

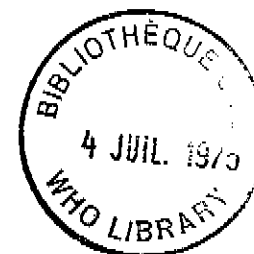


SOME UNSOLVED PROBLEMS IN DIPHTHERIA

by

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Introduction

During the nineteenth century, diphtheria swept across Western Europe and America as a major cause of illness and death, chiefly in young children. This pandemic began to subside in the latter half of the century, and since then has been brought largely under control in many countries through active immunization - first with "Toxin-antitoxin Mixture" discovered by Smith and applied to man by von Behring, and later by the use of formulon-detoxified toxin ("Toxoid" or "Anatoxin") established on a practical basis in the 1920s by Ramon. The earlier discovery and use of prophylactic and therapeutic antitoxin has saved many lives but epidemiologically cannot be regarded as having any bearing on diphtheria today.

Meanwhile, although it has repeatedly been shown that the major symptoms of diphtheria are due to a toxin, and that antigenically there is only one toxin involved, it has also been shown that the diphtheria bacillus (*Corynebacterium diphtheriae*) includes a variety of agglutinable serotypes, and more recently a range of bacteriophage types has been identified (Christensen, 1957; Saragea & Maximescu, 1966). In addition, Anderson and associates (1931, 1933) described three colony types which they thought were associated with different degrees of severity of clinical disease as indicated by their names: mitis, intermedius, gravis. However, subsequent experience has shown many exceptions to this correlation.

As noted above, the major problem of diphtheria control has been solved wherever widespread, systematic inoculation with diphtheria toxoid has been practised - provided that this is done in the most susceptible age-groups, i.e., preschool children. It is by nearly universal immunization of this age-group that in such areas as, for example, Massachusetts, the number of cases of diphtheria has been brought down from 5-10 000 a year half a century ago, to about 5-10 a year during the past decade. Nevertheless, and despite the fact that diphtheria is perhaps the only disease of which the pathogenesis is now completely worked out (Pappenheimer & Gill, 1973), certain problems remain.

Efficacy of diphtheria toxoid

(1) The degree of protection achieved with toxoid immunization is often less than satisfactory. The Annual Diphtheria Surveillance Report of the US Communicable Disease Centre regularly indicates that about 7-10% of the reported cases of diphtheria in the USA occur in individuals whose records indicate that they have been "completely" immunized. Apart from the possibility that some of these immunization records are inaccurate, it must be acknowledged that diphtheria toxoid is itself not nearly as good an antigen as, say, tetanus toxoid. For instance, a given weight in micrograms of diphtheria toxoid will induce fewer micrograms of antibody than will the same amount of tetanus toxoid antigen. Christie & Petersen years ago (1951) called diphtheria toxoid a "relatively poor antigen", and the British Medical Research Council found in 1962 that even as much as 300 Lf units (10-15 times the standard dose) of fluid diphtheria toxoid induced a relatively poor immune response. Thus the diphtheria toxoid antigen itself requires further study with the object of enhancing its immunizing potency. Obviously, any such study must be based on purified toxin to avoid the risk of enhancing the activity of unwanted antigens; however, pure toxin can be obtained by established methods so this presents no major problem.

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(2) Complicating the problem of the efficacy of diphtheria toxoid is the fact that the relationship between toxin and its neutralizing antitoxin is a quantitative one. Ipsen (1946) showed that this appeared to be the case in man, and he demonstrated in animals that the larger the dose of challenge toxin administered, the larger the dose of antitoxin that was required to protect the animal. This quantitative relationship has not been extensively studied in man, however, and warrants at least a confirmatory study.

(3) Whether the other antigenic components in a filtrate of a diphtheria culture are actually irrelevant to protection is not entirely settled. Numerous clinical observers have noted - but with a minimum of reports in the literature - occasional pseudomembranous lesions in the tonsils or fauces of patient's serum had a "protective" level¹ of antitoxin. Whether these cases represent highly localized diphtheria intoxication, hypersensitivity reactions to the proteins of the diphtheria bacillus, or some slight invasive property of certain strains of the diphtheria bacillus, independent of the classical toxin, remains to be studied.

Pathogenesis and toxicity of strains

All strains isolated from clinical cases should be completely characterized in a competent specialized laboratory, and the old findings of O and K antigens (Huang, 1942; Lautrop, 1950; etc.) should be brought up to date.

Localized disease, usually in the fauces, is frequently attributed to "non-toxigenic strains" of *C. diphtheriae*. Such strains should also be thoroughly examined and the definition of "non-toxigenic" should be clarified, since there is no good evidence, for instance, against the hypothesis that levels of toxigenicity exist below the level at which present techniques can detect toxin production.

(4) A major unsettled problem is the nature and scope of diphtheria in the tropics. Despite dozens of studies, there is still so much confusion on this topic that two books on Tropical Diseases can on the one hand describe diphtheria solely as a faucial infection (Felsenfeld, 1966) and on the other solely as a cutaneous infection (Hunter et al., 1966). For many years it has been widely believed (e.g., Watson, 1951) that conventional (faucial) diphtheria is virtually non-existent in the tropics. On the other hand it has been recognized for years (Bacon & Marples, 1954; Flor, 1961; Funt, 1961; Grasset, 1952; Gunatillake & Taylor, 1968; Liebow, 1958; Liebow et al., 1946; Marples & Bacon, 1956; McCarthy & Marples, 1954; Murray, 1943; Pasricha & Panja, 1940; Riddell, 1950; and Markham & Stenhouse, 1959) that cutaneous diphtheritic infection is very prevalent in widely separated areas of the tropics. Furthermore, several of the above investigators, as well as others (Barr & McGregor, 1962; Cauchi & Smith, 1934; Cobban, 1963; Franz et al., 1964; Jacobziner, 1947; Markham, 1960; Seaton, 1951; and Stransky, 1964), showed that children in many widely separated areas of the tropics became largely Schick-negative at an early age - without any history of diphtheria - so that frequently the Schick-negative rate was 80-90% by the time of school entry. It was an almost inescapable conclusion that the two findings were related, i.e., that skin diphtheria generally induced immunity at an early age, without as a rule producing clinical disease. However, it must be borne in mind that the difference between this situation and that prevailing in temperate climates in pre-immunization days was perhaps more quantitative than qualitative. Schick in his early studies in Vienna, and Park in New York a few years later, found that about 80% of adults raised in crowded urban neighbourhoods were Schick-negative, although only a fraction of this population was known to have had clinical diphtheria. Furthermore, Frost (1928) showed clearly that the vast majority of persons who became Schick-negative did so through multiple sub-clinical infections. But it is clear that, under certain conditions in the tropics - possibly dependent on humidity, village-type life, frequent minor skin injuries or insect bites, etc., diphtheria immunity becomes widely established in early childhood by cutaneous mixed infections including the frequent presence of *C. diphtheriae*, and with very little if any clinical evidence of diphtheria.

¹ Usually accepted as ≥ 0.01 antitoxin unit.

(5) Furthermore, recent studies have in fact shown that this phenomenon is by no means confined to the tropics (Belsey et al., 1969). But this is far from the whole story. Especially since World War II, faucial diphtheria has been recognized as an increasingly important problem in many tropical areas, particularly in cities. The overall change in the recognized problem is shown in the attached chart (Fig. 1) from Malaysia (Institute for Medical Research, 1951). The writer visited an 18-20-bed diphtheria ward in Kuala Lumpur in 1960, and Newell (personal communication) was familiar with a diphtheria ward in Jakarta in the late 1950s. Chackrabarty (1969) wrote a thesis on diphtheria in India, and many other examples could be cited, showing the extent and importance of classical diphtheria in the tropics today.

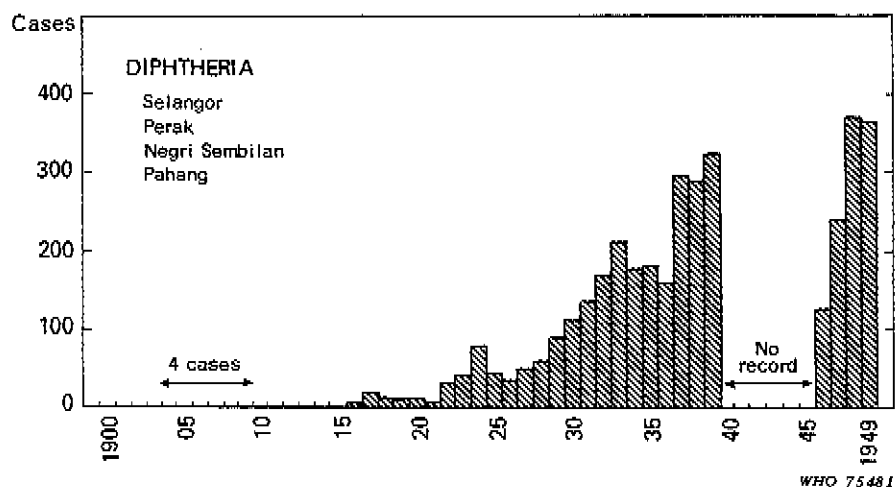
What has brought about this apparent change? Is it urbanization? If so, why has cutaneous infection ceased to play its benign role as the population moves into the city? Or has it really been so benign? Is there a racial difference in proneness to cutaneous infection? These and many other questions arise as one studies the scattered and conflicting data on diphtheria in the tropics.

Conclusion

Numerous unsolved problems regarding diphtheria infection remain. Each problem has a component which, for either laboratory or epidemiological reasons, will require highly specialized study of relevant isolates of C. diphtheriae or related organisms. The WHO Collaborating Centre for Diphtheria should serve as an excellent focal point for this aspect of the studies, but field collaboration will have to be sought in order to implement the studies suggested.

Various other problems, e.g., the possible role of cutaneous diphtheritic infection in enhancing the reactivity of tropical childhood populations to diphtheria immunization, could be raised, but this discussion has been deliberately limited to what appear to be established problems of relatively high priority.

FIG. 1
DIPHTHERIA IN MALAYSIA
(INSTITUTE FOR MEDICAL RESEARCH, 1951)



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