic prophylaxis for close contacts of diphtheria cases (see Annex 1). The principle reason for this recommendation is to prevent the development of secondary cases among contacts. In addition, by eliminating carriage of the organism from close contacts, further spread within the community will be prevented. This latter benefit is likely to have most impact in the overall control of diphtheria when there are relatively few cases, i.e. either early in an epidemic or in the latter stages of achieving control through immunization campaigns. However it likely also has benefit during the height of an epidemic. Several published reports have documented the important role that persons asymptomatically infected with *C. diphtheriae* (carriers) have in spreading diphtheria.[1-3] Persons who are fully immunized may carry the organism, transmitting the infection to susceptible persons. Thus antitibiotic treatment of carriers is an important aspect of diphtheria control.

By contrast with the WHO/UNICEF recommendation of treating all close contacts regardless of culture status, in many of the New Independent States, the current practice is to first culture all close contacts, and after receipt of the culture results, treat with antibiotics only those who are culture positive for toxigenic *C. diphtheriae*.

The following questions will be addressed by this document. (1) Is antibiotic prophylaxis effective in eliminating *C. diphtheriae* from infected carriers? (2) Is antibiotic prophylaxis of all close contacts more effective in preventing secondary cases among close contacts and in reducing spread of diphtheria in the community than the alternate strategy of waiting for culture results and treating only persons identified as culture positive for toxigenic *C. diphtheriae*? (3) Will wider use of antibiotic prophylaxis as advocated by the WHO/UNICEF strategy induce antibiotic resistance in *C. diphtheriae*, or (4) cause an unacceptable number of side effects among recipients? These questions will be addressed in turn, and selected English language medical articles have been attached (Annex 2).

This document has been prepared jointly by the World Health Organization Regional Office for Europe, the U.S. Centers for Disease Control and Prevention (CDC), and BASICS,[a] in order to address some concerns that have been raised by public health policy makers, epidemiologists, and clinicians in the New Independent States about the recommendations for antibiotic prophylaxis of contacts of cases included in the WHO/UNICEF strategy.

1. Is antibiotic prophylaxis effective in eliminating *C. diphtheriae* from infected carriers?

From the medical literature it is clear that both penicillin and erythromycin are highly effective, although not 100% effective, in eliminating *C. diphtheriae* from the nose and throat of respiratory carriers. Zalma and colleagues[3] during an epidemic in Austin, Texas from 1967 to 1969, treated 142 carriers with a seven to ten day course of intramuscular procaine penicillin, administering a dose of 600,000 to 2,000,000 units per day depending on the age of the treated person. One hundred twenty eight (90.1%) became culture negative. Those who remained culture positive after penicillin were treated with erythromycin for 7 days, with successful eradication of the organism in all cases. In an outbreak in San Antonio, Texas, in 1970,[4] households were randomly assigned to be treated with either (i) benzathine penicillin (a single intramuscular dose of 600,000 units for age 1-5 years and 1,200,000 units for age 5 years), (ii) erythromycin estolate by mouth for 7 days, or (iii) clindamycin by mouth for 7 days. The carrier state was terminated in 125 (89%) of 149 carriers treated with penicillin, 82 (92%) of 89 treated with erythromycin, and 52 (93%) of 56 treated with clindamycin. Although there is a trend towards apparent greater efficacy of erythromycin compared to penicillin, this difference fails to meet statistical significance.[b] Almost all patients were culture negative within 4 days of beginning antibiotics.

The findings of these two reports may be compared to studies conducted during the pre-antibiotic era which analyzed the rate of disappearance of *C. diphtheriae* from the nose and

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[b]In the article,it is stated that the difference is significantly different ($p<0.05$) by chi square. However the on recalculating chi square, the correct p value is 0.07, and for chi square with Yates continuity correction, $p= 0.1$.

throat of cases and carriers. Hartley and Martin[5] found that among 457 cases, approximately 50% still carried the organism at 15 days after illness onset. Weaver[6] studied the rate of disappearance of *C. diphtheriae* among 500 cases, and found that after the first week, approximately half of the cases that began the week culture positive became negative during the following 7 days. By three weeks after onset, 29% remained culture positive. The latter author also studied the rate of disappearance of *C. diphtheriae* in 52 carriers: by 2 weeks after identification of the carrier, 44% remained culture positive. Thus antibiotic treatment significantly shortens the duration of carriage.

In addition to households, erythromycin has also been used in the setting of institutional outbreaks to successfully eradicate toxigenic *C. diphtheriae*.[7]

2. Is antibiotic prophylaxis effective in preventing secondary cases among close contacts and in reducing spread of diphtheria in the community?

It has never been demonstrated by scientific studies that prophylaxis of all close contacts of cases more effectively prevents either secondary cases among close contacts or further spread of diphtheria in the community, than the alternative strategy of first culturing close contacts and treating only individuals who are found to be culture positive for toxigenic *C. diphtheriae*. Such trials would be difficult to design and conduct in a manner that would produce a scientifically valid result, and might be considered unethical in Western Europe and North America because of the concern about untreated contacts developing diphtheria.

However, even without such a study, several facts taken together argue in favor of the policy of treating all household contacts. Based on studies in the era before widespread vaccination, it is known that the risk of developing clinical diphtheria in the 30 days after onset of illness in the case is at least 10 times higher among household contacts of cases than it is among the general public.[1] Because the incubation period of diphtheria is usually 2 to 5 days, the highest risk of secondary cases is in the few days after the index case is identified. Rates of carriage of toxigenic *C. diphtheriae* of up to 25% among household contacts of cases are reported.[8] It usually takes a minimum of 48 hours, and often 3 to 5 days, for the laboratory to positively identify toxigenic *C. diphtheriae* from a throat culture. The sensitivity of culture for detection

of carriers is probably not 100%, and the sensitivity of toxigenicity testing to distinguish toxigenic from nontoxigenic strains is also not 100%. Thus cases may develop while waiting for the culture result, or an undetected carrier may spread toxigenic organisms in the community. All these facts argue in favor of the WHO/UNICEF recommended policy of treating all household contacts of cases.

In the San Antonio outbreak described above, antibiotics were given to all household members immediately after culture, without waiting for culture results. This is also the current recommendation for diphtheria control in the United States.[8]

3. Will antibiotic prophylaxis induce antibiotic resistance to *C. diphtheriae*?

The WHO/UNICEF strategy recommends a single injection of benzathine penicillin as the treatment of choice for carriers, for reasons of ensuring compliance. Penicillin resistance to *C. diphtheriae* has never been reported in the literature, despite treatment of tens, if not hundreds, of thousands of cases and the widespread community use of penicillins since the 1940s.[9-14] Studies that have examined strains that were not cleared from the throat by a course of penicillin have universally found such strains to remain sensitive to penicillin.[4] Thus while it is possible that penicillin resistance to *C. diphtheriae* could occur, this is quite unlikely. There is one report of erythromycin resistance among respiratory carriers that were not rendered culture negative for *C. diphtheriae* by a course of erythromcyin,[15] but in all other published reports of treatment of respiratory diphtheria cases and carriers, failure to eradicate the organism has not been associated with erythromcyin resistance. Plasmid-mediated erythromycin resistance to *C. diphtheriae* has been reported uncommonly from cutaneous diphtheria isolates.[16-18]

It should also be appreciated that there are many persons who are unrecognized carriers of *C. diphtheriae* and who receive antibiotics for various indications, without cultures for diphtheria being performed. Thus the organism is exposed to antibiotics regularly in the community, yet despite this has remained highly susceptible to the common antibiotics used to treat diphtheria.

4. Will antibiotic prophylaxis cause serious side effects among recipients?

Penicillin is a safe, narrow spectrum antibiotic, commonly used for chronic prophylaxis (for example in patients with rheumatic heart disease and sickle cell disease). Penicillin does not cause major disturbances to the bacterial flora of the gastrointestinal tract as may be seen with broad spectrum antibiotics. Significant side effects are extremely rare, and the risk to untreated close contacts of cases of developing diphtheria, and suffering complications or death as a result, are significantly higher than the risk of suffering serious side effects from antibiotic prophylaxis. Erythromycin frequently causes abdominal discomfort, but serious side effects are also rare.

In summary, the WHO/UNICEF recommendation for antibiotic treatment of all close contacts of diphtheria cases is likely to result in more effective prevention of secondary cases, and more effective prevention of further spread of *C. diphtheriae* in the community, than the existing practice of treating only those contacts identified as carriers of toxigenic strains. The negative impact of such increased antibiotic use is likely to be minimal.

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IAIN R.B. HARDY

Diphtheria Immunization

Effect Upon Carriers and the Control of Outbreaks

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A diphtheria epidemic in a small central Texas community centered in the elementary school. Epidemiological investigation at the school included throat cultures and immunization histories of 306 of the 310 students and staff. Of these, 104 (34%) had culture-proven diphtheria infections; 15 were symptomatic cases and 89 were carriers. There was no statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunizations. However, the risk of symptomatic diphtheria was 30 times as for those with none, and 11.5 times as great for those with inadequate immunizations as for those fully immunized. Diphtheria toxoid helps prevent symptomatic disease but does not prevent the carrier state nor stop the spread of infection. Identifying, isolating, and treating carriers are very important aspects in the control of diphtheria outbreaks.

With the increase in the number of cases of diphtheria in the United States during the past few years, the effect of immunization on the control of outbreaks has become an important question. In the Austin, Tex, diphtheria epidemic of 1967-1969[1] cases continued to occur despite the administration of 155,200 doses of diphtheria toxoid and the concomitant rise in immunization levels of school age children from 68% to 89%. Data from the Austin outbreak suggested that a large reservoir of carriers was important in the continued transmission of *Corynebacterium diphtheriae*. Other diphtheria outbreaks have shown that epidemics occur in populations with high immunization levels.[2-4] A diphtheria outbreak in an elementary school in Elgin, Tex, in the spring of 1970 provided an opportunity to study the effects of immunization on carriers and on the control of an epidemic situation.

Table 1.—Definitions of Immunization Status*

Status	Definition
Full	Primary series (three or more injections), or a primary series plus a booster, completed within ten years.
Lapsed	Primary series, or a primary series plus booster, completed more than ten years ago.
Inadequate	Uncompleted primary series (less than three injections) at any time.
None	No diphtheria toxoid ever received.

* Adapted from the Center for Disease Control.[5]

Materials and Methods

When it became obvious in the Elgin diphtheria epidemic (Older JJ et al, unpublished data) that cases were clustered in the elementary school, a special throat culture and immunization survey was begun there. Throat cultures were obtained from and immunization status was determined for 306 of 310 students and staff. Throat swabs were taken on three separate occasions from each person: April 7, April 17, and May 4. These were streaked on Loeffler blood serum or Pai medium and incubated overnight. Cystine tellurite blood agar and Tinsdale medium were used for isolation. Elek-King agar diffusion plates were used for toxigenicity determination.

Immunization status information was

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From the Epidemiology Program Center for Disease Control, Atlanta (Drs. Miller, Older, Drake, and Zimmerman); the Communicable Disease Services, Texas State Department of Health, Austin (Drs. Miller, Older, Drake, and Zimmerman); and the Department of Preventive Medicine, University of Maryland School of Medicine, Baltimore (Dr. Miller).

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obtained by personal interview and review of available school and medical records. The status of each person classified as "adequate," "lapsed," "inadequate," and "none," according to the definitions of the Center for Disease Control[3] (Table 1).

Any person with a sore throat or other symptoms compatible with diphtheria and a positive culture for *C diphtheriae* organisms was classified as a "case." A person without symptoms but who had a positive throat culture for *C diphtheriae* organisms was classified as a "carrier." The term "infection" applied to anyone with a positive culture regardless of his clinical state and, therefore, included both cases and carriers.

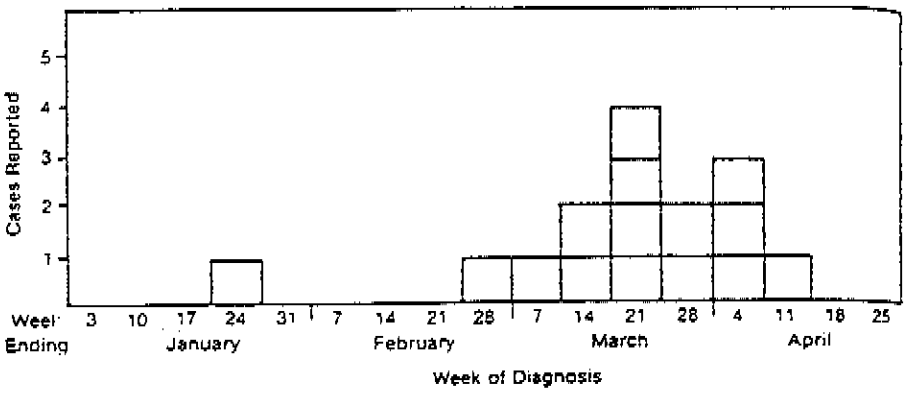
Results

When diphtheria was first diagnosed in the elementary school, 67% of the children and staff were already fully immunized, and 97% had had at least one dose of diphtheria toxoid. The first case in the elementary school population was diagnosed in late February 1970, and by April 8, 15 cases had occurred (Figure).

Throat cultures were done on 306 children and staff; toxigenic *C diphtheriae*, gravis type, was isolated from 104 (34%). Fifteen of these (14%) were cases, and 89 (86%) were carriers. There was *no* statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunization (Table 2). However, the risk of becoming a case was 30 times as great for those with no immunization and 11.5 times as great for those with inadequate immunizations as for those with full diphtheria immunization (Table 3). Among the 104 infected with *C diphtheriae*, the risk of being symptomatic was 13.3 times as great for those inadequately immunized and 37.0 times as great for those with no previous immunizations as for those who were fully immunized (Table 4).

Comment

The importance of carriers in the spread of diphtheria was well documented by Doull and Lara[4] in the



Diphtheria cases in Elgin, Tex, elementary school, spring 1970.

Table 2.—Immunization and Culture Status of Students and Staff, Elgin, Tex, Elementary School, Spring 1970

Immunization Status	Culture Status: Positive	Culture Status: Negative	Total	Diphtheria Infection Attack Rate (per 100)
Full	73	132	205	35.6
Lapsed	0	4	4	0
Inadequate	28	59	87	32.4
None	3	7	10	30.0
Total	104	202	306	34.0

Table 3.—Immunization Status of Diphtheria Cases, Elgin, Tex, Elementary School, Spring 1970

Immunization Status	Cases	No. at Risk	Diphtheria Case Attack Rate (per 100)
Full	2	205	1.0
Lapsed	0	4	0
Inadequate	10	87	11.5
None	3	10	30.0
Total	15	306	4.9

Table 4.—Risk of Symptoms and Immunization Status of Students and Staff With Positive Diphtheria Cultures, Elgin, Tex, Elementary School, Spring 1970

Immunization	Symptomatic Cases	Asymptomatic Carriers	Total Infected	Symptom Attack Rate (per 100 Positive Cultures)	Relative Risk
Full	2	71	73	2.7	. . .
Inadequate	10	18	28	35.8	13.3
None	3	0	3	100.0	37.0
Total	15	89	104	14.4	. . .

early 1920s. In very thorough investigations, only about 20% of diagnosed diphtheria cases could be traced to another suspected case, and the remaining 80% of the cases were attributed to asymptomatic carriers in the population. Recent epidemics in Austin and Elgin,[2] Tex, provided ample evidence that carriers continue to play a very important role in the transmission of diphtheria.

When diphtheria toxoid became available, it was generally believed that it induced immunity that protected individuals from symptomatic illness but not from asymptomatic infection. This was based on the observation that immunity is related to the neutralization of toxin elaborated by *C diphtheriae* and not interference with diphtheria infection.

In 1936, Frost et al[7] alluded to a paucity of observations on record concerning antitoxic immunity and the carrier state. Nonetheless, he stated that the limited data suggested that there is little, if any, difference between those individuals with and those without antitoxic immunity in their risk of becoming infected.

More recently, Tasman and Lansberg[8] put forth the hypothesis that toxoid use reduces the number of carriers. This is based on surveys that showed a steady decline in the prevalence of carriers. Since toxoid immunization does prevent cases and since cases are more contagious than carriers,[4] the decline in carriers could be due to the decrease in contagious cases rather than to the direct effects of immunization.

The findings in Elgin corroborate the assumptions of Frost et al[7] and show that there is no difference in the risk of diphtheria acquisition among those with full, lapsed, inadequate, and no immunizations. However, they also demonstrate the value of immunization in reducing the risk of disease and show that the protection against symptomatic illness afforded those infected with *C diphtheriae* is directly related to their immunization status.

Some authors[4] have estimated that if 70% or 80% of the population were adequately immunized against diphtheria, spread of diphtheria would be prevented. However, diphtheria outbreaks have been described in populations with as much as 94% of the people being previously immunized.[2,3] These outbreaks, the known importance of carriers in the spread of diphtheria, and the demonstrated failure of toxoid to prevent the carrier state lead us to conclude that the concept of herd immunity is not applicable in the prevention of diphtheria. A high level of community immunization will not stop the transmission of diphtheria, but it will limit the number of contagious cases. At the first appearance of a diphtheria case, control activities should be directed toward identifying, isolating, and treating carriers, as well as toward immunizing persons with less than full immunization status. This dual approach will reduce or eliminate the spread of infection by reducing the number of carriers, and it will reduce the number of cases by improving the immunization status of exposed individuals.

Roy Morris, MD, Elgin city health officer, treated the majority of cases and arranged for treatment of carriers; Milton Saxon, Elgin school superintendent, and Eva C. Danklefs, Elgin school nurse helped arrange culture surveys; M.S. Dickerson, MD, coordinated federal, state, and local assistance and support; Will Callihan assisted in culture surveys, interviews, and immunization of patients; Jesse V. Irons, ScD, and Carl D. Heather, DVM, coordinated state laboratory assistance; H.D. Bredthauer and Lucie M. Hickman, Texas State Department of Health, processed bacteriological specimens and Wallis Jones, PhD, Susan Bickham, Geraldine Wiggins, and Jane McLaughlin, Laboratory Division, Center for Disease Control, Atlanta, processed specimens and performed all typing of *C diphtheriae* organisms. All isolates from the initial throat cultures were typed by the Bacteria Immunology Unit, Center for Disease Control.

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AIN R.B. HARDY

Treatment of Diphtheria Carriers: Benzathine Penicillin, Erythromycin, and Clindamycin

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Asymptomatic carriers of toxinogenic *Corynebacterium diphtheriae* were treated by either a single injection of benzathine penicillin or a 7-day oral course of erythromycin or clindamycin. Nasopharyngeal cultures were obtained from all carriers before treatment and after therapy was started. The carrier state was terminated in 84% of those receiving benzathine penicillin, 92% of those receiving erythromycin, and 93% of those receiving clindamycin. These results differ from our previously reported 1-year study. Benzathine penicillin could be used, however, to treat diphtheria carriers when patients cannot be relied upon to complete a 7-day course of oral therapy. Clindamycin is an alternate antibiotic that will terminate the diphtheria carrier state. There was no change in the sensitivity of *C. diphtheriae* to penicillin or erythromycin in those whose carrier state persisted.

MODERN METHODS to control diphtheria depend on maintaining artifically induced antitoxic immunity, early detection, isolation of either symptomatic or asymptomatic patients harboring *Corynebacterium diphtheriae* in the nasopharynx or on the skin, and termination of the carrier state by antibiotic therapy (1, 2). Eradication of *C. diphtheriae* from the nasopharynx may be difficult to accomplish (2, 3). Antibiotic regimens currently recommended use aqueous procaine penicillin, oral penicillin, or oral erythromycin for from 4 days to 1 week (3, 4) and are similar to those recommended for the treatment of active disease. Carrier treatment has been an integral part of the control of recent epidemics of diphtheria in the United States (5-7). A carrier treatment program requiring multiple injections or using the oral route for 7 days is vulnerable to failure through lack of cooperation by the patient. A regimen that would successfully eliminate the diphtheria carrier state with a single injection requiring only a single contact with the health care worker would promote control of diphtheria epidemics.

From 1970 to 1972 we maintained a carrier treatment program in San Antonio, comparing the effectiveness of benzathine penicillin and erythromycin in eradicating *C. diphtheriae* from the nasopharynx. From 1972 to 1973 clindamycin was also used in the carrier treatment program to evaluate clindamycin as an alternative antibiotic for diphtheria carriers who may be allergic to penicillin or who might not tolerate erythromycin.

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Patients, Materials, and Methods

CARRIERS

When a diagnosis of diphtheria was made clinically or confirmed bacteriologically, nasopharyngeal cultures from all members of the patient's household plus the patient's consorts outside the home were obtained by a nurse or physician in a standardized fashion previously described (5). By assignment from a random number list, each patient's *family unit* was treated by one of three methods: [1] intramuscular injection of 600 000 units (ages 1 to 5 years) or 1 200 000 units (older than 5 years) of benzathine penicillin; [2] erythromycin estolate by mouth for 7 days in a dosage regulated by weight, 0.4 to 22 kg [1 to 50 lbs], 250 mg twice a day; 22 to 45 kg [50 to 100 lbs], 250 mg three times a day; or more than 45 kg [100 lbs], 250 mg four times a day; or [3] clindamycin, 150 mg by mouth four times a day for 7 days.

Nasopharyngeal cultures were obtained on the eighth and ninth day. Members of the family unit, excluding the breadwinner, were confined to the home until it was known that all eighth and ninth day cultures were free of diphtheria bacilli. Whenever possible nasopharyngeal cultures were obtained 30 days after the injection of benzathine penicillin and 14 days after termination of clindamycin treatment. No carriers received diphtheria antitoxin.

BACTERIOLOGIC METHODS

Nasal and pharyngeal swabs were processed for isolation of *C. diphtheriae* by standard methods described previously (5). Colonies with suspicious morphology were confirmed as *C. diphtheriae* biochemically (8). Toxinogenicity was confirmed by the modified in-vitro Elek plate method (9, 10). Bacteria identified as toxinogenic *C. diphtheriae* were confirmed by the Laboratory Division, Center for Disease Control (Dr. Wallis Jones).

ANTIBIOTIC SENSITIVITY TESTING

The minimum inhibitory concentration and minimum bactericidal antibiotic concentration (MBC) were determined by testing 10^5 cells of *C. diphtheriae* in trypticase soy broth containing 10% fetal bovine serum against serial twofold dilutions of cephalexin, clindamycin, erythromycin, oxacillin, penicillin, and rifampin. Incubation was for 24 hours at 37 °C. Ampicillin, colistin, lincomycin, and tetracycline were also tested using the disc agar diffusion method modified by the addition of sheep erythrocytes (7.5%) to Mueller-Hinton agar to insure adequate growth of diphtheria bacilli (11).

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Results

The relation of the minimum bactericidal concentration of six antibiotics to the cumulative percent of *Corynebacterium diphtheriae* strains killed by that antibiotic is presented in Figure 1. These in-vitro data show that all three antibiotics used in this study would be expected to terminate the diphtheria carrier state since penicillin, erythromycin, and clindamycin (among others) are bactericidal for *C. diphtheriae* at concentrations attainable by recommended doses of each antibiotic. When tested by the disc method also, penicillin, erythromycin, and clindamycin (as well as tetracycline) inhibit most strains of *C. diphtheriae* isolated during the San Antonio epidemic.

The population treated using any of the three regimens was homogenous, being composed mostly of Latin-American children less than 15 years of age residing in the southwestern part of San Antonio.

The data in Table 1 are derived from the treatment of diphtheria carriers—all confirmed bacteriologically as harboring diphtheria bacilli in the nasopharynx before receiving antibiotic treatment as prescribed in one of the three treatment plans. A success was only recorded as such when both nasopharyngeal cultures obtained on the eighth and ninth day after therapy was started were bacteriologically negative for *C. diphtheriae*. Any other result was recorded as a failure. Benzathine penicillin treatment produced fewer successes than erythromycin treatment (chi-square = 4.1; $P < 0.05$). No treatment program eradicated diphtheria bacilli from the nasopharynx of all carriers. All cultures (28 of 28) obtained 30 days after the injection of benzathine penicillin were free of *C. diph-*

Table 1. Antibiotic Treatment of Diphtheria Carriers—3-Year Study

Treatment Method	Failures*	Successes	Total
	no. (%)	*no.* (%)	*no.*
Benzathine penicillin	24 (16)†	125 (84)	149
Oral erythromycin	7 (8)†	82 (92)	89
Oral clindamycin	4 (7)	52 (93)	56
Totals	35 (12)	259 (88)	294

* Defined as recovery of diphtheria bacilli on the eighth or ninth day after treatment.
† Chi-square = 4.1; $P < 0.05$.

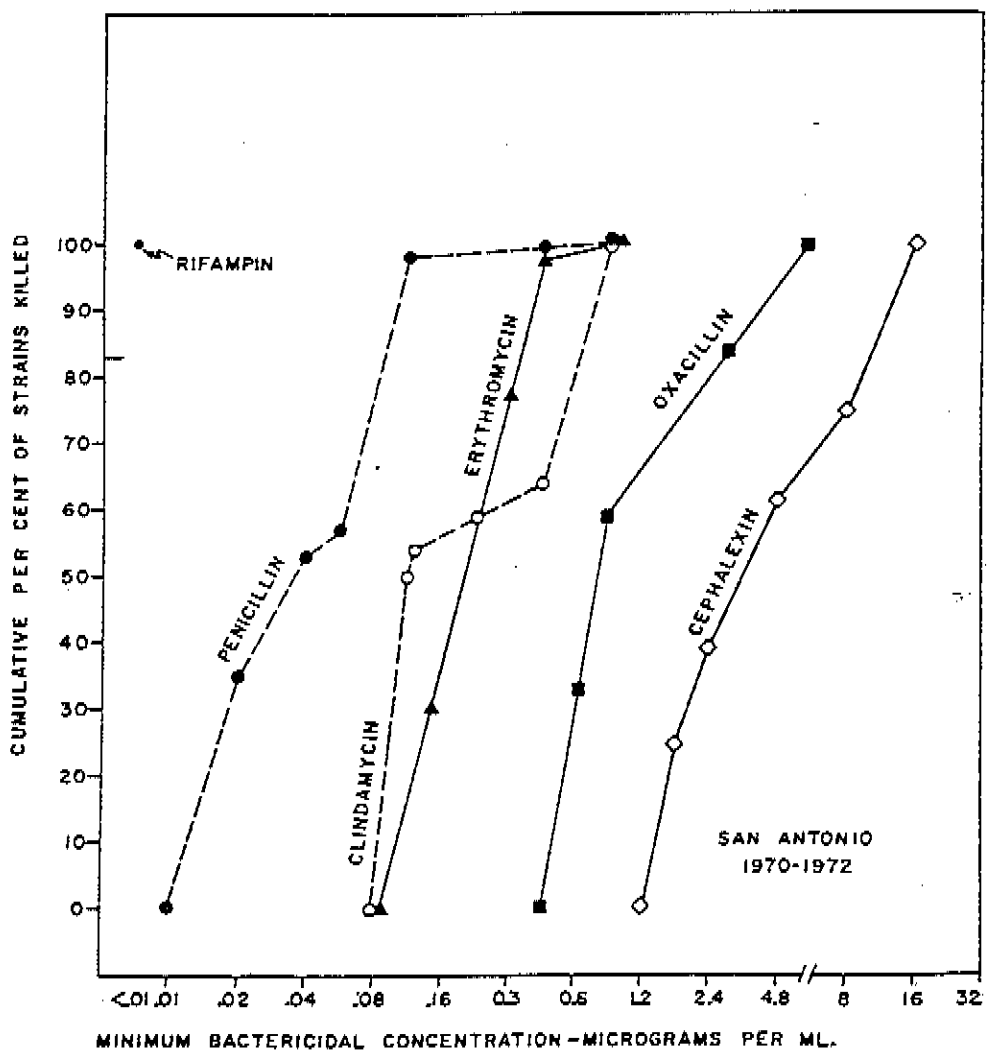

Figure 1. Antibiotic sensitivity of strains of *Corynebacterium diphtheriae* isolated during the San Antonio epidemic.

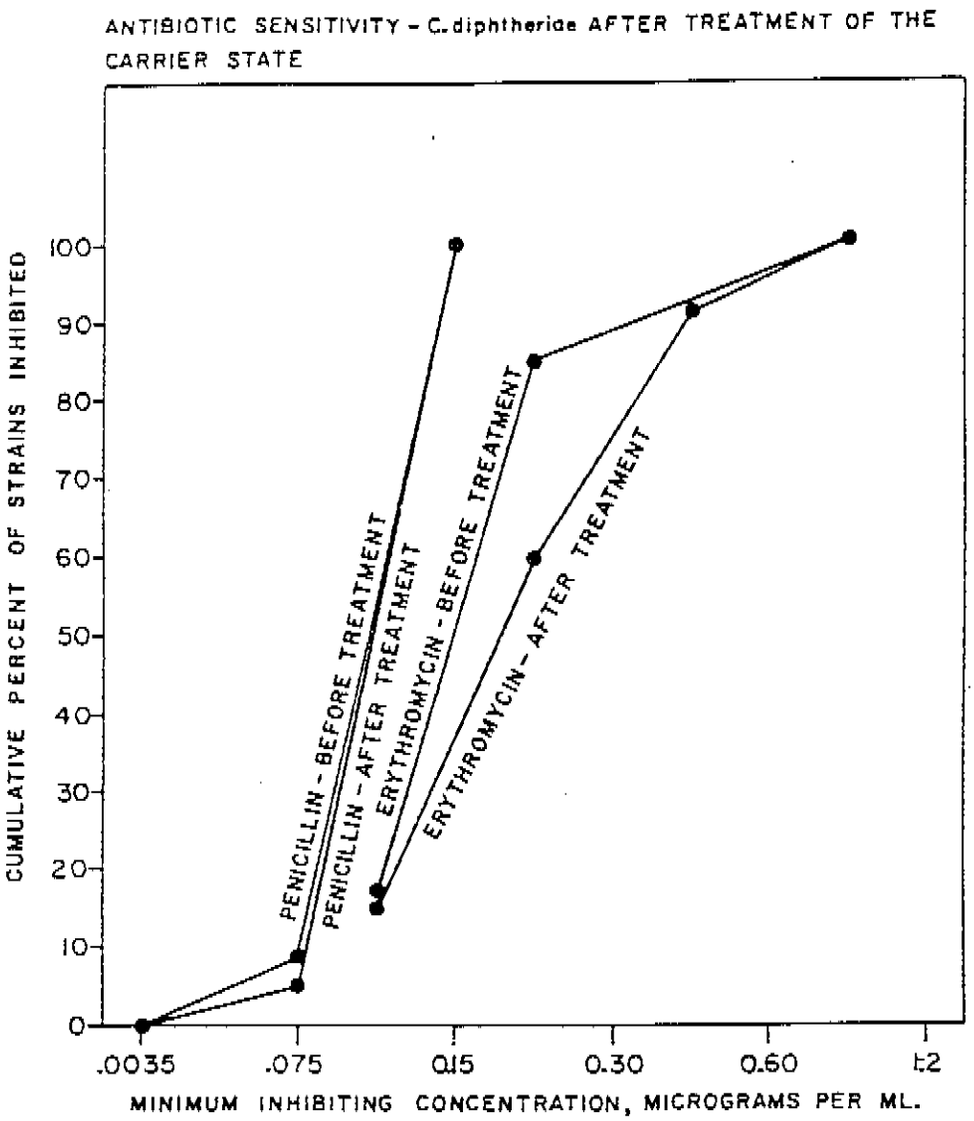

Figure 2. Antibiotic sensitivity pattern of 30 strains of *Corynebacterium diphtheriae* isolated from nasopharynx of carriers before and after treatment with either erythromycin or penicillin. No significant differences were found in minimum inhibitory concentrations before or after treatment ($P > 0.1$).

theriae. Three of the four failures after clindamycin therapy were caused by inadequate therapy because the patients failed to take the prescribed amount of clindamycin. Two weeks after the termination of clindamycin treatment, the nasopharyngeal cultures from 25 of 26 carriers were free of *C. diphtheriae*. No enterocolitis was observed among those receiving clindamycin.

Those patients whose diphtheria carrier state persisted after treatment raised the possibility that failure was caused by the emergence of strains of diphtheria bacilli resistant to the antibiotic used. The data in Figure 2 show that there was no significant shift in the antibiotic sensitivity of *C. diphtheriae* isolated from the nasopharynx before and after treatment with penicillin or erythromycin.

Nine patients hospitalized with diphtheria were treated with clindamycin (150 mg by mouth four times daily) in addition to diphtheria antitoxin and supportive care as outlined previously (5). The bacteriologic and clinical result was indistinguishable from those treated with either penicillin or erythromycin.

Discussion

Antibiotics are used in the treatment of diphtheria to eliminate *C. diphtheriae* from the nasopharynx or skin of patients with clinical disease and to terminate the asymptomatic carrier state. The early use of diphtheria antitoxin is still the only specific method of treatment (1, 2). Treatment of the diphtheria carrier state is properly applied to those asymptomatic patients who harbor toxinogenic diphtheria bacilli in the the upper respiratory tract or skin. All treatment programs are associated with some failures to terminate the carrier state (3, 12-14). Treatment of the carrier state with antibiotics is superior to no treatment at all, because the carrier state terminated spontaneously in only 12% of patients followed for 1 month (15). Persisting strains of *C. diphtheriae* did not become resistant to the antibiotics used, as similarly observed by other investigators (11). Repository benzathine penicillin can be used as an alternate method of antibiotic therapy for the diphtheria carrier state. The use

of benzathine penicillin may prove particularly helpful in situations where the physician is unsure of patient cooperation. In a previous report (5) benzathine penicillin seemed to be equally effective when compared to erythromycin in terminating the carrier state. The results of this 3-year study, however, show that benzathine penicillin is not as effective as erythromycin. Erythromycin, then, is recommended as the preferred antibiotic in the treatment of the diphtheria carrier state. Clindamycin is a bactericidal antibiotic for diphtheria bacilli at concentrations that can be attained by recommended dose schedules. Because enterocolitis may occur after the use of clindamycin, erythromycin is recommended as the drug of choice for treatment of the diphtheria carrier state.

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Fatal Respiratory Disease Due to *Corynebacterium diphtheriae*: Case Report and Review of Guidelines for Management, Investigation, and Control

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Dramatic reductions in the incidence of diphtheria and high levels of childhood vaccination in recent decades have led the United States to establish the goal of diphtheria elimination among persons ≤25 years of age by the year 2000. In 1990, an unimmunized 25-month-old child died of respiratory diphtheria in Dade County, Florida, before treatment with diphtheria antitoxin could be instituted. Twenty-three asymptomatic household contacts and other close contacts of the child were identified, cultured for *Corynebacterium diphtheriae*, given antimicrobial prophylaxis, and vaccinated with diphtheria toxoid when indicated. Three contacts (13%) had pharyngeal cultures positive for toxigenic *C. diphtheriae* of the same type as that causing infection in the deceased child, but no additional cases developed. Although the source of infection was not determined, three other close contacts had recently been to Haiti, where diphtheria is endemic. A serological survey of 396 children <5 years of age who received care at a medical center in Dade County revealed that 22% lacked protective immunity to diphtheria. Attainment of the goal of diphtheria elimination among persons ≤25 years of age—and ultimately among all persons—will depend on the maintenance of a high level of clinical awareness of the disease, the prompt institution of preventive measures among close contacts of patients with sporadic cases, and improved vaccination levels among infants, children, and adults.

In the 1920s, an average of more than 125,000 cases and 10,000 deaths due to diphtheria were reported annually in the United States. After the widespread use of diphtheria toxoid in the 1940s, the incidence of diphtheria declined steadily, with dramatic reductions in the middle to late 1970s. In the 1980s, 27 sporadic cases of respiratory diphtheria were reported to the Centers for Disease Control (CDC) (range, zero to five cases per year), including eight cases (30%) in persons <25 years of age and three fatal cases (11%). The sustained low incidence of diphtheria and the high levels of childhood vaccination in recent decades have led the United States to establish the goal of diphtheria elimination among persons ≤25 years of age by the year 2000 [1].

In spite of the extremely low risk of indigenously acquired diphtheria in the United States and other industrialized countries, importation of the organism from developing countries where diphtheria remains endemic poses a constant threat, particularly among subgroups of individuals with low vaccination levels [2–8]. Although appropriate management of diphtheria requires prompt recognition, treatment, and control measures to prevent secondary cases, few health-care providers in the United States are familiar with the disease. We report the first case of respiratory diphtheria in Dade County, Florida, since 1969 [9]; describe the ensuing epidemiological investigation; and review guidelines for case management, contact tracing, and preventive measures.

Methods

Case Investigation and Contact Tracing

After notification by hospital staff, the Dade County Public Health Unit initiated an investigation of a presumed case of diphtheria in which the patient, a 25-month-old boy, died. Clinical information was obtained by a retrospective review of medical records and by interviews with the child's family. Attempts were made to identify all close contacts who were exposed to the case-patient during his illness or within the previous week, when secondary transmission could have occurred. In addition, to determine the source of infection, attempts were made to identify any close contacts who had traveled to a diphtheria-endemic area within several months before the case-patient's illness. Close contacts were defined as household members and other persons who had intimate contact with the child (e.g., relatives and friends) as well as hospital staff directly exposed to his respiratory secretions. Hospital contacts were enumerated by infection control

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staff. Information on other close contacts was obtained through family interviews. After initial visits to the homes of close contacts to screen for signs and symptoms of diphtheria and to implement preventive measures, identified close contacts were monitored for at least 1 week by home visits, telephone contacts, and clinic visits. . .

Laboratory Procedures

During the first 2 weeks of the investigation, pharyngeal swabs obtained for culture of *Corynebacterium diphtheriae* were inoculated directly onto tellurite agar and Tinsdale's medium at the hospital's laboratory. Thereafter, swabs were transported on Pai slants to the Florida Department of Health and Rehabilitative Services Laboratory in Jacksonville, where they were inoculated onto tellurite agar, Tinsdale's medium, blood agar, and chocolate agar. All isolates suspected to be *C. diphtheriae* were biochemically characterized and tested for toxigenicity by the method of Elek [10] at the CDC's diphtheria reference laboratory.

Serological Survey for Antibodies to Diphtheria Toxin

Sera from a sample of children <15 years of age who had been randomly selected for a survey of human immunodeficiency virus (HIV) seroprevalence [11] and who were found to be seronegative for HIV were tested for antibodies to diphtheria toxin by toxin neutralization in VERO cells [12] at St. Christopher's Children's Hospital in Philadelphia. These children had received care at some point during the period from January through August 1990 at a community medical center that predominantly serves indigent patients in Dade County and had had blood submitted to the chemistry laboratory. For each child, information on race and age group (<5 or 5–14 years), but not on vaccination history, was available.

Case Report

Summary of the Case

On 13 January 1990, a previously healthy, 25-month-old, unimmunized boy with a 3-day history of cough and fever presented to the pediatric emergency department at a community hospital in Dade County, Florida. The child was born in the United States of parents who had immigrated from Haiti in 1981. He did not attend day care outside of his home and had no history of travel or disease exposures. At presentation he had a temperature of 39.4°C, pharyngeal erythema, wheezing, stridor, cervical swelling, and cervical lymphadenopathy. A chest radiograph showed subglottic narrowing and bilateral lung hyperinflation. Initial diagnoses were wheezing-associated acute respiratory infection and croup. Despite bronchodilator therapy in the emergency department, respiratory symptoms worsened, and on 14 January the boy required endotracheal intubation. The procedure was uncomplicated, and the epiglottis appeared normal.

By 17 January multiple complications had developed, including anuric renal failure, pneumonia with pleural effusion, transient ventricular tachycardia, and hypertrophic cardiomyopathy (demonstrated by echocardiography). On 18 January, during endotracheal tube replacement, the observation of thick gray pharyngeal and tracheal membranes that bled upon attempted removal led to a presumptive diagnosis of diphtheria. By then, the child had received cefotaxime, trimethoprim-sulfamethoxazole, and oxacillin. After collection of a pharyngeal swab for culture, treatment with intravenous penicillin was started. Diphtheria antitoxin was obtained promptly, but the child developed multiple cardiac dysrhythmias and died before it could be administered. Tonsillar, palatal, epiglottic, and laryngeal membranes were noted at autopsy. Although the culture of the pharyngeal swab obtained before the child's death was negative and postmortem histopathologic examination did not suggest diphtheritic myocarditis, the diagnosis of diphtheria was confirmed on 8 February on the basis of a postmortem epiglottic culture that yielded toxigenic *C. diphtheriae* of the mitis type.

Epidemiological Investigation

Household and other close contacts. The child had an extended family consisting of relatives and friends who lived in separate households but who typically ate meals together and slept at one another's homes. On 19 January health department staff located 11 close contacts of the child, including his parents and their seven remaining children, who lived in a two-bedroom apartment, and an adult and a child from another household. Although initially apprehensive because of language and cultural barriers, the family eventually enumerated 14 additional close contacts. Of these, 10 children (10 months to 9 years of age) and two adults from a third household were located on 5 February. All 23 contacts who were located had been exposed to the case-patient around the time of his illness. A child and an adult from the third household recently had been in Haiti for 8 months and 2 weeks, respectively, and had returned to Dade County ~6 weeks before the case-patient's illness. The remaining two contacts, including a woman who frequently traveled to Haiti, could not be located. More detailed travel and exposure histories for these two contacts could not be obtained.

For 19 of the 23 contacts located, vaccination histories were verified by vaccination cards or medical records. Five children who had not yet received three doses of diphtheria toxoid, three adults who had not received a dose within the previous 5 years, and two adults and two children whose vaccination histories were unknown were given a dose of

diphtheria toxoid. After pharyngeal swabs were obtained for culture, each of the contacts, regardless of vaccination status, was given antimicrobial prophylaxis with either one dose of intramuscular benzathine penicillin (children) or a 10-day course of oral erythromycin (adults). Except for coryza in a 10-month-old infant, all contacts remained asymptomatic.

Final culture results, reported on 2 February, indicated that three contacts (13%) were infected with toxigenic *C. diphtheriae* of the mitis type; these contacts were siblings of the case-patient and were 2, 4, and 5 years of age, respectively. Two of the three had previously received one dose each of diphtheria toxoid, and one had an unknown vaccination history. Follow-up cultures of pharyngeal swabs obtained both 1 week and 2 weeks after receipt of penicillin were negative.

Hospital contacts. Infection control staff enumerated 94 hospital employees who worked in areas where the case-patient had received care. Pharyngeal cultures were initially recommended for those who may have been exposed to his respiratory secretions. However, because the closeness of contact was not systematically ascertained and culture media were not readily available, no cultures were performed. Vaccination records indicated that eight (9%) of the 94 employees had most recently received diphtheria toxoid within the previous 5 years, 74 (79%) during the previous 6–10 years, and 12 (13%) more than 10 years earlier. Of the 86 employees in the latter two groups, 72 were given a booster dose of diphtheria toxoid at the employee health clinic and 14 were lost to follow-up. Of the 12 employees who had not received a dose within the previous 10 years, four received erythromycin prophylaxis and eight were lost to follow-up.

Neighborhood contacts. Although the family indicated that the case-patient had had no neighborhood contacts, a limited investigation was conducted because of uncertainty about the reliability of the interviews. On 6 February interviews with six other families who resided in adjacent homes confirmed the family's reports. Of cultures of pharyngeal swabs obtained from 24 persons who were at home during these visits, none were positive for *C. diphtheriae.*

Contacts of carriers. The three siblings with positive cultures had no additional close contacts. However, a preliminary report of a suspicious result of a culture for *C. diphtheriae* in their 7-year-old sibling led to his exclusion from school and to further investigation. Of five teachers and 26 students with whom he had close contact, three teachers who had not received diphtheria toxoid within the previous 5 years and one student in need of the fourth dose of diphtheria and tetanus toxoids and pertussis vaccine (DTP) were vaccinated at school. Of 26 contacts available for cultures, none were infected with *C. diphtheriae.* Final results of the initial culture and two follow-up cultures from the case-patient's 7-year-old sibling were also negative.

Table 1. Antibodies to diphtheria toxin in sera from a sample of children who attended a community medical center in Dade County, Florida, January through August 1990.

Race/ethnic group, age group (y)	No. tested	Percentage with indicated antibody level (IU/mL)	
		≥0.01*	≥0.1†
White‡			
0–4	103	79	56
5–14	73	90	73
Black§			
0–4	148	78	46
5–14	109	94	71
Haitian			
0–4	29	76	52
5–14	18	100	83
Hispanic			
0–4	116	78	52
5–14	105	96	76
All groups			
0–4	396	78	51
5–14	305	94	74

* A level of <0.01 IU/mL is generally considered nonprotective [13].
† The upper limit of antibody to diphtheria toxin that may permit breakthrough disease is generally considered to be 0.1 IU/mL [13].
‡ Hispanics are excluded.
§ Hispanics and Haitians are excluded.

Serological Survey

Levels of serum antibodies to diphtheria toxin were measured in 701 children. Of 396 children <5 years of age, 22% lacked protective immunity to diphtheria toxin (antibody level, <0.01 IU/mL) [13] (table 1). Whereas this proportion varied little by racial/ethnic group, a higher proportion of children 5–14 years of age had protective levels of diphtheria antitoxin (table 1).

Discussion

In the United States and other industrialized countries, improved control of diphtheria during the past 50 years and its near elimination in recent decades reflect the remarkable success of childhood vaccination programs. Not only does immunization against diphtheria confer individual protection; vaccination of ≥70% of a population may also provide herd immunity [14, 15]. In addition, as described by Pappenheimer, widespread immunization with diphtheria toxoid may lead to the elimination of circulating toxigenic strains of *C. diphtheriae* [2]. Diphtheria toxin is not an essential protein for the bacteriophage that carries its structural gene or for the bacterium itself [2]. However, in unimmunized populations, toxigenic strains may have a selective advantage over nontoxigenic strains because diphtheria toxin causes local

tissue destruction at the site of membrane formation, which, in turn, promotes multiplication and transmission of the bacterium [2, 16, 17]. This selective advantage of toxigenic strains is not expected in populations with high levels of immunity against diphtheria toxin. Pappenheimer's view is supported by population data on diphtherial immunity and carriage of *C. diphtheriae* in Romania from 1958 through 1972 [2] as well as by data from carriage surveys in other highly vaccinated communities [5, 7, 18–23] (table 2). Although the prevalence of circulating toxigenic *C. diphtheriae* in the United States is not known, only 13 (25%) of 52 isolates submitted to the CDC's diphtheria reference laboratory from 1981 through 1990 were toxigenic; the corresponding figure was 1,043 (56%) for 1,876 isolates submitted from 1971 through 1980 (Robert Weaver, personal communication).

In spite of what is apparently an extremely low risk of indigenously acquired diphtheria in the United States, evidence exists for subgroups of susceptible individuals. Recent surveys in 16 states and nine cities suggest that only 40%–60% of 2-year-old children, including approximately one-third of those living in Miami, have received all of the routinely recommended childhood vaccines [35–37]. Low levels of preschool vaccination are also reflected in our serological survey, in which more than 20% of preschool-aged children lacked immunity to diphtheria toxin. Moreover, our results likely underestimate community levels of susceptibility to diphtheria among preschool-aged children because those without access to medical care were not assessed. The higher level of protective immunity among children 5–14 years of age reflects state laws requiring vaccination before school entry. In other recent serological surveys, 20% to >50% of selected adolescents and adults lacked immunity to diphtheria toxin [38–42], with particularly low levels among the elderly, possibly due to lack of natural exposure during the vaccine era, low rates of vaccination, and/or waning vaccine-induced immunity [39].

As was demonstrated by diphtheria outbreaks in Sweden and Denmark in the 1980s [13, 43], epidemics may occur in unvaccinated population subgroups despite widespread childhood vaccination. As has been mentioned, importation of toxigenic *C. diphtheriae* from developing countries where diphtheria remains endemic poses a constant threat and has accounted for most cases of diphtheria in recent years in industrialized countries [2, 6–8, 20]. Although the source of infection was not documented in our investigation, the history of travel to Haiti among contacts of the case-patient and the absence of reported diphtheria in Dade County for more than 20 years suggest importation as a possibility. Because carriage of *C. diphtheriae* by untreated, asymptomatic persons lasts an average of 10 days [44, 45], some contacts may have had infections that cleared by the time pharyngeal swabs were obtained for culture. Furthermore, not all contacts were located; those who could not be found included one woman who frequently traveled to Haiti. Studies of the molecular biology of diphtheria suggest that conversion of nontoxigenic *C. diphtheriae* to a toxin-producing strain by lysogenic transfer of the gene coding for toxigenicity could have occurred [4], but no nontoxigenic strains were recovered from contacts.

Recommendations for Prevention and Control of Diphtheria

The need for rapid clinical and public health responses to diphtheria, a potentially fatal but rare disease, prompted us to review the recommendations and underlying rationale for the management of cases, the investigation of contacts, and the institution of preventive measures. On the basis of our review, we developed an algorithm to guide management and investigation of diphtheria (figure 1) should suspected or proven cases occur in the future.

Clinical Diagnosis

Because respiratory diphtheria may progress rapidly, a high index of suspicion needs to be maintained. Classical respiratory diphtheria is characterized by insidious onset, membranous pharyngitis with fever, enlarged anterior cervical lymph nodes, and edema of surrounding soft tissue, which gives rise to a "bull neck" appearance [14, 16, 47]. Although not always present, the membrane is typically gray, thick, fibrinous, and firmly adherent. Laryngeal diphtheria is characterized by gradually increasing hoarseness and stridor and most commonly occurs as an extension of pharyngeal involvement in children [14, 47].

Laboratory Diagnosis

Because the successful isolation of *C. diphtheriae* depends on rapid inoculation of special culture media, the laboratory should be notified as soon as the diagnosis is suspected. With routinely available throat or nasopharyngeal swabs, samples preferably should be obtained from the membrane (if present) or from beneath its edge. Although nasal diphtheria in the absence of pharyngeal involvement is uncommon, culturing of both nasal and pharyngeal secretions may improve the rate of isolation of *C. diphtheriae* [5, 51, 52]. Methods for the bacteriologic diagnosis of diphtheria have been described in detail elsewhere [53–55]. In brief, a confirmatory diagnosis may take several days and requires culture and isolation of the organism, biochemical typing, and toxigenicity testing. In some instances, a presumptive diagnosis may be made within <24 hours on the basis of cellular morphology on a methylene blue–stained smear of growth obtained after incubation on Loeffler or Pai medium [54, 55]. However, micro-

Table 2. Results of selected surveys of carriers of toxigenic *C. diphtheriae*, by setting and year.

Setting, year(s)	Location [reference]	No. of cases	No. of carriers/no. of persons cultured (carriage rate, %)	Comments
Household				
1986	Stockholm, Sweden [24]	5	0/NA* (. . .)	Swabs from household and other close contacts were cultured.
1985	Manchester, United Kingdom [6]	1	0/3 (. . .)	. . .
1975–1982	Ontario, Canada [25]	18	2/39 (5)	. . .
1970	London, United Kingdom [26]	1	1/4 (25)	The case-patient had a mild, recurrent sore throat for >2 y.
1969–1970	Chicago, Illinois [27]	21	7/73 (10)	Information on toxigenicity of isolates among carriers was not available.
1969	Dade County, Florida [9]	11	22/83 (27)	. . .
School				
1985	Ontario, Canada [8]	1	0/NA (. . .)	Swabs from classmates and teachers of the case-patient were cultured.
1985	Manchester, United Kingdom [6]	2	8/132 (6)	. . .
1980	Athens, Greece [19]	0	0/895 (. . .)	Swabs from a random sample of children in selected primary schools were cultured.
1975	Birmingham, United Kingdom [28]	5	0/51 (. . .)	. . .
1970	Athens, Greece [18]	0	0/818 (. . .)	Swabs from a random sample of children in selected primary schools were cultured.
1970	Elgin, Texas [29]	15	89/291 (31)	. . .
Hospital				
1984–1985	Göteborg, Sweden [22]	12	0/328 (. . .)	Swabs from hospital employees who cared for diphtheria patients were cultured.
1985	Manchester, United Kingdom [6]	1	0/NA (. . .)	Swabs from hospital employees who cared for the case-patient were cultured.
1982	Milwaukee, Wisconsin [30]	1	0/NA (. . .)	Swabs from hospital employees who cared for the case-patient were cultured.
1982	Westminster, United Kingdom [7]	1	0/81 (. . .)	Swabs from hospital contacts of the case-patient and of two hospitalized carriers were cultured.
1981	Ontario, Canada [31]	1	0/NA (. . .)	Swabs from 66 persons, including unspecified numbers of hospital employees, patients, and household contacts, were cultured.
1975	Birmingham, United Kingdom [28]	5	0/17 (. . .)	Swabs from nine patients and eight hospital employees were cultured.
Mental institution				
1972	Pontypool, United Kingdom [32]	1	36/824 (4)	Of 483 patients and 341 employees, 34 (7%) and 2 (0.6%), respectively, were infected.
1957	United Kingdom [33]	3	29/NA (NA)	Of an unspecified number of employees and 161 patients, 0 and 29 (18%), respectively, were infected.
Community				
1984–1985	Göteborg, Sweden [22]	12	0/NA (. . .)	More than 17,000 swabs for culture were obtained from an unspecified number of persons.
1982	Westminster, United Kingdom [7]	2	5/NA (NA)	More than 4,000 swabs for culture were obtained from an unspecified number of persons. Five infected persons were identified, all of whom had had direct contact with a case-patient.
1981	Hodeida, Yemen Arab Republic [34]	149	0/93 (. . .)	Swabs from children with no known exposure to diphtheria who visited an outpatient clinic were cultured.
1980	Manchester, United Kingdom [21]	1	34/24,000 (0.1)	. . .
1971	Manchester, United Kingdom [5]	9	28/>3,000 (<1)	Swabs for culture were obtained from household and school contacts and from persons with no documented exposure to a case-patient. Most carriers were school contacts.
1967	Alabama [23]	20	4/7,600 (<0.1)	Pharyngeal cultures for suspected streptococcal infections were screened for *C. diphtheriae*.

* NA, indicates that data are not available.

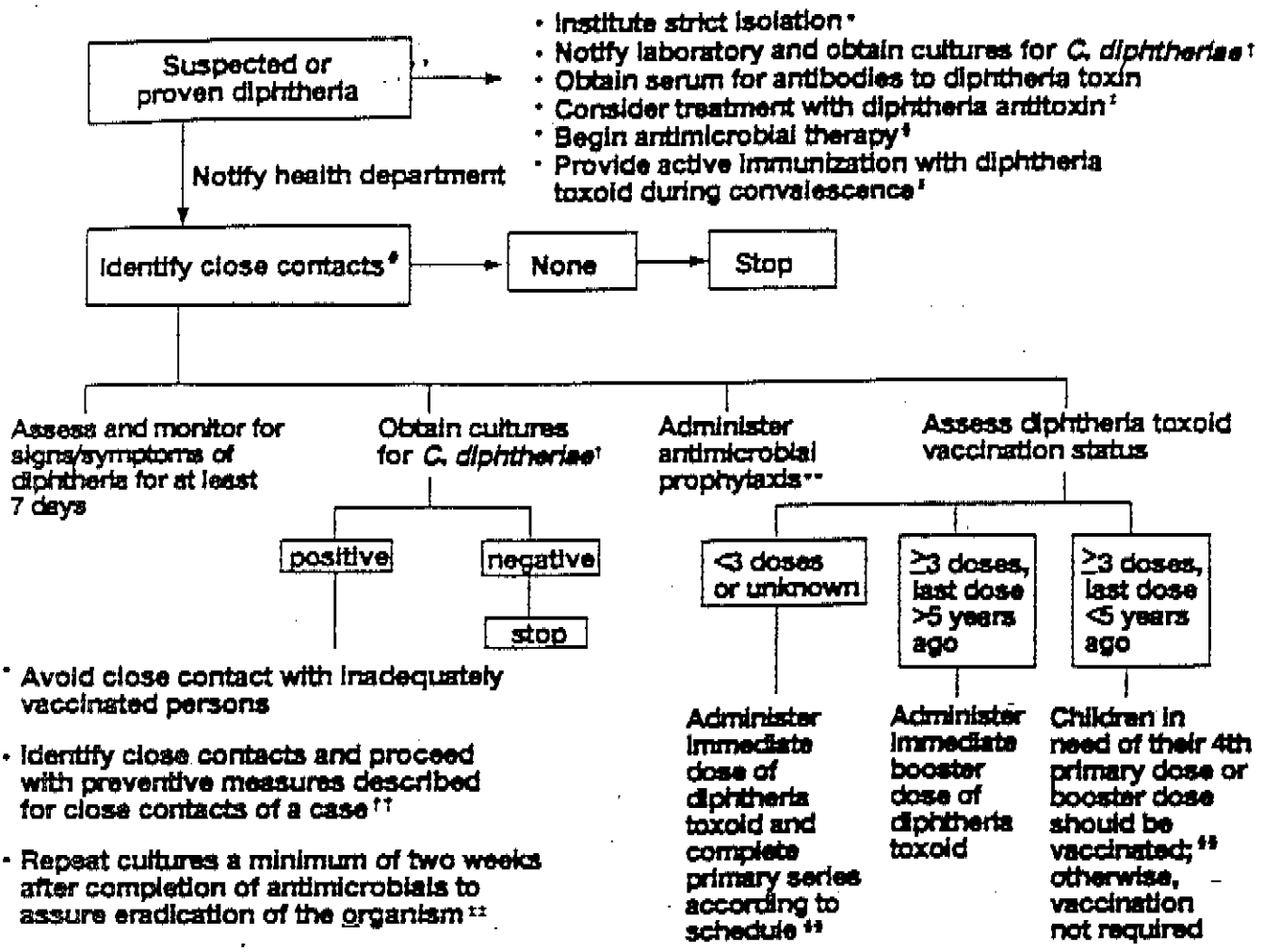

Figure 1. Respiratory diphtheria: recommendations for case management and investigation of close contacts. *Maintain isolation until elimination of the organism is demonstrated by negative cultures of two samples obtained at least 24 hours apart after completion of antimicrobial therapy [46]. †Both nasal and pharyngeal swabs should be obtained for culture. ‡Equine diphtheria antitoxin can be obtained from either the Division of Immunization, Centers for Disease Control, Atlanta (telephone 404-639-2888), or Connaught Laboratories, Swiftwater, PA. Before its administration, patients should be tested for sensitivity to horse serum and, if necessary, desensitized. The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations can be obtained from the package insert and other publications [14, 46–48]. §Antimicrobial therapy is not a substitute for antitoxin treatment. Intramuscular procaine penicillin G (25,000 to 50,000 units/[kg · d] for children and 1.2 million units/d for adults, in two divided doses) or parenteral erythromycin (40–50 mg/[kg · d], with a maximum of 2 g/d) has been recommended [46, 49] until the patient can swallow comfortably, at which point oral erythromycin in four divided doses [46, 49] or oral penicillin V (125–250 mg four times daily) [49] may be substituted for a recommended total treatment period of 14 days [46, 49]. ‖Vaccination is required because clinical diphtheria does not necessarily confer immunity. #Close contacts include household members and other persons with a history of direct contact with a case-patient (e.g., caretakers, relatives, or friends who regularly visit the home) as well as medical staff exposed to oral or respiratory secretions of a case-patient. **A single dose of intramuscular benzathine penicillin G (600,000 units for persons <6 years of age and 1.2 million units for persons ≥6 years of age) or a 7- to 10-day course of oral erythromycin (40 mg/[kg · d] for children and 1 g/d for adults) has been recommended [46, 50]. ††Preventive measures may be extended to close contacts of carriers but should be considered a lower priority than control measures for contacts of a case. ‡‡Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin and should submit samples for follow-up cultures [46, 50]. ‖‖Refer to published recommendations for the schedule for routine administration of DTP [46, 50].

scopic examination of direct-stained or fluorescent antibody–stained smears is generally considered unreliable [46, 53, 54, 56, 57].

Although not a widely available test, the measurement of antibodies to diphtheria toxin in serum collected before administration of antitoxin may support the diagnosis if the level is nonprotective (<0.01 IU/mL) [50]. This information may be particularly useful when a patient's cultures are negative as a result of prior antimicrobial therapy or for other reasons.

Management

Patients with suspected respiratory diphtheria should be placed in strict isolation and treated on clinical grounds; therapy should not be delayed until bacteriologic confirmation is available [14, 46, 48, 50]. Diphtheria antitoxin—hyperimmune antiserum produced in horses—is the mainstay of therapy. Because antitoxin neutralizes only circulating toxin that is not yet bound to tissue, prompt administration is critical. Although not a substitute for antitoxin, penicillin or erythromycin should also be administered so that the organism will be eradicated, toxin production terminated, and the likelihood of transmission decreased [14, 46, 47, 49].

Clinical attention should be directed to signs of airway obstruction, acute systemic toxicity, and toxin-mediated myocarditis and neuritis [14, 58, 59]. Myocarditis may present acutely, with congestive heart failure and circulatory collapse, or more insidiously, with progressive dyspnea, weakness, diminished heart sounds, and gallop rhythm [14, 47]. Electrocardiographic abnormalities, such as T-wave alterations and first-degree heart block, may occur in the absence of clinical signs [47, 59] and progress to severe block, atrioventricular dissociation, and other potentially fatal arrhythmias [58, 59].

Neurological complications consist primarily of motor loss involving cranial or peripheral nerves [14, 47]. Palatal and pharyngeal paralysis may occur acutely. Oculomotor and ciliary paralysis and, most commonly, lower-extremity peripheral neuritis may manifest 2–8 weeks after the onset of illness. Dysfunction varies from mild weakness to total paralysis and almost always resolves completely.

Mechanical airway obstruction and myocarditis account for most diphtheria-related deaths. The case-fatality rate for respiratory diphtheria has been nearly 10% in the United States in recent decades [60, 61] and was 18% (3/17) in the recent Swedish outbreak [43].

Identification of Secondary Cases and Carriers

Whenever the diagnosis of diphtheria is strongly suspected, local public-health officials should be notified, and measures to prevent additional cases should be instituted promptly. Infection with *C. diphtheriae* may result in asymptomatic carriage or disease of varying severity [14, 17]. In view of the short incubation period of diphtheria (1–6 days) and the delays encountered in bacteriologic diagnosis, the primary means of detecting cases is to monitor close contacts daily for at least 7 days [46, 48, 50]. Asymptomatic carriers should also be identified because they may transmit the organism [15, 26, 29, 51, 62]. In addition, finding a carrier among close contacts may support the diagnosis of diphtheria in the absence of bacteriologic confirmation. Although diphtheria toxoid protects against clinical diphtheria and complications, it has not been associated with the prevention of either infection or carriage [14, 17, 25, 29, 63, 64]. Thus, in the search for cases and carriers, nasal and pharyngeal swabs should be obtained from all close contacts, regardless of vaccination status [46, 48, 50].

Because the risk of infection is directly related to the closeness and the duration of contact and the intensity of exposure [14–16, 65, 66], the search for infected contacts should usually begin in the case-patient's household and be limited to settings in which intimate respiratory or physical contact with the case-patient may have occurred [46, 50]. Reported rates of carriage of toxigenic *C. diphtheriae* among household contacts of case-patients have ranged from 0 to 25% [6, 9, 24–27] (table 2); the carriage rate was 13% in our investigation. This variation may be due to differences in intensity of exposure, antimicrobial use, timing of cultures, and laboratory techniques. Whereas spread of diphtheria has been reported in institutions for mentally handicapped persons [32, 33], transmission in modern hospitals in the United States and other developed countries was not demonstrated in studies we reviewed [6, 7, 22, 28, 30, 31] (table 2). Investigation of casual contacts and of persons in the community without known exposure to diphtheria has generally yielded extremely low figures for carriage rates [5, 7, 21–23, 34] (table 2) and is not routinely recommended.

Antimicrobial Treatment for Contacts

A single dose of intramuscular penicillin or a 7- to 10-day course of oral erythromycin is recommended for all persons exposed to diphtheria, regardless of vaccination status, as soon as samples are obtained for culture [46, 50]. Whereas the efficacy of postexposure antimicrobial prophylaxis in preventing diphtheria is presumed but not proven, each of these drugs has been shown to eradicate *C. diphtheriae* from the respiratory tract of carriers [5, 21, 33, 64, 67–69]. Although available data suggest that erythromycin may be more effective [68, 69], intramuscular penicillin should be used if the patient's compliance is in doubt. Because neither regimen is 100% effective [67, 69] and bacteriologic relapse is possible [64], specimens from carriers should be cultured a

minimum of 2 weeks after the completion of therapy to ensure that the organism has been eradicated [64, 70].

Vaccination of Contacts

The vaccination status of all persons exposed to diphtheria should be assessed, and diphtheria toxoid should be administered according to the algorithm shown in figure 1. The rapid increase in diphtheria antitoxin expected with booster immunization [71, 72] is theoretically protective against the effects of diphtheria toxin.

Contacts of Carriers

On the basis of historical studies of diphtheria transmission, Doull and Lara estimated that the risk of developing diphtheria is sevenfold higher after household exposure to an individual with clinical diphtheria than after household exposure to a carrier (2.1% and 0.3%, respectively) [62]. Local destruction of tissue at the site of membrane formation in clinical diphtheria is thought to promote bacterial multiplication, which, in turn, enhances transmission [16, 17]. Thus, close contacts of persons with clinical diphtheria must be assigned the highest priority for preventive measures. Contacts of carriers should be given secondary priority. Moreover, prompt administration of antimicrobial prophylaxis to all persons exposed to diphtheria should reduce the likelihood of transmission by carriers. The benefits of excluding carriers from school or work may be minimal if their identification is delayed.

Routine Community-Wide Vaccination

The most important measure for preventing diphtheria is an ongoing community-wide program of active immunization that emphasizes on-time vaccination of children and booster immunization of adults. After completion of a primary series of diphtheria toxoid injections, all persons should receive a booster dose every 10 years [46, 50]. Combined diphtheria and tetanus toxoids should be given whenever the use of tetanus toxoid is indicated (e.g., for wound management) [46, 50].

Summary

Our investigation illustrates the potentially devastating consequences of the introduction of toxigenic *C. diphtheriae* into a community and emphasizes the need for a high index of suspicion regarding diphtheria, especially in inadequately vaccinated patients. Maintenance of a high level of clinical awareness of diphtheria, prompt investigation of sporadic cases with systematic identification and management of close contacts, and improvement of vaccination levels in the community are needed to prevent further morbidity and mortality due to diphtheria. In view of the continued occurrence of diphtheria in developing countries and the frequency of international travel in the current era, such measures will be necessary if the United States is to achieve its goal of eliminating diphtheria among persons ≤25 years of age by the year 2000. The ultimate goal will be to eliminate this disease among persons of all ages.

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DIPHTHERIA CARRIERS *

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While carriers of diphtheria bacilli have been objects of study for many years, so much interest attaches to them as potential spreaders of infection that it may be profitable to add the results of several years' experience with such cases in a hospital for contagious diseases. A study of the manner and speed with which the bacilli disappear from the nose and throat after diphtheria throws some light on the origin of carriers, and furnishes a standard by which to estimate the value of measures directed toward the elimination and destruction of the bacilli. A study of the persons in whom the bacilli persist may lead to the detection of underlying conditions which are responsible for the carrier state and so allow efforts toward their correction to be made along intelligent lines.

For these purposes I have tabulated 500 consecutive cases of diphtheria which were treated in Durand Hospital between February, 1918, and September, 1920. Patients with laryngeal diphtheria and those who died early are excluded. The series includes fifteen cases in which operative measures were employed in getting rid of the bacilli. The frequency with which two negative cultures are followed by positive ones early led us to adopt three consecutive negative cultures taken at intervals of from one to three days from both nose and throat as a standard for release. Hartley and Martin [1] have estimated that the average stay in hospital of patients with diphtheria released on one negative culture would be twenty-one days; on two negative cultures, thirty-four days; and on three negative cultures, forty-five days. In this discussion cases are considered as having been negative on the day when the first of three successive negative cultures was secured. If more than one day intervened between the last positive and the first of three negative cultures, the day of the first negative culture has been placed midway between the two.

It will be noted (Table 1) that after the first week, approximately half of the cases that began any week as positive became negative during the following seven days. Three weeks after the onset, 71.2 per cent. of the cases had become negative. At the end of four weeks, 83.2 per cent. were free of bacilli; and after seven weeks, less than 1 per cent. yielded positive cultures. In only a single instance were cultures positive after eleven weeks.

The outcome in the fifteen persons who were operated on if there had been no operation cannot be predicted. Of the 500 patients, eighty-four, or 16.8 per cent., became carriers, that is, gave positive cultures after twenty-eight days.

The number of cases that were positive at five day intervals is graphically shown in the accompanying chart. Hartley and Martin [1] have pointed out that diphtheria bacilli disappear from the throat with such regularity that the rate may be expressed by a mathematical formula. The rate of disappearance of the bacilli in our 500 cases and in the 457 cases of Hartley and Martin is shown in Table 2.

Differences in the percentages in the two series may depend in part on the intervals at which cultures were made, opportunities for reinfection and the character of the material. The patients of Hartley and Martin were all young adults in a military camp, and the cultures were made at weekly intervals, while ours were of all ages with little opportunity for reinfection, and the cultures were made at shorter intervals. The greater rapidity with which our cases became negative may perhaps be partly due to the constant efforts put forth to remove local conditions favoring the persistence of the bacilli. In both series the decrease of positive cases occurred with considerable regularity. After five days from the onset, of each 100 cases which are positive at any time, five or six may be expected to become negative within twenty-four hours.

During 1913 to 1920, fifty-two patients entered Durand Hospital as carriers and were observed until free from bacilli with no operative interference. Of these, 55.8 per cent. were free of bacilli after two weeks, and 80.8 per cent. after four weeks. The rates of disappearance of the bacilli did not show any such regularity as was observed in the series following diphtheria (Table 3). Of the fifty-two patients, nineteen had been in contact with diphtheria, and twelve gave histories of recent sore throat. The bacilli were located in the nose in nine, in two of which there was an associated foreign body in one nostril.

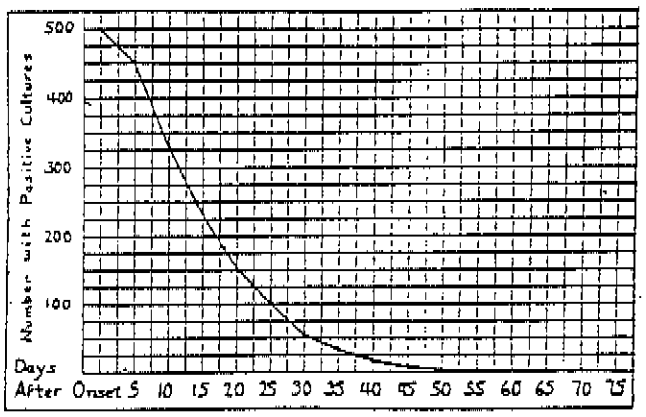
In ten of the fifty-two patients the bacilli persisted longer than four weeks. In four of these, cultures were obtained from the pharynx only, in one from the nose alone, and in four from both pharynx and nose. The persistent pharyngeal cultures were associated with abnormal tonsils, usually enlarged, with deep crypts and roughened surface. In the nasal cases there were discharges associated with enlarged adenoids and chronic rhinitis, usually secondary to accessory sinus disease. Cultures from six of these patients were tested for virulence, and a single one was nonvirulent. The most persistent carrier of this group was a baby of 4 months with a nasal discharge. He was very cachetic, had a

* From the John McCormick Institute for Infectious Diseases.

1. Hartley and Martin: Proc. Roy. Soc. Med., Sec. Epid. and State Med. 28: 277, 1920.

negative Schick test constantly, and the cultures were virulent for guinea-pigs for eleven months, the last test preceding their final disappearance a few days.

Another patient was a boy of 6 years, from one of whose nostrils virulent diphtheria bacilli had been cultivated for more than two months. When a solution of epinephrin was sprayed into the nostril, preliminary to further examination, a cherry pit dropped out. Two days later the cultures became negative. One adult who had been a constant carrier of virulent bacilli for five



The part of 500 cases of diphtheria which gave positive cultures at the end of five day periods.

weeks and refused tonsillectomy developed an acute tonsillitis, during which the bacilli disappeared. In other instances we have observed a disappearance of diphtheria bacilli during an acute tonsillitis. It seems quite reasonable that acute swelling with passage into the tonsils of abundant blood and escape of active leukocytes and opsonin might be followed by destruction of the bacilli. In a similar manner we may explain some favorable results reported to follow hyperemia produced by local applications of agents of an irritating nature. Two additional patients entered the hospital as carriers with no history of recent illness. They became free of bacilli one and eight days, respectively, after tonsillectomy.

As is the case with many bacteria, the largest factor in the removal of diphtheria bacilli from the body appears to be destruction by leukocytes. An essential factor in this process of phagocytosis is suitable opsonin. Tunnicliff [2] has shown that, in the course of diphtheria, immune opsonins for diphtheria bacilli appear in the blood in considerable amount. They may be detected on the fourth or fifth day of the disease, and they remain at their height until about the tenth to the fifteenth day and then gradually decrease, reaching normal about the nineteenth or twentieth day. The period during which the amount of opsonin in the blood is greatest corresponds to the time when the largest number of persons with diphtheria become free of bacilli. Of the 500 cases tabulated herewith, more than 70 per cent. got rid of their bacilli within three weeks from the onset.

In diphtheria carriers also Tunnicliff [3] found the phagocytic power of the blood for diphtheria bacilli increased. In spite of this, bacilli may persist in the throat and nose. This seems usually dependent on local conditions which interfere with suitable contact of the specific destructive agents and the bacilli.

2. Tunnicliff, Ruth: J. Infect. Dis. 5: 14, 1908.
3. Tunnicliff, Ruth: J. Infect. Dis. 19: 97 (July) 1916.

Gelien, Moss and Guthrie [4] attempted by direct introduction of large numbers of diphtheria bacilli into the nasal passages to produce carriers in cats, guinea-pigs and rabbits. The bacilli rapidly disappeared, and nothing corresponding to carriers as seen in man was observed.

These local conditions may result from secondary infections with abrasions and ulcerations of the mucous membranes and inflammations of accessory sinuses with imperfect drainage, and from mechanical injury by foreign bodies with associated infections. In tonsillar carriers, Brown [5] found diphtheria bacilli in certain areas where the surface epithelium of the tonsil was necrotic. Keefer, Friedberg and Aronson [6] demonstrated diphtheria bacilli in the submucosa of a tonsil from the surface of which a pure culture had been previously obtained. Hartley and Martin [1] saw diphtheria bacilli in sections of tonsils deep in the crypts but not invading the tissues. In one of our cases there was an ulceration of the mucous membrane of the turbinated body in the nostril from which diphtheria bacilli were constantly cultivated. Local treatment of the ulcer was promptly followed by disappearance of the bacilli. In two cases persistent positive cultures from one nostril were promptly terminated by the removal of foreign bodies from the nose; in one a shoe button, in the other a cherry pit. In a search for diphtheria carriers among 400 institutional children, Rabinoff [7] found five children, with shoe buttons in the nose, who were carriers. The cultures became negative after removal of the buttons. Bloomfield [8] attempted to produce human carriers of Friedländer's bacillus by artificial inoculation, but failed. He concludes from his study that the carrier state depends on a focus of diseased tissue which affords a breeding place for the bacteria. When we consider the circumstances under

TABLE 1.—RATE OF DISAPPEARANCE OF DIPHTHERIA BACILLI BY WEEKS FROM THE NOSE AND THROAT OF FIVE HUNDRED PATIENTS WITH DIPHTHERIA*

Week After Onset	Cases Beginning Week (Excluding Patients Operated on Same Week)	Cases Becoming Negative During Week (Excluding Patients Operated on Same Week)	Per Cent. Negative During Week (Excluding Patients Operated on Same Week)	Cumulative Per Cent. Negative
1	500	103	20.6	20.6
2	397	157	39.5	60.1
3	240	96	40.0	80.1
4	143 (144—1)	60	41.9	92.0
5	75 (83—8)	37	49.3	97.4
6	35 (38—3)	20	57.1	99.4
7	14 (15—1)	9	64.4	99.8
8	4 (5—1)	1	25.0	99.8
9	3	1	33.3	99.8
10	2	1	50.0	99.8
11	0 (1—1)	0	0.0	99.8

* Patients operated on are deducted from those at the beginning of the week during which they came to operation.

which diphtheria bacilli persist in the throat and nose it is not surprising that of all the local washes, sprays, gargles, etc., none has proved of marked value in persistent carriers. They seem to be useful so far as they remove secretions and exudates, and facilitate the con-

4. Gelien, Moss and Guthrie: Bull. Johns Hopkins Hospital 32: 381, 1920.
5. Brown, M. W.: J. Infect. Dis. 19: 565 (Oct.) 1916.
6. Keefer, F. R.; Friedberg, S. A., and Aronson, J. D.: A Study of Diphtheria Carries in a Military Camp, J. A. M. A. 71: 1206 (Oct. 12) 1918.
7. Rabinoff, Sophie: The Problem of Diphtheria Carriers, J. A. M. A. 67: 1722 (Dec. 9) 1916.
8. Bloomfield: Bull. Johns Hopkins Hosp. 32: 10 (Jan.) 1921.

of underlying local conditions. The administra- of diphtheria antitoxin has been of no advantage, practically all carriers have considerable antitoxin blood.

2.—RATE OF DISAPPEARANCE OF DIPHTHERIA BACILLI IN FIVE DAY PERIODS

NOSE AND THROAT IN FIVE HUNDRED CONSECUTIVE CASES OF DIPHTHERIA AT DURAND HOSPITAL

Day After Onset	Positive Cases at the Beginning of Period (Less Patients Operated on During Period)	Cases Becoming Negative During Period of Five Days (Excluding Patients Operated on)	Cases Becoming Negative During Period of Five Days per Hundred at Beginning	Cases Becoming Negative per Day of Period per Hundred at Beginning
5	500	47	9.4	1.9
10	453	124	27.4	5.5
15	329	100	30.4	6.1
20	229	75	32.8	6.6
25	154	51	33.1	6.6
30	101 (103—2)	38	37.7	7.5
35	56 (63—7)	18	32.1	6.4
40	35 (38—3)	15	42.9	8.6
45	19 (20—1)	10	52.7	10.5
50	9	4	44.4	8.9
55	4 (5—1)	1	25.0	5.0
60	3	1	33.3	6.7
65	2	0	....	....
70	2	1	50.0	10.0
95	0 (1—1)	0	....	....

FROM THROAT IN FOUR HUNDRED AND FIFTY-SEVEN CASES OF DIPHTHERIA REPORTED BY HARTLEY AND MARTIN

Day After Onset	Positive Cases at the Beginning of Period	Cases Becoming Negative During Period of Five Days	Cases Becoming Negative During Period of Five Days per Hundred at Beginning	Cases Becoming Negative per Day of Period per Hundred at Beginning
5	457	65	14.2	2.8
10	392	90	23.0	4.6
15	302	70	23.2	4.6
20	232	38	16.4	3.3
25	194	38	19.6	3.9
30	156	38	24.4	4.9
35	118	26	22.0	4.4
40	92	22	23.9	4.8
45	70	18	25.7	5.1
50	52	11	21.5	4.3

e local use of antitoxic serum and of serum pro- uced by immunizing with the bacterial bodies has not been followed by any satisfactory results. Vaccines have not been of any certain value, and this was to be expected, as carriers usually have an abundant supply of opsonins and their blood leukocytes are active.

Our efforts to clean up carriers are now confined to such measures as aid in removing local conditions that favor the retention of the bacilli. Washes are employed to remove secretions and discharges. Measures are used to facilitate drainage from the accessory sinuses and the nostrils. Irritating solutions are especially avoided. When the bacilli persist after such treatment, operative procedures are instituted if the localization of the bacilli is such that any benefit can be expected. The operations performed have been tonsillectomy and, when the adenoids are enlarged, adenoidectomy. Early disappearance of the bacilli has followed the operations in every case. The first case came to operation in June, 1915. To Dec. 31, 1920, forty patients had been operated on. In all cases the tonsils were enucleated, and in five adenoids were also removed. All of the patients had clinical diphtheria in the hospital, and the operation followed from twenty-one to seventy-three days after the onset. After operation the bacilli usually disappear very promptly. In many, no positive cultures could be secured after the operation. All except four were negative within a week, and only one was as long as eighteen days in becoming negative (Table 4). The only complication observed was a moderate secondary hemorrhage in one case on the sixth day.

The first six in our series of operative cases were reported by Friedberg.[9] Shortly afterward Ruh, Miller and Perkins[10] reported favorable results from tonsillectomy and adenoidectomy in carriers. Among their nineteen cases a single one was as long as seventeen days in becoming negative. In a large army camp, Keefer, Friedberg and Aronson[6] employed tonsillectomy to clear up carriers. Of 294 persons operated on, 91.3 per cent. were negative by the end of two weeks. From other army camps favorable results from tonsillectomy were reported. Pegler,[11] in 1905, reported the removal of tonsils and adenoids to get rid of lingering bacilli. Since this appeared only in a discussion on diphtheria and not as an original communication, it was apparently overlooked by American writers. Hartley and Martin[1] have found that the best treatment of carriers with large tonsils and deep crypts is radical enucleation of the tonsils. Friedberg pointed out the fact that the tonsil harboring the bacilli need not be enlarged. We advise removal of the tonsils and enlarged adenoids at the end of a month if the bacilli persist, or as soon afterward as the general condition of the patient warrants. In small children, in whom prolonged isolation is not very objectionable and in whom operative measures are less satisfactory, we are accustomed to wait for the natural disappearance of the bacilli, making use of such local measures as seem indicated. When the bacilli persist in the nose, local

TABLE 3.—RATE OF DISAPPEARANCE OF DIPHTHERIA BACILLI FROM THE THROAT AND NOSE IN FIFTY-TWO CARRIERS*

Days in Hospital	Positive Cases at Beginning of Period	Cases Becoming Negative During Period of Five Days	Cases Becoming Negative During Period of Five Days per Hundred at Beginning	Average Number of Cases Becoming Negative per Day of Period
5	52	17	32.7	6.5
10	35	9	25.7	5.1
15	26	4	15.4	3.1
20	22	3	13.6	2.7
25	19	7	36.8	7.4
30	12	2	16.7	3.3
35	10	1	10.0	2.0
40	9	2	22.2	4.4
45	7	1	14.3	2.9
50	6	1	16.7	3.3
55	5	0	0.0	0.0
60	5	2	40.0	8.0
65	3	0	0.0	0.0
70	3	1	33.3	6.7
75	2	1	50.0	10.0

* One case persisted for eleven months.

TABLE 4.—RATE OF DISAPPEARANCE OF DIPHTHERIA BACILLI AFTER OPERATION

Day After Operation When Cultures Were Negative	Number of Cases
1	7
2	7
3	2
4	8
5	9
6	3
8	1
9	2
18	1

9. Friedberg, S. A.: Removal of Tonsils and Adenoids in Diphtheria Carriers, J. A. M. A. 66: 810 (March 11) 1916.
10. Ruh, H. O.; Miller, M. J., and Perkins, R. G.: Studies on Diphtheria, J. A. M. A. 66: 941 (March 25) 1916.
11. Pegler: Brit. M. J. 2: 651, 1905.

lesions in the nostrils, and in children foreign bodies, are looked for.

One of the earliest efforts to determine the frequency of diphtheria carriers among well persons was made by a committee of the Massachusetts Association of Boards of Health [12] in 1902. The report of the committee was based on the results of a cooperative study which it instituted and which was participated in by a number of well qualified investigators. They concluded that in urban communities at least 1 or 2 per cent. of well persons among the general public are infected, and that when well persons are exposed to diphtheria, as in families, schools or institutions in which cases of diphtheria exist, the number infected is much larger, and may range from 8 to 5 per cent. Graham-Smith [13] reviewed the findings of various investigators as to carriers. The available data indicated that in close contacts the proportion of carriers may be as high as 36.6 per cent., in hospital wards and institutions 14 per cent. and among scholars of infected schools 8.7 per cent. I [14] found that 15.2 per cent. of the nurses in a hospital for contagious diseases became carriers, as detected by biweekly cultures extending over a period of two years.

Hachtel and Bailey [15] cultivated diphtheria bacilli from the throat and nose of 9.86 per cent. of contacts.

Goldberger, Williams and Hachtel [16] in the city of Detroit examined 4,093 apparently healthy persons with no history of contact, of whom thirty-eight, or 0.928 per cent., harbored morphologically diphtheria bacilli.

Gelien, Moss and Guthrie [4] made a cultural study of the throat in 2,507 presumably healthy individuals most diverse as to age, sex, race and social position in the city of Baltimore. Diphtheria bacilli were cultivated from eighty-nine, or 3.55 per cent. Later they added the results of cultures from 800 schoolchildren, of whom eighty-five, or 10.62 per cent., were positive for diphtheria bacilli.

These and other studies have established the fact that diphtheria bacilli, as recognized by cultures, are present in the throat and nose of a considerable proportion of healthy persons, and in a much larger proportion of those who have been closely associated with cases of diphtheria.

Supplemental studies, however, have determined that only a small part of the bacilli from noncontacts are virulent and a source of danger to other persons. Of the strains from noncontacts or "healthy" carriers, the proportion of virulent ones as determined by the committee of the Massachusetts Association of Boards of Health [12] was about 17 per cent.; by Goldberger, Williams and Hachtel,[16] 10.5 per cent., and by Gelien, Moss and Guthrie [4] from 10.9 to 18.1 per cent. These results appear to show that the proportion of individuals who have not knowingly been in contact with diphtheria but who are carriers of virulent diphtheria bacilli varies from about 1 in 75 to 1 in 1,030. There appears to be considerable variation in different communities, and the higher proportion occurs among children of school age. Such a proportion of unsuspected carriers of virulent bacilli, scattered among the people of cities, offers a ready explanation of the endemic presence of diphtheria and emphasizes the difficulty of eradicating the disease.

In distinction to the bacilli from "healthy" or noncontact carriers, those cultivated from persons who have recently had diphtheria, "convalescent" carriers or those who have been in contact with cases of diphtheria, "contact" carriers, are virulent in a large proportion.

The committee of the Massachusetts Association of Boards of Health [12] decided that bacilli from persons who had been in close contact with cases of diphtheria are usually virulent. I [14] concluded from my study that such cultures were practically always virulent. Utheim [17] found cultures from seventy-nine convalescents and eleven carriers uniformly virulent.

Hachtel and Bailey [15] found ninety-seven out of 100 cultures from immediate contacts to be virulent. Wadsworth [18] found cultures from convalescent carriers virulent in 92.5 per cent., and from contact carriers in 80 per cent.

The part that carriers play in the spread of diphtheria is doubtless considerable. The transfer of bacilli from a carrier to a susceptible person may originate a case of clinical diphtheria, and to immune persons may multiply the numbers of carriers which again become potential spreaders of the disease. There is little evidence that the bacilli lose their virulence to any considerable degree when they reside in the throat and nose of a carrier, even for a long time.

What to do with diphtheria carriers is a difficult problem for those dealing with public health matters. In this, as in many other instances, the first effort is to be directed toward prevention, especially by isolation of cases of diphtheria, and by the protection of attendants from infection. Immunization with diphtheria antitoxin of contacts who are susceptible to infection, as determined by the Schick test, limits the cases of diphtheria. It does not prevent the production of carriers. To prevent the transfer of bacilli from the sick to those about requires the application of a technic that often cannot be carried out because of lack of intelligent appreciation and training. The use of properly constructed gauze masks by those in contact with cases of diphtheria will doubtless limit the dangers of infection.

Gelien, Moss and Guthrie found that 37.94 per cent. of schoolchildren with positive cultures had pathologic throat conditions, as compared with 26.36 per cent. among children with negative cultures. It is likely that diseased tonsils, enlarged adenoids and infected nasal sinuses will render the individual more suitable for a carrier. The correction of such local conditions should reduce the likelihood of contraction of diphtheria and especially of becoming a carrier.

When an individual has become a carrier the measures to be instituted should vary according as the bacilli are or are not virulent. In all noncontact carriers the virulence of the bacilli should be tested. This allows most such individuals to be dismissed as not dangerous to others. Convalescent and contact carriers must always be considered sources of danger. If the carriage is persistent, a test of virulence will occasionally reveal a nonvirulent bacillus and allow the possessor to be released from restraint.

Persistent carriers of virulent bacilli generally present some local pathologic condition in the throat or

12. J. Massachusetts Assn. of Boards of Health, 1902, p. 1202.
13. Nuttall and Graham-Smith: Bacteriology of Diphtheria, 1908, p. 157.
14. Weaver, G. H.: J. Infect. Dis. 20: 125 (Feb.) 1917.
15. Hachtel, F. W., and Bailey, M. S.: Am. J. Pub. Health 10: 42 (Jan.) 1920.
16. Goldberger, Williams and Hachtel: Bull. 101, Hyg. Lab., U. S. P. H. S., 1915, p. 29.
17. Utheim, K.: Norsk Magazin f. Lægevidenskab, 78: 678, 1918; abst. J. A. M. A. 72: 695 (Aug. 24) 1918.
18. Wadsworth, A. B.: Virulence of Diphtheria Bacilli from Diphtheria Patients and from Carriers, J. A. M. A. 74: 1695 (June 21) 1920.

the correction of which is usually followed by appearance of the bacilli. No satisfactory means been devised for destroying the bacilli. When local sures are of value it is usually because they aid in recting abnormal conditions which interfere with destruction of the bacilli by the natural bactericidal cesses of the body. If such local treatment has been successful, removal of tonsils and adenoids will ually be followed by the disappearance of the bacilli.

INDUSTRIAL LEAD POISONING*

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Lead poisoning is almost as old as written history. cient Rome used lead pipe in its wonderful water-rks system, and many of the inhabitants became flicted with the disease. It has received the attention physicians ever since the dawn of medical science, d every age has witnessed contributions on the sub-t by medical men. The more recent additions to our owledge of the problem have been made through the searches and writings of such authorities as Oliver, gge, Goadby, Hamilton and Hayhurst. Notwith-anding all these contributions, there still remain a few oints about which there is some disagreement, and the resent paper, not intended as a thorough discussion of ll the phases of plumbism, is offered for what it is orth as an aid in clearing up a few of these points. The material is drawn from experience gained during study of lead poisoning in several industries, during hich I made thorough physical examinations, includ-ng laboratory work, of more than 900 workers exposed o the lead hazard. Eighty of these were found to be uffering from lead poisoning in various degrees of everity, and ninety-five others had sufficient signs and mptoms of plumbism to warrant a tentative diag-osis.

ETIOLOGY

By far the greatest amount of lead poisoning occurs among industrial workers. There are now approxi-mately 200 American industries in which lead in some form is used, and in which there is consequently a possibility of the workers' contracting plumbism. As industry is becoming more and more diversified, this number is constantly being increased.

With the possible exception of the silicates, it seems that lead in any form is capable of producing poisoning. This danger is more apparent with the soluble salts and with the fumes from the molten metal. It decreases as the salts become less soluble, and as the temperature of molten metal is decreased. Thus, with lead sulphid, a salt relatively insoluble in the gastric and intestinal juices, and with the cold metal itself, there is compara-tively little danger.

Aside from the industrial sources, lead poisoning occasionally occurs in domestic life. Formerly this type was fairly frequent, owing to the lead absorbed from lead pipes by drinking water. Cases have also occurred from eating canned food, because of the dissolving action of certain fruit juices, etc., on the lead in the solder. Other cases have occurred through the use of cosmetics, hair dyes, etc., containing lead.

The "portals of entry" by means of which lead enters he body are threefold. The most important of these is through the digestive tract, as when lunches are kept or eaten in rooms in which there is dust containing lead; when food or tobacco is handled with hands dirty with lead compounds; when water or food containing lead is used; and when men working in atmospheres contaminated with lead dust swallow either the dust which accumulates in their nasopharynx or what is dissolved in their saliva.

The second channel of entrance is by way of the respiratory tract through breathing of lead fumes and dust containing lead. Lead poisoning may occur from the fumes of molten lead even when the temperature of the latter does not reach the boiling point. I have demonstrated by means of sodium sulphid papers that lead fumes are given off from pots of molten lead at a temperature of approximately 750 F., and have found cases of lead poisoning among the men working with lead at this temperature. It is quite likely that fumes are given off at temperatures even lower than this. Most of the lead dust breathed is caught in the nasopharynx and swallowed. Lehman and Saito have shown experimentally that when dust is breathed only 12 per cent. reaches the lungs, whereas 70 per cent. reaches the alimentary canal.

The third and least important channel of entrance is through the skin. Some investigators have denied that lead poisoning can be caused in this way, but enough cases have been encountered with apparently no other possible means of absorption to entitle it to considera-tion. As mentioned in a previous paragraph, cosmetics and hair dyes containing lead have been known to cause plumbism. A case was encountered in Cleveland, which had apparently developed from the use of a cane with a lead head. This case is similar to that of the harness-maker reported in the literature who developed lead poisoning from the use of a small piece of metallic lead with which he was in the habit of pounding the leather. I myself encountered two mild cases among men who handled 100-pound lead pigs. In this case there is, of course, the possibility that they breathed and later ingested tiny bits of metallic lead dust or lead oxid worn off the pigs in handling.

The lead that reaches the stomach is converted into the chlorid by the action of the gastric juice. In this form it is capable of osmosis and so enters the blood stream, where it combines with proteins, forming an albuminate. The lead that reaches the lungs passes through the alveolar and capillary walls and forms the same compound. If lead is really absorbed through the skin, it is likely that this compound is formed there also.

Some of the lead albuminate is excreted by the kid-neys; the remainder passes into the tissues, where it remains insoluble so long as the reaction is neutral. It may remain here for long periods, doing no harm until some change occurs in metabolism to alter the reaction of the tissues. This renders the albuminate soluble and capable of reabsorption. It is thus able to reenter the blood stream and once more exert its harmful effects. For this reason it is sometimes unwise to give iodids to patients who have worked in lead, as the iodids may release the albuminate and cause the lead to be reabsorbed, with resulting mani-festations of acute plumbism. Any sudden unusual exposure, a drinking bout, or an infection such as influenza, may produce the same effects.

Lead that is not acted on by the gastric juice passes out in the feces as a sulphid. The gastric juice is capable of exerting more solvent action on lead when

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