THE DIAGNOSIS OF DIPHTHERIA TODAY.

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PREFACE.

It is first necessary to explain why the title of this work was so chosen and why it is considered that the diagnosis of diphtheria merits further detailed consideration. It is not intended to suggest that there has recently been any fundamental change in the nature of the disease, when it occurs, or that any radically new diagnostic methods have been introduced; but it is considered that the present-day epidemiological circumstances, which are quite unprecedented, are such as to demand reconsideration of the fundamental diagnostic criteria of the disease. As illustrative of this point, it may be mentioned that during the year commencing 1st September 1947 (when the clinical observations forming the principal basis of the work were made) no fewer than 523 diphtheria-suspects were admitted to Ruchill Hospital, of whom only 109 (21%) were found to be actually suffering from the disease. As was apparent when the diagnosis was assured, many of these patients were suffering from relatively mild infections and did not require treatment in hospital. It was considered (and still is considered, even now when the number of diphtheria-suspects admitted is very much smaller) that much needless disturbance of patients and expenditure of public money could be prevented if it were possible - without prejudice to the welfare of patients suffering from diphtheria and their contacts - to achieve greater efficiency in diagnosis.

In order to determine which points are of most/

most importance in the diagnosis of the disease, it was decided to make a detailed clinical and bacteriological study of a series of patients admitted to Ruchill Hospital with the notified diagnosis of diphtheria, or suspected diphtheria. The series consists of 313 of the 523 diphtheria-suspects admitted during the year commencing 1st September 1947. The reason for the exclusion of the others - who were those admitted at certain periods, and those admitted to the ward set aside for the treatment of 'croup' - is mentioned subsequently.

In giving an account of the results of the work, it is thought necessary, prior to discussing the points relevant to the diagnosis of diphtheria, to describe the characteristics of the disease as it now occurs. In this preliminary study, particular attention is paid to the features encountered when the disease occurs in previously inoculated subjects, and to those atypical forms of the disease, without the formation of membrane and with only signs of follicular or catarrhal tonsillitis, which have been diagnosed with increasing frequency since bacteriological facilities have become widely available. In this study of 'present-day diphtheria', the author is fortunate in that reports are available on two other series (of cases occurring during the years 1942 and 1951 respectively) with which his own series (of cases occurring in 1947-48) can readily be compared; it is because this comparison shows that the features of the disease were much the same at each of these periods that it is considered that/

that his series can be regarded as being representative of the 'present-day' disease.

It is also thought necessary to consider in some detail the nature of the conditions which are most commonly mistaken for diphtheria. As an aid to the interpretation of the bacteriological findings in the cases in which the diagnosis of diphtheria was not confirmed, the investigations carried out in the series of diphtheria-suspects were also applied to 50 'normal' school-children and to 50 cases of scarlet fever.

Because it has recently been suggested that infection with a non-virulent strain of C. diphtheriae is a possible cause of diphtheria, the cases with evidence of this infection are considered in a separate chapter. The question, whether non-virulent strains are potentially pathogenic, is discussed.

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With regard to the bacteriological investigations, I was particularly fortunate in having the assistance of Dr. H. S. Carter who, in the course of his studies on the types of C. diphtheriae occurring in Glasgow, examined one or more swabs from each of the cases in my series. He also gave me much invaluable advice on bacteriological methods, and was always willing to give me the benefit of his experience in the identification of cultures. I am deeply indebted to him for his freely-given assistance and encouragement.

I wish to express my appreciation to Dr. T. Anderson,/

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CHAPTER I.

THE NATURAL HISTORY OF DIPHTHERIA IN GLASGOW IN RECENT YEARS.

SECTION I.

EPIDEMIOLOGICAL CHANGES.

It is apparent from many official and other reports that there has been an unprecedented fall in the incidence of diphtheria in this country during recent years. Regarding the position in Glasgow, Carter (1947 and 1952) made a comprehensive study of the epidemiological changes which have occurred during the past forty years. He showed that the incidence of the disease remained fairly constant between the years 1914 and 1940, except for certain epidemic periods, the last and most extensive of which reached its peak in the latter year. Since then, the incidence has diminished most strikingly - very much more than after any previous epidemic - until by 1950 the case rate per 100,000 of the population had fallen to 1/15 of the lowest annual rate recorded between 1914 and 1940 (the rate for 1917), that is to 1/60 of the rate for 1940.

Regarding the severity of the disease, and considering first the case-fatality rate, Carter showed that there was a gradual decline in this rate until about ten years ago. Thus the average annual percentage rates for successive quinquennia from 1911-15 to 1946-50 inclusive were 10.3, 10.0, 7.5, 5.2, 5.1, 4.4, 2.8, and 2.5 respectively. But from 1941 to 1951, while the rate has fluctuated considerably, it has shown no sustained decrease. It is apparent, then, that the fatality of diphtheria has been gradually but progressively diminishing/

diminishing over a relatively long period, but that there has not been any such striking change in the past ten years as in the case of the incidence of the disease.

Regarding complications, it was shown in a report by the Department of Health for Scotland (1948) that, as would be expected, the lowering of the fatality rate has been accompanied by a decline in the incidence of toxic complications and of cases with extensive membrane formation.

SECTION II.

THE CAUSES OF THE RECENT EPIDEMIOLOGICAL CHANGES.

In considering the possible causes of the recent changes in the epidemiology of diphtheria, it is important to bear in mind that, as pointed out by Logan (1947 and 1949), there has been a similar - but even more marked - long term reduction in the fatality of certain other common infectious diseases (in particular, scarlet fever, measles, and whooping cough), but that there has not been any comparable (short term or other) reduction in the incidence of these diseases. Brief comment follows below on the factors which might be held to be of importance.

(a) Improved nutritional and hygienic state of the community.

Logan (1947), who discussed this factor fully, concluded that it may well have contributed to the long-term reduction in the fatality of diphtheria - and of/

of the other infectious diseases mentioned above - but that it could not be held to account for the recent extraordinary decrease in the incidence of the disease.

(b) Variations in age of attack.

Picken (1937), Carter (1943, 1947, and 1952), and Logan (1949) have shown that since about 1926 there has been a marked upward age-shift of cases of diphtheria from the under-5-years age-group to the over-5-years group. Since the case-fatality rate in the former group has always been much higher than in the latter, it might be thought that the reduction in the over-all case-fatality rate was attributable to this age-shift. But Logan has pointed out that it alone cannot be credited with having played more than an almost insignificant part in this respect: he calculated that the age-shift which occurred between 1916-20 and 1941-45 was only sufficient to account for 1/10 of the reduction in the case-fatality rate which occurred during that time.

While the cause of this age-shift is debatable, if the conclusions of Cheeseman, Martin, and Russell (1939) about the position in London are applicable to Glasgow, changes in family-size and improved social conditions may be regarded as being important factors.

(c) More early diagnosis.

Increasing realisation of the paramount importance of the early administration of serum in diphtheria, and the policy which has been in force in/

in Glasgow for many years of encouraging the free admission to hospital of suspected cases of the disease, without waiting for conclusive clinical or bacteriological proof of the diagnosis, may well have played important parts in reducing the fatality and complication rates of the disease and, perhaps, to some extent, in lessening its incidence. Here again, however, it is not possible to find an explanation for the recent decline in the incidence of the disease.

(d) More accurate diagnosis.

In recent years it has become increasingly realised that the typical manifestations of diphtheria may never appear, and that the clinical picture of the disease may be scarcely distinguishable from follicular tonsillitis (British Medical Journal, Leading Articles, 1947). If, as is probable, more atypical cases of the disease have been recognised and notified recently, this will certainly have contributed to the lessening of the fatality and complication rates; while it may have had two opposing effects on the apparent incidence of the disease (a direct effect by increasing the number of cases notified, and an indirect effect by leading to the isolation of a larger proportion of infectious patients and thus reducing the real incidence of the disease), it can scarcely be held to explain the recent changes in this respect.

(e) Changes in prevalent types of C. diphtheriae.

It is apparent from Carter's work (1952) that/

that there is no evidence to suggest that the recent epidemiological changes may be ascribed to changes in the prevalent types of C. diphtheriae. With the exception only of a period of less than two years (during 1948 - 1950), gravis - the type commonly associated with particularly severe epidemics - has been the most prevalent type in Glasgow since 1938. Admittedly, there has been a marked increase in the proportion of atypical strains (nearly all non-virulent) since 1945; but this only occurred after the epidemiological changes were well advanced, and its significance with regard to the question at issue is debatable.

(f) Increased natural immunity.

As the decline in the incidence of diphtheria after the epidemic which had its peak in 1940 was altogether unprecedented in magnitude, it does not seem possible that increased natural immunity (which is a normal post-epidemic phenomenon) alone can have played more than a contributory part.

(g) Large scale artificial immunisation.

An intensive inoculation campaign has been conducted in Glasgow since 1940. As similar happy results have followed in many other areas, and for other reasons, there would seem to be no doubt that this campaign has been largely responsible for the present unprecedented state of affairs. Out of the large body of evidence pointing to the efficacy of inoculation, particularly impressive are/

are such observations as those of Scott (1943), Stott (1945), and Hartley et al. (1950) which show that, in a given community, an inoculated child is many times less likely to contract diphtheria than an uninoculated one, and that if he should contract an attack it is most unlikely to be severe.

To summarise this section, it would appear that large-scale artificial immunisation, and the usual circumstances of a post-epidemic period, have been mainly responsible for the recent extraordinary decline in the incidence of diphtheria, and may have contributed to some extent to the lessening of the severity of the disease; and that other factors, such as the improved nutritional and hygienic state of the community, more early diagnosis, and more accurate diagnosis, have been mainly responsible for the long-term lessening of the severity of the disease and may have contributed to some extent to the recent decline in its incidence.

SECTION III.

THE EFFECTS OF THE RECENT EPIDEMIOLOGICAL CHANGES ON THE DIAGNOSIS OF THE DISEASE.

In some respects the diagnosis of diphtheria is probably less beset with pitfalls when the disease is epidemic and its prevalence is high as compared with that of those other diseases which may simulate it to a greater or lesser extent (e.g. certain forms of streptococcal tonsillitis). Under these circumstances it would be/

be expected that a severe case of diphtheria would be more likely to be promptly diagnosed and treated - for practitioners and others would be alert to the dangers of the disease and aware of its prevalence. Further, these circumstances would perhaps have the effect of simplifying the diagnosis of cases with clinical evidence very suggestive, but not absolutely indicative, of diphtheria - for as in any one clinically suspicious case the chances of the diagnosis being diphtheria would be high, so that diagnosis could perhaps be regarded as being adequately confirmed on the strength of less complete bacteriological investigations than would be desirable in other circumstances.

If, on the other hand, diphtheria still occurred, but was relatively rare (as in the case of Glasgow at present), the following points might be expected to be of importance: first, that in order to avoid dangerous delay in the treatment of the occasional fairly severe case, it would still be necessary for practitioners to investigate, and to give such treatment as might be indicated to, suspicious cases - even although they knew, in light of their previous experience and their knowledge of the epidemiological circumstances, that the chances of any one such case actually being a case of the disease were remote; and, second, that, as diphtheria was a rarity, so it would be desirable to have as conclusive proof of that diagnosis as possible (i.e., more complete/

complete bacteriological and other investigations would be required to establish the diagnosis with a reasonable degree of certainty).

The position nowadays is further complicated by the realisation that diphtheria may occasionally occur in the guise of such a condition as simple catarrhal or follicular tonsillitis (British Medical Journal, Leading Article, 1947): so that it becomes necessary to bear the possibility of the disease in mind not only in cases with signs suggestive of it, but also in other cases.

The dangers of minimising the possibility of the occurrence of diphtheria are well illustrated by Thomson and Clementson (1952) who point out that the disease still occurs in Glasgow, and still kills.

CHAPTER II.

THE DIAGNOSTIC CRITERIA OF DIPHTHERIA, HISTORICAL AND MODERN.

Introductory note.

The sources of the information given in this chapter on the historical aspects of the subject are, unless otherwise stated, the works of Bretonneau (1826 and 1855), Loeffler (1908), and Andrewes et al. (1923).

SECTION I.

THE CLINICAL CONCEPTION OF DIPHTHERIA.

The work of Bretonneau receives considerable attention in this section, mainly because after this has been done there remains but little to be said on the historical or modern aspects of the clinical conception of diphtheria, but also because his method of classification of certain of the clinical features was adopted for the purposes of the present work.

The first of Bretonneau's five memoirs on diphtheria was submitted in 1821, and in that and his subsequent works he described in detail the disease and the problems which may arise in its diagnosis. It was he who gave it what is, essentially, its present name - derived from the Greek 'diphthera' (hide or leather). Generally speaking, the key diagnostic criteria, as he saw them, were, first, the presence of membrane, and, second, a strong tendency for the membrane to spread to the larynx. He realised the infectious nature of the disease and, in his fifth memoir, mentioned the deaths which occur from toxaemia, not from laryngeal obstruction. His description/

description of the membrane as it typically occurred was that it was thick, tough, and adherent; that the throat had the appearance of advanced gangrene, but that when the membrane separated there was seen to be no destruction of tissue, or, at the most, very superficial ulceration.

In addition to his explicit description of classical diphtheria, Bretonneau made other comments which are still particularly helpful, even today, in diagnosis. Thus, he realised that the membrane was not always typical - that it could be soft and cheesy in consistency, or that at the beginning of the illness it might consist of only a small spot. He emphasised the great difficulty which may occur in differentiating between nasal diphtheria and simple coryza in young children, and the need to be constantly on the look-out for the former condition when severe diphtheria is epidemic. Referring to what would now be called 'streptococcal tonsillitis', he stated: "Whether the rash appears in scarlet fever or not, it is always possible to distinguish it from diphtheria .....". He was convinced that they (scarlatinal angina and diphtheria) "are absolutely separate diseases. They have nothing in common except for one symptom only ..... the membranous inflammation of the tonsils". The main criteria on which the differential diagnosis was based were the general appearance of the patient, the pulse and temperature, the degree and extent of reddening of the throat, the consistency of the exudate, and the subsequent course of/

of the illness. He observed that an attack of the one disease does not give protection against the other, and argued from this in support of his contention that he was describing two distinct entities.

Bretonneau's description of the different types of exudate which may occur in diphtheria and in scarlatinal angina was found to form a most useful basis for the classification of the appearances encountered while conducting the clinical part of the present work. He stated that the characteristic membrane of diphtheria was tough and adherent, but that it could be separated from the underlying mucosa. In scarlatinal angina, on the other hand, the membrane was often relatively soft and could fairly easily be furrowed and broken up; but in some cases there was superficial ulceration of the tonsil which then appeared to be covered by an intimately adherent rind-like membrane which could not be separated from the underlying tissues. In the present work, these different categories of membrane are termed respectively 'typically diphtheritic membrane', 'friable membrane', and 'intimately adherent membrane'.

Since the time of Bretonneau, the clinical conception of diphtheria, as it typically appears, has remained essentially the same. It is true that later work has amplified certain aspects of the subject which his writings only lightly touched on - for example, the toxic complications of the disease - but no major changes in the/

the diagnostic criteria took place until after the introduction of bacteriological methods of investigation.

SECTION II.

THE IMPACT OF BACTERIOLOGY.

Following the discovery of C. diphtheriae by Klebs and Loeffler in 1883-4, bacteriological confirmation of the diagnosis of diphtheria became possible. Loeffler again emphasised, like Bretonneau, the importance of the distinction between true diphtheria and 'scarlatinal diphtheria'. He found, however, that there was a minority of cases of apparently true diphtheria in which C. diphtheriae could not be found, and also that the organism was occasionally found in non-diphtheritic throat lesions and in healthy throats. As a result of his and other work it became established that those strains of the organism which were isolated from cases of diphtheria were lethal when injected parenterally into guinea-pigs, but that other strains existed which were non-virulent to guinea-pigs, and also other diphtheroid organisms which resembled C. diphtheriae more or less closely when grown on a serum medium. Following the introduction of Neisser's stain in 1897, and the systematic study of the fermentation reactions of the organism undertaken in 1904, the methods of laboratory diagnosis remained essentially the same for many years.

The next outstanding event in the history of this subject was the publication of the work of McLeod and/

and his colleagues (Anderson et al.) in 1931. This work proved to have a most far-reaching influence on the understanding of the epidemiology of the disease, but it is its influence on the methods of bacteriological diagnosis which is considered here. Although tellurium compounds had been added to the media used for the isolation of C. diphtheriae by various earlier workers (the first account of its use appeared in 1912), it was not until after the publication of McLeod's work that the method began to come into general use. From the point of view of diagnosis, the advantages of a blood tellurite agar medium, such as McLeod's, are these: first, it is more selective for C. diphtheriae than is a serum medium such as Loeffler's; second, as it can more readily be used in the form of plates, instead of slopes, it facilitates the study of individual colonies; and third, it has been found that it lessens the need for virulence tests. McLeod (1943), reviewing the literature on this subject, stated that "the general conclusion is that strains which appear to be gravis and intermedius to experienced observers, and to be typical, do not need virulence tests". That conclusion was based on observations which showed that, in Europe at least, gravis and intermedius strains were almost always virulent, while mitis and atypical strains were not uncommonly non-virulent. Many other workers have confirmed these claims for the tellurite medium, and have found that it gives a higher percentage of positive/

positive results from cases of diphtheria than does Loeffler's. On the other hand, however, a relatively small number of cases have been found to be positive with Loeffler's medium but negative with tellurite (among those who have reported this finding are McLeod et al. 1931, and Cruickshank, 1943). This finding appears to be due to the existence of relatively rare 'tellurite-shy' strains. Its frequency partly depends on the type of tellurite medium used (Carter, 1948, personal communication).

Another medium which may be used for diagnostic purposes is blood agar (Wilson and Goldsworthy, 1939). Its principal advantages are, first, that C. diphtheriae grows more rapidly on it than it does on most of the tellurite media in common usage - whereby it is usually possible to determine, within twenty-four hours, whether that organism is present or not and, if present, to determine its type - and, second, that it is possible to detect the presence of other organisms - such as Streptococcus haemolyticus - which may be associated with those other diseases which may simulate diphtheria. Its principal disadvantage is that it is less selective for C. diphtheriae than is tellurite. (It may be mentioned that in carrying out the work described here the opinion was formed that blood agar is an extremely valuable medium for the bacteriological investigation of suspected cases of diphtheria - for the search not only for organisms such as Streptococcus haemolyticus but also for C. diphtheriae.)

A major advance in bacteriological technique/

technique which remains to be mentioned is the in-vitro toxigenicity test which was introduced by Elek (1948). Elek claimed that toxigenicity, as demonstrated by the test, and virulence, as demonstrated by the results of animal inoculation, are completely correlated; this claim has since been confirmed by several other workers, some of whom have also suggested relatively minor modifications of the technique. The test facilitates the complete investigation of mitis and atypical strains, and also permits of the same complete investigation of gravis and intermedius strains, so that the occasional non-toxigenic strain occurring among the latter can readily be detected. While it is difficult, as yet, to assess its full value, there is no doubt that the test greatly simplifies the bacteriological investigation of suspected cases of diphtheria.

SECTION III.

THE IMPACT OF IMMUNOLOGY.

In addition to their use in epidemiology and in the prophylaxis of diphtheria, immunological investigations have also been applied to the diagnosis of the disease; but, as is explained in this section, their value for this purpose is distinctly limited. The possible methods of study are these: (1) the Shick test, (2) estimation of the blood anti-toxin concentration at the beginning of the illness, and (3) serial estimations of the blood anti-toxin concentration. The value and limitations of each/

each of these methods are considered in this section. Apart from these methods, it is often possible to make an estimate of the probable state of immunity of a patient to diphtheria by consideration of the previous history with regard to prophylactic inoculation, previous attacks of the disease, and the environment in which he was brought up (whether he is likely to have experienced subclinical attacks or not).

(1) The Shick Test.

Since the introduction of the Shick test in 1913, a simple method has been available of assessing whether an individual has a certain degree of antitoxic immunity to diphtheria or not. It appeared for a time that the significance of the test might be such that it could be said that a negative reactor had complete immunity to diphtheria and that it followed that any disease that he happened to be suffering from could not be that disease. But experience has shown that a negative reaction does not necessarily signify absolute immunity to diphtheria and that the disease does occasionally occur in such reactors, although usually only in a mild form. Goodall, for example, stated in 1928 that "The Shick test is of no value in the diagnosis of diphtheria. It might be argued a priori that a Shick-negative patient presenting signs clinically resembling diphtheria could not be suffering from that disease. It is not at all uncommon, however, to meet with cases of that nature, in/

in which virulent diphtheria bacilli are recovered from the local lesion, although such cases are rarely toxic." Others who have reported the occurrence of diphtheria in known Shick-negative reactors include Parish and Wright (1935), Fanning (1947), and Hartley et al. (1950). The last-mentioned workers found that recently Shick-negative subjects were not immune to even severe attacks (e.g. one of their patients developed a severe attack, with membrane of pharyngeal distribution, eight weeks after the Shick test had been found to be negative).

The occurrence of diphtheria in Shick-negative reactors may be explained in terms of two other observations. First, Parish and Wright (1938) pointed out that a negative reaction does not necessarily signify that the subject has an effective concentration of, or any, antitoxin in the blood; but it does signify that his tissues have had previous experience of the toxin or toxoid of C. diphtheriae and will therefore react to the secondary stimulus of infection with that organism relatively rapidly. Second, Hartley et al. (1950) showed that under such circumstances some four days may elapse between the secondary stimulus of infection and the response in the form of increase of the blood antitoxin concentration. It is thus not difficult to understand how a massive infection could produce considerable, rarely perhaps even fatal, toxic damage before the defences of the body are mobilised. As is in accordance with clinical/

clinical experience, it would be expected that the disease would usually be mild: for although the organism might make some headway locally before the defences were mobilised, there would not be sufficient time, except in overwhelming infections, for much toxic damage to take place. It is also not difficult to understand how it comes about that it is usually the more rapidly invasive strains of C. diphtheriae (in particular, gravis and intermedius strains) that succeed in overcoming the defences of Shick-negative subjects (Cruickshank, 1943).

Just as a Shick negative reaction does not necessarily signify complete immunity to diphtheria, so a positive reaction by no means necessarily indicates that the subject will contract the disease if infected with the causative organism. In fact, figures from the pre-immunisation days (Frost, 1928, and Dudley, 1932) suggest that such an individual is three to ten times more likely to acquire a degree of immunity (as indicated by his becoming Shick-negative) without developing clinical signs of diphtheria than to suffer a clinical attack. Similarly, Dudley found that while carriers of a virulent strain of C. diphtheriae are nearly always Shick-negative, occasionally they are Shick-positive; but in the case of the Shick-positive carriers he encountered (five in number) the test was found to be negative a month later. It is not known why some subjects with no antitoxic immunity develop the disease when infected with the causative organism, while the majority develop immunity/

immunity without showing clinical signs of the disease. In this respect, Frost demonstrated that the odds are weighted by age and race, and probably by the number of organisms with which the subject is infected. There can be little doubt that the type of the organism which is prevalent in the community is also of great importance in determining the ratio of clinical to subclinical infections. Further, as suggested by Hartley et al. (1950), the fate of the infected individual may also depend on other factors such as the state of the tissues at the site of lodgement of the organisms, the presence at that site of other organisms of a type facilitating invasion of the tissues by C. diphtheriae, and the presence in the blood of an antibacterial factor independent of its antitoxin content.

With regard to the value of the test in the differentiation of mild diphtheria (without the characteristic membrane formation) from tonsillitis, due to some other infection, occurring in a carrier, it seems clear that if the result is negative this by no means excludes diphtheria - for a Shick negative reactor who developed the disease would most probably suffer from just such a mild and atypical attack. If, on the other hand, the result is positive, it could be argued that, as the mucous membrane was breached - whether originally by C. diphtheriae or by some other organism - and the patient had no (or insufficient) antitoxic immunity, diphtheria/

diphtheria was either present or impending and that the case should therefore be classed as one of that disease. Yet, three cases were encountered in the present series in which, although the Shick test was positive and a virulent strain of C. diphtheriae was present at the site of the local lesion, the clinical evidence pointed strongly to a diagnosis other than diphtheria (these cases are described in Chapter V, p. 111). If these patients were suffering from some other disease and (as a result of that and of their lack of antitoxic immunity) an attack of diphtheria was impending, in two of the cases, in which antidiphtheritic serum was administered (as was the normal practice in all cases), the development of diphtheria may have been prevented by the serum, but in the third, although no serum was given, no further developments occurred. The occurrence of these cases has led the writer to doubt whether any certain conclusion as to the diagnosis can be drawn from even a positive Shick result in the difficult type of case (with clinical signs of tonsillitis but bacteriological findings suggestive of diphtheria) in which many authorities (e.g. a Committee of the London County Council in 1936) consider, or used to consider, the result of the test to be the key diagnostic criterion.

(2) Estimation of the Blood Antitoxin Concentration at the Beginning of the Illness.

Although methods of estimating the/

the concentration of antitoxin in the blood were known for some time before the discovery of the Shick test (the first method was described in 1892), the procedure has never been so widely practised as the latter test because it requires considerable technical facilities and is scarcely feasible in routine work. With regard to the correlation of the results of the two procedures, this was shown by Parish and Wright (1938) and Vahlquist and Högstedt (1949) to be considerable but not absolute: thus antitoxin is usually, but not always, present in relatively large amounts in the blood of Shick negative reactors; while it is usually absent in positive reactors, it may be present in small or moderate, but never very large, amounts. With regard to the amount of antitoxin present in the blood at the beginning of the illness in cases of diphtheria, it was shown by Ipsen (1946), Hartley et al. (1950), and Edward and Allison (1951) that there is usually little or none, but occasionally relatively large amounts. Ipsen concluded that there is no particular blood antitoxin level which can be said to give complete immunity to diphtheria, or even to a severe attack of the disease, but that the greater the antitoxin concentration, the less the chances become of a subject contracting the disease, and the more likely it becomes that, if contracted, the disease will be mild. Owing to the absence of a clear-cut threshold level, it would seem that this estimation is not likely to be of much more/

more assistance than the Shick test in the diagnostic problem referred to earlier - the differentiation of mild diphtheria from other disease occurring in a carrier.

(3) Serial Estimation of the Blood Antitoxin Concentration.

The estimation of the blood antitoxin concentration at the beginning of the illness, and then again in convalescence, is a procedure which may assist in the diagnosis of doubtful cases (but only in those in which the therapeutic administration of antitoxin is considered to be unnecessary). If the concentration is found to rise, this might be taken as giving firm confirmatory evidence to the diagnosis of diphtheria. Thus Hartley and his colleagues (1950) found that an increasing concentration occurred in certain of their cases in which the clinical signs were those of a mild attack of follicular tonsillitis (in most cases inflammation of the tonsils was absent or minimal; in some the only exudate present was a minute spot on either or both tonsils) and argued from this in support of their contention that the cases (and other similar cases in their series) were indeed instances of diphtheria. Parish (1949), on the other hand, suggested that a rising concentration need not necessarily be regarded as being indicative of diphtheria. He stated: "To take an extreme case, there is no reason why a patient with a high level of circulating antitoxin who carries virulent K.L.B. in /

in his throat, should not from time to time develop tonsillitis due to, say, Haemolytic streptococci. The infection is predominantly streptococcal but he might conceivably show a rise in the titre of circulating diphtheria antitoxin as a result of the illness." Parish considered that the Shick test should not be made the key-point of the differentiation between mild diphtheria and tonsillitis in a carrier and that serial blood antitoxin estimations would be unlikely to assist further. A point which seems to suggest that some of Hartley's patients may have been carriers suffering from non-diphtheritic tonsillitis is that infection with Streptococcus haemolyticus was significantly more frequent in the 'inoculated' group of cases (in most of which the typical signs of diphtheria were lacking) than in the 'uninoculated' group (in which the typical signs were usually present). Admittedly that organism was not isolated in 65% of the 'inoculated' group, but Dingle et al. (1944) and Landsman et al. (1951) have shown that recognised pathogens often cannot be found in those cases of tonsillitis in which - as in most of Hartley's 'inoculated' group - there are only signs of a slight degree of inflammation and relatively little exudate.

While serial estimations of the blood antitoxin concentration may give evidence which, when considered in conjunction with the other circumstances of the case, may be of assistance in differentiating between/

between mild diphtheria and other disease in a carrier, they are scarcely feasible in routine practice. Further, if there is any doubt as to whether the therapeutic administration of serum is necessary or not, the test is contraindicated.

SECTION IV.

THE SIGNIFICANCE OF ATYPICAL ATTACKS OF DIPHTHERIA.

Reference has been made in the preceding pages to that atypical form of diphtheria which it may be virtually impossible to differentiate from other disease occurring in a carrier (unless the epidemiological or other circumstances point strongly to one or the other diagnosis). It is sometimes implied that this is a new form of diphtheria which seldom occurs except in previously inoculated subjects. On the other hand it is known that atypical attacks do occur in the uninoculated, although much less frequently relative to the incidence of typical attacks*, and it is suggested here that such attacks are no new thing and were probably much more frequent than typical attacks in the pre-immunisation days.

It was pointed out earlier in this chapter that in former times many more people developed a degree of immunity to diphtheria by subclinical attacks of the/

*Hartley et al. (1950) reported that the clinical picture was typical of follicular tonsillitis in 38% of 95 inoculated subjects who contracted diphtheria, and in 14% of 141 uninoculated patients.

the disease than by clinical attacks. Although the atypical form of diphtheria referred to here is 'clinical', there can be no doubt that even today - but more particularly in former times - many similar cases occur which remain 'subclinical' either because the patient or his parents do not seek medical advice, or because the physician, observing only the signs of catarrhal or follicular tonsillitis or pharyngitis, does not institute bacteriological investigation. That the subclinical attacks of former times frequently appeared in such a guise is, of course, a supposition which cannot be proved. But Ker (1909) certainly encountered occasional cases of mild diphtheria, with signs of only catarrhal or follicular tonsillitis; and in view of the lack of generally-available bacteriological facilities, and the conception then held of the nature of diphtheria, it would be surprising if more than an exceedingly small fraction of such cases were to reach the wards of the fever hospitals and thus become 'clinical'. Conversely, the increased incidence of (clinical) atypical attacks (relative to the incidence of typical attacks) nowadays is partly explicable in terms of the widened conception of the nature of diphtheria now held and of the general availability and large-scale usage of bacteriological facilities. But in the case of immunised children there are two other operative factors: first, they are almost entirely protected from severe attacks of the disease; and, second,/

second, their parents are, on the whole, likely to be more concerned about their welfare than are other parents - so that mild infections are probably more likely to attract clinical attention.*

If the theory suggested above is substantially true, it has an important bearing on the treatment of those mild and atypical cases of diphtheria referred to. For while it would probably be agreed that it would be desirable to isolate the patient and to take steps to free him from infection, it might be considered unnecessary and meddlesome to treat him in other respects as if he were suffering from diphtheria - when it is considered that it is probable that in former times such patients almost invariably recovered spontaneously. Yet one such case in the present series (case no. 15 in Appendix tables VI and VII, described on p. 86) showed that even with the most trivial initial illness the possibility of the subsequent development of toxic complications cannot be entirely dismissed; and Ker (1909) and expert opinion in the British Medical Journal ('Any Questions?', 1947) concur with this conclusion./

*In the series of cases reported by Hartley et al., which was mentioned on p. 24, there is yet another possible explanation of the occurrence of a much larger proportion of clinically atypical cases in inoculated patients than in those not inoculated; that as the type of infection prevalent at the time was exceptionally severe, so it is probable that an unusually large proportion of the total attacks sustained by uninoculated subjects were 'clinical' (both in the sense that they attracted clinical attention and that they were clinically typical).

conclusion. There is no doubt that the management of these cases - in which the diagnosis (whether diphtheria or not) often remains uncertain - calls for much judgement and consideration.

CHAPTER III.

METHOD OF SELECTION OF THE CLINICAL MATERIAL AND COMPARISON OF THE COMPONENT CASES WITH THE OTHER ADMISSIONS DURING THE YEAR: DESCRIPTION OF THE TWO CONTROL ('NORMAL' AND 'SCARLET FEVER') SERIES.

(1) Selection of the Clinical Material.

The 'main series' of cases, which forms the principal basis of the present study, consists of all cases, with certain exceptions, admitted to Ruchill Hospital with a notification of diphtheria, or suspected diphtheria, during the year commencing 1st September 1947. The exceptions are, first, cases admitted to the ward set aside for the treatment of croup (cases in which croup was the presenting symptom, or was sufficiently severe to warrant admission to that ward), and, second, cases admitted during the following periods: 1/9/47 to 23/10/47; 26/12/47 to 4/1/48; 10/1/48 to 25/1/48; and 4/7/48 to 17/7/48. The reason for the omission of cases admitted during the first-mentioned period is that preparations to begin the investigations had not then been completed, and for the omission of cases admitted during the other periods, that the author was absent from the hospital.

(2) Outline of the bacteriological investigations carried out in all suspected-diphtheria cases admitted during the year commencing 1st September 1947.

To enable a comparison to be made between the 'main series' and the other admissions during the year - a comparison primarily with regard to the proportion of cases in which the diagnosis of diphtheria was confirmed - it is first necessary to outline the main investigations carried out in all cases and to define certain terms/

terms which were used for classification purposes. These matters are considered in this and the following section of this chapter. The special investigations carried out in the 'main series' of cases, and the method of classification of these cases, are fully described in the following chapter.

In all cases admitted during the year, at least one (more than one if the clinical signs were strongly suggestive of diphtheria) throat swab (and swabs from other sites if indicated) was taken and sent promptly to the Central Laboratory of the Glasgow Public Health Department where investigations to detect the presence of C. diphtheriae were conducted by Dr. H. S. Carter. If that organism was found to be present, its type was determined. Virulence tests (by guinea-pig inoculation) were performed on all mitis and atypical strains, but not normally on gravis and intermedius strains, which were assumed to be virulent without testing.* Other bacteriological investigations were also conducted by the author in the hospital laboratory. In the event of a positive result being obtained by him in a case in which Dr. Carter's investigations had yielded negative results,/

*Carter and Wilson (1949) applied the in-vitro toxigenicity test to 66 gravis strains, and 26 intermedius strains, isolated from Glasgow cases, many being cases in the series described here. All but one of the former type, and all of the latter, were found to be toxigenic. It is therefore probable that practically all of the gravis and intermedius strains in the present series were virulent.

results, the culture was sent to Dr. Carter for confirmation of its identity.

(3) Definition of the terms used for classification purposes.

To consider first 'diphtheria': cases were classed as being instances of this disease if there was a local inflammatory lesion from which a virulent strain of C. diphtheriae was isolated (some of the cases so classed may have been carriers suffering from other disease; this question and the justification for the adoption of the above definition are discussed in Chapter V). In one case, however, - not in the 'main series' - the appearance of the local lesion was considered sufficient to warrant the diagnosis, even although the organism could not be isolated. Classed as 'carriers' were those in whose case a virulent strain of C. diphtheriae was isolated from a site which showed no signs of inflammatory disease. For reasons which are considered subsequently, the remaining cases were divided into two main groups - as to whether a non-virulent strain of C. diphtheriae was isolated or not - if so, in the 'non-virulent' group, if not, in the 'negative' group.

(4) Comparison of the clinical material (the 'main series' of cases) with the other admissions during the year.

Information as to the final diagnosis and classification of the total admissions during the year/

year is given in Appendix table I, where it is shown that the diagnosis of diphtheria was confirmed in only 21% . Although the diagnosis was confirmed in a considerably larger proportion of the 'main series' than of the other admissions (24% as against 16%), this was largely due to the inclusion of the 'croup' cases in the latter group: for if these were discounted, the second proportion quoted would then become 21%.

Other differences, not shown in the table, between the 'main series' and the other admissions were that in the latter group the proportion of cases in the under-5-years age-group was higher, as also were the diphtheria case-fatality and toxic-complication rates (the actual rates are quoted in Chapter VI). Here again, the differences were due to the features of the 'croup' admissions: for almost all the patients in this group were infants or very young children; and included were three cases of particularly severe diphtheria, in which the larynx, as well as other sites, was the seat of the local affection (two of these cases were fatal).

In general it appeared, on scrutiny of the material, that the 'main series' could be regarded as constituting an unbiased sample - except for the exclusion of cases of croup - of the total suspected-diphtheria cases admitted to the hospital during the year.

(5) Description of the control ('normal' and 'scarlet fever') series./

(5) Description of the control ('normal' and 'scarlet fever') series.

Except that swabs were not sent to Dr. Carter, the same bacteriological investigations that were applied to the 'main series' of cases (these are described in the following chapter) were carried out in a group of 50 'normal' children and in a group of 50 cases of scarlet fever.

The 'normal' group consisted of children attending a Glasgow school clinic during the Spring of 1948. While care was taken to exclude from the series any child with symptoms or signs of disease of the throat or nose, signs of previous disease - particularly hypertrophy of the tonsils and slight enlargement of the upper cervical lymph glands - were not taken as a bar (if they had been so taken it would have required quite a prolonged search to find sufficient material for the investigation; further, the series, as it was, almost certainly constituted a more representative sample of Glasgow children than it would have if subjects with the signs specified had been excluded; it was thus a truer control).

The 'scarlet fever' group consisted of patients admitted to the wards of Ruchill Hospital during the same period. The criteria for selection were that there was no doubt as to the diagnosis, that the local lesion was sited in the fauces, and that no penicillin or other treatment likely to have affected the bacteriological results had been given.

CHAPTER IV.

METHODS AND TERMINOLOGY.

A description is given in this chapter of the routine which was adopted for the examination of the 'main series' of cases and for recording and classifying the observations made. The chapter is divided into six sections, in which the following subjects are dealt with:-

Section I ..... The Clinical History.

Section II ..... The 'Local Signs'.

Section III ..... The Signs indicative of Toxaemia, and particularly of the toxic complications of diphtheria.

Section IV ..... Bacteriological Methods.

Section V ..... Immunological and Other Investigations.

Section VI ..... Method of Classification of the cases.

SECTION I.

THE CLINICAL HISTORY.

The information recorded in each case under this heading was the age and sex of the patient, the duration of illness prior to admission to hospital, the symptoms, the previous medical history, the treatment prior to admission (if any), the basis of notification of the case, the name of the notifying practitioner, and any other relevant epidemiological or other information. The method of recording the inoculation history - the data as to previous active immunisation against diphtheria - is, however,/

however, described in Section V of this chapter.

Brief explanatory notes are appended on certain of the factors mentioned above:-

(a) Previous medical history.

Particular attention was paid to the previous occurrence of confirmed or suspected attacks of diphtheria, and to liability to other diseases which could be confused with that disease (e.g. quinsy).

(b) Treatment prior to admission.

Attention was directed mainly to such treatment as might have affected the bacteriological investigation of the case - especially the administration of sulphonamides or (more important) systemic or local penicillin therapy. If anti-diphtheritic serum had been given, this was also recorded.

(c) Basis of notification.

Cases could be divided into two categories - those in which the suspicions of the practitioner who had notified the case (and thought that hospitalisation for suspected diphtheria was indicated) were founded solely on his clinical observations, and those in which his suspicions had been further strengthened by the receipt of a (provisionally) positive bacteriological report. The former category of case was termed 'notified clinical', the latter 'notified positive'.

It requires to be mentioned that included in the 'notified clinical' group were eight cases in which the/

the notification was of scarlet fever in addition to diphtheria.

(d) Epidemiological and other information.

In each case it was recorded if there was any known contact with suspected or confirmed diphtheria, scarlet fever, or any other condition which might be relevant to the diagnosis. It was likewise noted if the patient had been transferred from another hospital or institution. A record was made on the housing conditions (ratio of inhabitants per room) - not so much because of such bearing as this factor may have on epidemiology, but more because it seemed probable that the information might, in some cases, help to explain why the notification of diphtheria had been made (for there is reason to believe that in Glasgow at the time of the study it was often difficult to arrange for the reception in hospital of a patient suffering from acute sore throat unless the notification of diphtheria was made; there was evidence that, in at least a few of the cases studied, it was this difficulty which had led to the notification of the disease - not that its presence was suspected).

As an example of the other information recorded, one case may be mentioned in which a history of trauma was considered to be relevant: the patient, who had been admitted thought to be suffering from nasal diphtheria, was found to be suffering from a fracture of the nasal cartilages.

SECTION II.

THE 'LOCAL SIGNS'.

Diphtheria is a disease of which one of the most important diagnostic criteria is the presence of a more or less characteristic local lesion. This being so, the methods adopted for the description and classification of the observations made relating to the throat, nose, and other possible sites of infection are discussed here in detail. Attention was also directed to certain other sites, particularly the tongue, cervical lymph glands, and ears, not because these are commonly the site of the local lesion in diphtheria (which they are not), but because it was thought that such study might give information which would assist in the diagnosis and differential diagnosis of the disease.

The section is divided into six parts, dealing with the following regions: (A), The Throat; (B), The Nose; (C), The Cervical Glands; (D), The Tongue; (E), The Ears; (F), Other Sites.

(A) The Throat.

The observations made concerning the throat (and mouth) were classed as follows:-

(1) Classification of cases by type of exudate present.

(2) The classification of the cases in which more than one type of exudate was present, and other observations concerning the exudate.

(3) The degree of hyperaemia.

(4) The degree of oedema.

(5) The occurrence of foetor.

(6) Other observations.

It may incidentally be mentioned that by far the largest part of this chapter is taken up by consideration of the first-listed subject - concerning the exudate.

(1) Classification of cases by type of exudate present.

(a) Definition of the terms 'exudate' and 'membrane' (the latter being considered to be synonymous with 'patch' and 'confluent exudate').

Prior to describing the method of classification used, it is considered necessary to discuss and define the terms 'exudate' and 'membrane'. These terms are in very frequent use, but are used in different ways by different clinicians: thus while some appear to regard them as being practically synonymous, others use them to describe contrasting findings.

In this work, the term exudate is used to describe any deposit in the throat which appears to have originated, in part or in whole, from the mucosa or submucosa (either by secretion from the mucosal glands or by exudation from the submucous tissues). It is thus used as a very general term to describe almost any deposit in the throat except a foreign body. For example, diphtheritic/

diphtheritic membrane, which, in its most characteristic form, consists of an abundant fibrinous exudate laid down around the framework of the superficial layers of the mucous membrane (as described by Mallory, 1908, and many others), is partly composed of exudate and has therefore been classed as such here.

The term membrane is sometimes used to denote the characteristic membrane of diphtheria referred to above, but is also not infrequently used to describe more or less any form of exudate occurring in the throat. In this work, membrane (syn. patch, confluent exudate) is used to describe any continuous mass of exudate which appears to have the quality of 'sheet-likeness' (i.e. which appears to cover an area of mucosa which is large as compared with its (the exudate's) observed or presumed thickness).

(b) Primary classification by type of exudate.

The primary classification of the 'throat' cases (cases in which the throat was affected, with or without lesions elsewhere) of the 'main series' as to the type of exudate present is shown in Appendix table III, the more detailed classification being shown in table IV. With regard to the primary classification, it may be seen that the cases were divided into six groups. In describing these groups, it is convenient to consider the last three first.

In the 'clean throats' group were classed cases in which no exudate was seen in the throat (but the/

the throat was inflamed); in the 'ulcer' group, those with definite evidence of ulceration of more than a superficial degree, and also those in which there appeared to be only a superficial erosion, provided that no exudate was present; and in the 'scum' group, four cases with signs of stomatitis in which the only exudate present in the throat or mouth was a thin semi-transparent film of what appeared to be little more than dried mucus.

The remaining cases were classified as to whether the exudate was judged to be 'sheet-like' or not - if so, in the 'patches' group, if not, in one or other of the two 'spots' groups ('semi-confluent spots' and 'discrete spots'). In the cases in the 'spots' groups, one or, more often, multiple deposits of exudate were present, usually, but not always, situated on the tonsils; it was considered essential that no individual spot could, as far as could be judged, be classifiable as being 'sheet-like' (if that was so, the case was classified in the 'patches' group - for cases with both 'spots' and 'patches' were classified in the latter group). Cases with 'spots' were classed in the 'discrete spots' group if there was no coalescence between the individual deposits, but in the 'semi-confluent spots' group if there was slight coalescence. It occurred not infrequently that coalescence of two or more 'spots' produced a deposit which covered such an area that the application of the term 'patch' almost became indicated; under such circumstances cases were only classed in the/

the 'semi-confluent spots' exudate-group if the individual nature and origin of each 'spot' could be clearly seen and if there was only a slight degree of coalescence; otherwise they were classed in the 'patches' group (these points are illustrated in the diagrams on pp. 41 & 42).

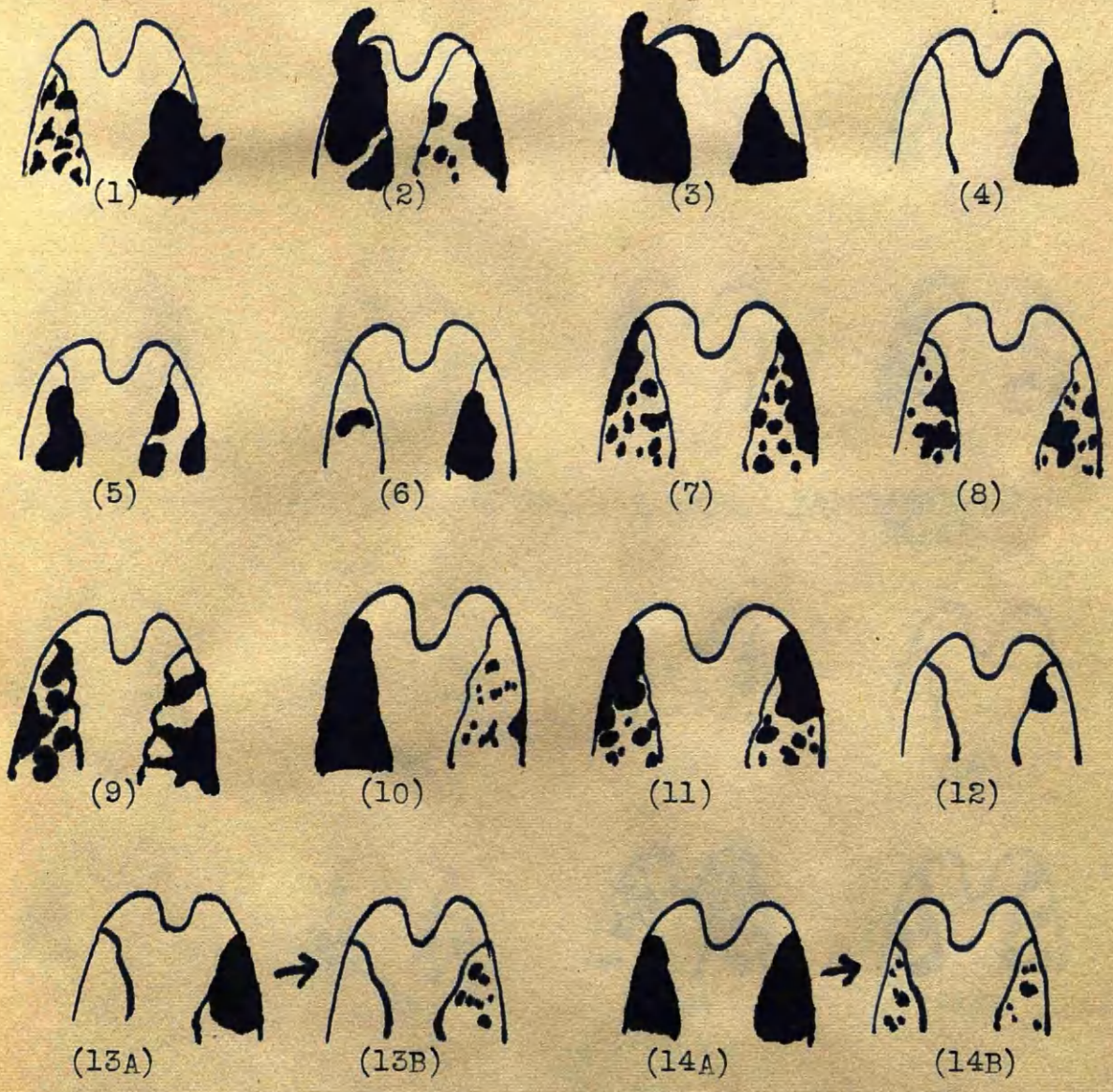
It is important to note that in the cases in the 'spots' exudate-groups, the exudate seemed most often to be situated in the tonsillar crypts or glands (to which situation could usually be ascribed the lack of 'sheet-likeness'); while in the cases in the 'patches' groups, it covered part, or the whole of, the free surface of the tonsils or other parts of the fauces or pharynx.

The further classification of the cases in the 'patches' exudate-group and, to a less extent, of those in the other groups was based on the findings as to the consistency of the exudate, which subject (in particular, the definition of the terms 'adherent' and 'coherent') is considered next.

(c) Definition of the terms 'adherent' and 'coherent' (the latter being considered to be synonymous with 'tough') as applied to exudate.

For the purposes of this work, exudate was said to be adherent if it could only be lifted from the underlying mucosa (with an ordinary bacteriological swab) with difficulty, if at all, and if such separation was followed by bleeding from the surface so exposed; and it was said to be/

Cases in the 'Patches' Exudate-Group: Representative Diagrams.



Note: The diagnosis in the cases from which these (and the subsequent) diagrams were taken is not stated: this is because, with the exception of a few of the diagrams, similar appearances were encountered in both the 'diphtheria' and 'other' groups of cases. The diagnostic significance of the various different types of clinical picture is discussed in Chapter VIII.

Diagrams 13 and 14 present a common finding in cases with 'friable membrane': the appearances on admission are shown in 13A and 14A; on swabbing the throat the exudate was easily removed except for 'spots' remaining in the crypts beyond the reach of the swab; the appearances after swabbing are shown in 13B and 14B.

Cases in the 'Semi-confluent Spots' Exudate-Group: Representative Diagrams.


(15)


(16)


(17)


(18)


(19)


(20)


(21)


(22)

Cases in the 'Discrete Spots' Exudate-Group: Representative Diagrams.


(23)


(24)


(25)


(26)


(27)


(28)


(29)


(30)


(31)


(32)


(33)


(34)

Note: Diagrams 23 to 30 are representative of the cases in the 'medium and large spots' exudate-group; 31 to 33, of those in the 'specks' group; and 34, of those in the 'spots of (?) typically diphtheritic membrane' group. Re. diagram no. 34, see also no. 38 (overleaf).

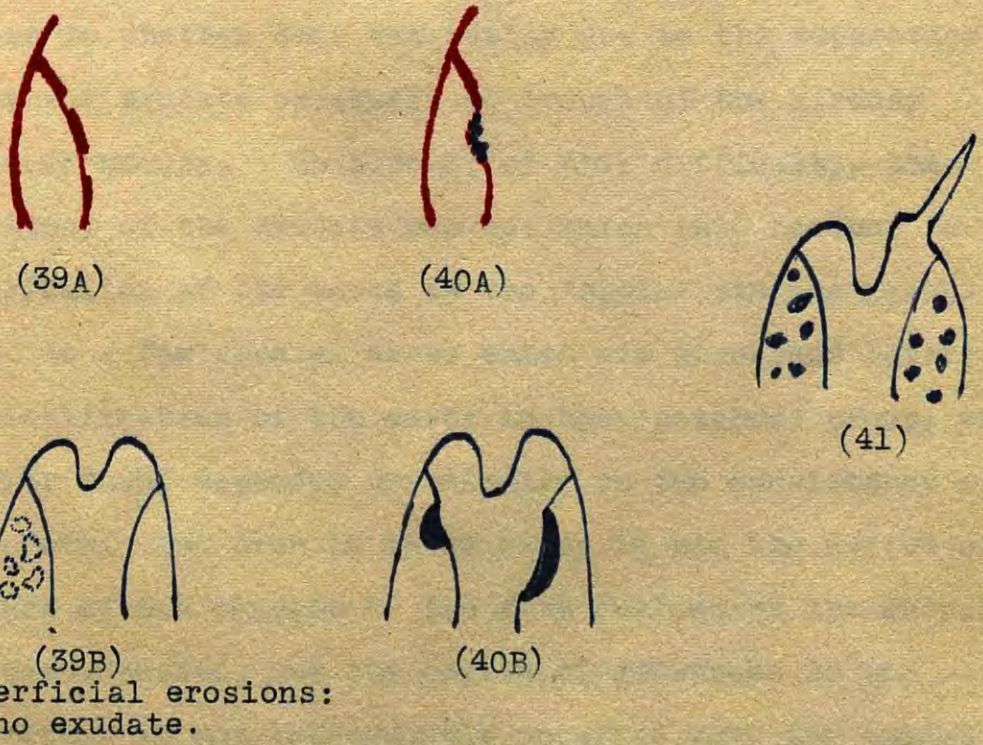
The 'spots' represented in diagram no. 30 were classed as being 'exceptionally large'; the distinction between 'spots' of this nature and 'patches' is explained on p.57.

Hypothetic Cross-Sections of Different Types of 'Spots'.

(35) (36) (37) (38)

Note: The significance of diagrams 35 to 37 is explained on p. 56. Diagram no. 38 represents a 'spot of (?) typically diphtheritic membrane': this type of exudate is discussed on p. 58.

Cases in the 'Ulcer' Exudate-Group: Diagrams showing the depth of the ulceration and the distribution of the exudate.



(39A) (40A) (41)

(39B) (40B)

Note: Diagram no. 39 (A and B) represents a case with 'minimal' ulceration; no. 40 (A and B), a case with 'moderately deep' ulceration; and no. 41, a case with 'deep' ulceration. These diagrams are discussed on pp. 60 & 61.

be coherent (i.e. tough) if it was not possible to break off a piece (from the throat) with a swab or if this could only be effected with great difficulty - but only provided that (in respect of both adherence and coherence) the exudate was reasonably accessible and that the patient's tolerance was such as to permit of adequate examination. The proviso of accessibility was made to cover the many cases, mainly in the 'spots' exudate-groups, in which the exudate was situated in the crypts and sulci of the tonsils where its consistency could seldom be adequately 'tested' with a swab. In these cases, if an energetic attempt was made to separate the exudate, bleeding sometimes resulted, but there was often doubt as to whether this was really due to the separation of an adherent exudate or simply to trauma of the already hyperaemic mucosa. On account of this difficulty, the consistency of the exudate was not taken into account in the classification of the cases in the 'spots' exudate-groups (except in a few special cases which are discussed later). The classification of the cases in the 'patches' group, on the other hand, depended principally on the consistency of the exudate; but even in these cases it was the degree of adherence of the exudate to the free surface of the mucosa which was assessed, not the degree of adherence to the crypts (thus it not infrequently occurred that the exudate could easily be loosened from the free surface although part of it remained in the crypts - probably owing to its inaccessibility; in such a case, it was not considered to/

to be adherent). The proviso as to the patient's tolerance was made because it was considered more accurate, in certain cases, at certain times (e.g. on the day of admission to hospital), simply to state that it was not possible to 'test' the exudate: for example, it is clear that bleeding which follows the forcible manipulation of a swab in a retching and struggling child's throat does not necessarily indicate the presence of an adherent exudate.

(d) Detailed classification by type of exudate.

The detailed classification of the 'throat' cases as to the type of exudate present is shown in Appendix table IV. In the following pages each of the various categories is discussed and defined.

'Patch' (syn. 'membrane', 'confluent exudate').

Definition: 'Exudate' with the quality of 'sheet-likeness'.

'Typically diphtheritic membrane'

Definition: 'Membrane' which is 'coherent' and 'adherent' but which can, to some extent, be separated from the underlying mucosa.

It is submitted that the above definition is essentially in accordance with the description of the characteristic local lesion of diphtheria as given by many authorities including Bretonneau (1826) and Ker (1909). In its most characteristic form, the membrane is loose at the edge, or can fairly easily be loosened there. The presence or absence of this feature was used to classify/

classify 'typically diphtheritic membrane' into two types - the type 'with free edge' and the type 'without free edge'. This further classification was made because it was thought to be useful to group apart the former type of exudate on account of its particularly characteristic appearance. It may incidentally be mentioned that the presence of a 'free edge' greatly facilitates the study of the characteristics of the exudate - for a bacteriological swab may conveniently be insinuated below the edge to test for 'sheet-likeness', 'coherence', and 'adherence'.

'Tough but loose membrane'

Definition: 'Membrane' which although 'coherent' is not 'adherent'.

A distinction is made in certain standard text-books of pathology (in particular, Adami, 1909, and Muir, 1951) between a fibrinous membrane and a diphtheritic membrane. Although the former is not necessarily of quite the same nature as 'tough but loose' membrane as defined here, it is proposed to refer briefly to the description given by the pathologists because of the light it throws on the probable nature of the various types of exudate. A (typical) diphtheritic membrane is believed to be formed by the deposition of fibrin on the surface of an epithelium and between the (damaged) epithelial cells. Being partly composed of the superficial layers of the epithelium, the membrane is adherent, and bleeding occurs if it is forcibly separated. A fibrinous exudate, on the other hand, (as/

(as occurring on the tonsils) is thought to arise when an exudate, rich in fibrin factors, is poured out from the follicles, and, spreading over the free surface and there clotting, forms a membrane which, although tough, is not adherent except, perhaps, by fibrinous processes extending from the depths of the crypts.

It is probable that a number of the 'tough but loose' membranes which were encountered were essentially 'fibrinous' - having been formed as described above. But it is also possible that, in some of the cases, the membrane had originally been 'typically diphtheritic' but had separated spontaneously by the time the patients were admitted to hospital. It may be that histological examination of the detached membrane (to detect the presence of layers of altered epithelial cells) might have settled this point; but this was not carried out.

As stated in the definition of 'tough but loose' membrane, exudate was only so classed if it was not adherent - that is, if it was found to be fairly easy to separate it from the free surface of the underlying mucosa, and if the latter, when so exposed, was seen to be intact and normal apart from a degree of hyperaemia commensurate with that of the other parts of the throat. But although there was no attachment of such membrane to the free surface of the underlying parts (usually the tonsils), it was often the case that the sheet of membrane was attached to the tonsil by one or more slender processes extending from the depths of (one/

(one or more of) the tonsillar crypts. Frequently it was possible, with an ordinary bacteriological swab (which was the only instrument used in 'testing' the exudate), to break these attachments and to remove, in one piece, the sheet of membrane from the throat; but occasionally, although the exudate could be moved about freely, it was not possible to obtain sufficient purchase, by the means employed, to sever it from its remaining attachment to one of the crypts.

'Intimately adherent membrane'

Definition: 'Membrane' which is 'coherent' and 'adherent', in which the degree of adherence is exceptional and such that no line of cleavage can be forced between the membrane and the underlying mucosa.

'Intimately adherent membrane', while coherent like the forms of membrane previously described, differed from these other forms by its extreme adherence. For while 'tough but loose' membrane could easily be separated from the underlying mucosa, and the edge of 'typically diphtheritic membrane with free edge' was loose or could fairly easily be loosened, and a line of cleavage could, with difficulty, be forced (at the edge) between 'typically diphtheritic membrane without free edge' and the surrounding mucosa, in the case of 'intimately adherent membrane' no line of cleavage could be made at all. There seemed reason to believe that this form of 'membrane' did not consist of 'exudate' at all, but that the appearance, as if of exudate, was due to the occurrence of some form of necrotic or other change in a/

a circumscribed area of the mucosa, as a result of which the colour of that area had become changed. Support for this view was also obtained by consideration of the method of clearing of the different types of 'exudate'. For while all the other forms of exudate became detached, sooner or later, piece-meal or whole, the patches of 'intimately adherent membrane' appeared to clear in a different way: in some instances, the affected area of mucosa gradually became smaller as the days passed; in others, the white colour of the 'exudate' gradually altered so that eventually the patch became scarcely distinguishable from the surrounding mucosa.

Although this form of 'membrane' may not have consisted of 'exudate' at all, the reason for classifying it as such is that the appearances on inspection of the throat were indistinguishable from those in the cases in which other forms of membrane - indubitably partly consisting of exudate - were present.

It may be mentioned that similar, but less marked, abnormalities affecting parts of the mucosa were not infrequently seen after the separation of other forms of exudate; but the cases in which this occurred were primarily classified according to the type of exudate originally present, not according to the appearances seen after its separation. In these cases (and perhaps also in the cases in which 'intimately adherent membrane' was the only type of 'exudate' seen) a possible explanation of the occurrence is that there had previously been a superficial erosion which/

which had healed prior to the separation of the exudate but had caused, in some way, a temporary change in the appearance of the mucosa.

'Friable membrane'

Definition: 'Membrane' which is not 'coherent'.

The essential difference between 'friable membrane' and the other categories of 'patch' is that the former was not 'tough' - that is, it could be relatively easily broken up with a swab applied to the throat. It had been expected that patches of this nature would be fairly easily divisible into two classes - as to whether the exudate appeared to be liquid or solid in nature. In fact, however, a frankly liquid 'membrane' was only encountered on one occasion; but this is perhaps not surprising - for the reason that it is probable that such an exudate, which had had its source in the follicles and had spread over the free surface of the tonsils, would not remain at that site but would be swallowed (unless it, to some extent, solidified by drying or clotting). Frequently the exudate seemed to consist of a delicate fibrinous pellicle but, as this could be fairly easily broken up on swabbing, it was not considered to be tough enough to justify its inclusion in either the 'tough but loose membrane' or the 'typically diphtheritic membrane' category. In other cases its consistency could perhaps best be described by the word 'pultaceous' - the exudate appearing to be composed of a thick liquid containing small masses of solid material which were probably fibrin /

fibrin clots.

The pathological conception of the term 'fibrinous membrane', and of the way in which such membrane is formed, was discussed in the section on 'tough but loose membrane', where it was suggested that many of the membranes classed as being 'tough but loose' were 'fibrinous'. It is also probable that, with regard to pathogenesis, the majority of the 'friable membranes' were essentially of the same nature. Thus in those instances in which the membrane, after its removal from the throat with a swab, was examined on a slide, there were seen to be irregularly-shaped pieces of tough tenacious matter which could only be broken up with difficulty and, which, when put into a glass of water, sank gradually to the bottom without disintegrating. As far as toughness - when tested in vitro - was concerned, it was scarcely possible to differentiate between these small pieces of material - derived from 'friable membrane' - and the similar - but usually larger - pieces derived from 'tough but loose membrane' and 'typically diphtheritic membrane'. The essential differential criterion was thus toughness as determined clinically - the ease with which it was possible to break up the membrane on swabbing the throat - not as determined by examining the isolated material on a slide.

It was suggested that it is possible that some of the 'tough but loose membranes' may earlier have been 'typically diphtheritic' in nature, having spontaneously loosened before the patients' admission to hospital./

hospital. Similarly, as 'typically diphtheritic membrane' sometimes separates by disintegration rather than by 'peeling off' whole, it is possible that some of the 'friable membranes' may also have been 'typically diphtheritic' before the patients were admitted. On the other hand, however, as 43 (78%) of the 55 patients with 'friable membrane' were admitted after an illness of not more than two days' duration, it is unlikely that many of them had been ill for long enough to permit of the formation and disintegration of 'typically diphtheritic membrane'.

Owing to the possibility of disintegration of the exudate, every effort was made to determine its category as soon as possible; this was, in fact, effected, as a rule, either on the day of the patient's admission to hospital or on the following morning. Exceptions to this rule were a small number of cases with membrane on admission which it was not possible to 'test' adequately for consistency at that time (owing to difficulty due to oedema of the throat or intolerance of the patient), and which had become free of membrane by the following day (the throat then either being 'clean' or with 'spots' of exudate in the crypts only). Owing to the rapidity with which the membrane had cleared away in these cases, it seemed most probable that it had been 'friable' in nature, and, for the purposes of classification, this was assumed to be so. Apart from these, there were two other cases, classified in the 'friable membrane' exudate-group, in which it was not possible to 'test' the /

the exudate satisfactorily until (in each case) the patient's fourth day in hospital. Here, also, it is possible that the presence of 'typically diphtheritic membrane' was overlooked owing to the delay in examination.

While the consistency of 'friable membrane' is defined by its name, and has been further discussed above, its degree of adherence has not yet been described. In nearly all the cases the membrane was not 'adherent', it being easily separable from the underlying mucosa with a swab, and the surface of the mucosa so exposed being seen to be intact. In many cases the entire membrane could be wiped off piece-meal, leaving the throat free of exudate except, perhaps, for 'spots' remaining in the tonsillar crypts out of reach of the swab. In other cases, owing to the intolerance of the patient, it was only possible to 'test' part of the membrane; but if that part was found to be friable and non-adherent, it was assumed that the remainder was of the same nature, unless subsequent observations indicated otherwise. There were, however, four cases in which the membrane did appear to be adherent. In these, the distinguishing feature from 'typically diphtheritic membrane' was the lack of toughness. When rubbed with a swab, the membrane came away 'piece-meal' fairly easily; yet it appeared to be adherent basally, and the mucosa, when exposed, was seen to be lightly eroded and bleeding.

'Semi-confluent Spots' (syn. 'Semi-confluent Exudate')/

'Semi-confluent Spots' (syn. 'Semi-confluent Exudate')

'Discrete Spots'

The above terms were discussed and defined on p. 39 ff., where it was explained that no systematic classification of these types of exudate, according to adherence and coherence, was attempted - for the reason that the exudate was most often situated in the tonsillar crypts, where it was more or less inaccessible for the purposes of 'testing'. With regard to the analysis of these types of exudate, reference to Appendix table IV will facilitate understanding of the rather complicated system of classification which it was considered necessary to adopt in order to make provision for a relatively small number of cases in which the features of the exudate were unusual. It is convenient to describe first the classification of the cases in which there were 'discrete spots', only, of exudate, and to postpone, until after this, comment on the (essentially similar) cases in which there was some confluence of the individual deposits (i.e. 'semi-confluent exudate').

'Discrete Spots'

Most of the cases in which 'discrete spots' were the only form of exudate occurring (the stipulation as to 'only form occurring' is made because, as stated before, cases in which both 'discrete spots' and other exudate - 'semi-confluent spots' or 'patches' - were present, were grouped according to the other type of exudate) were classed/

classed primarily as to whether some or all of the deposits (in any one case) were relatively large or whether they were all mere specks - the former cases forming the 'medium and large spots' exudate-group, the latter the 'specks' group. Not so classified were three cases in which the exudate was thought to have such special features as to warrant classification in a different group termed, for reasons considered later, the 'spots of (?) typically diphtheritic membrane' exudate-group.

'Medium and Large (Discrete) Spots'

The characteristics of exudate of this type were essentially those described previously with regard to 'spots' in general - lack of 'sheet-likeness' being the essential feature, another feature being that the exudate was most often situated in the tonsillar crypts. Although it was often difficult to determine the consistency of the exudate with certainty, frequently it seemed to be friable, or to be pultaceous, or frankly liquid. It was observed that the shape and size of the individual 'spots' varied greatly from case to case (see diagrams nos. 23 to 30, p. 42), these features being largely determined, it seemed, by the configuration of the tonsils: thus when, as a result of hypertrophy of the tonsillar lobes, the 'crypts' were represented by deep slits, the exudate therein, if in the form of 'discrete spots' (and more often, under these circumstances, the 'spots' were 'semi-confluent', the exudate having spread along these slits), consisted of very/

very irregularly-shaped elongated 'spots' (e.g. see diagram no. 29); or when the mouths of the crypts were shallow (more or less saucer-shaped), due, probably, to previous ulcerative disease at these sites, the exudate consisted of relatively large spots, regular or irregular in shape.

While most often the outer surface of the exudate seemed to be more or less flush with the surrounding free surface of the tonsil (see diagram no. 36), and occasionally to be heaped up and projecting beyond the tonsillar surface (as in diagram no. 35), more rarely it was concave, so that the exudate itself appeared to be little more than a thin, almost membranous, sheet, spread over the mouth of the crypt (see diagram no. 37). In the last-mentioned instance, it was since the exudate was almost entirely situated in the crypts, and since there was doubt as to its 'sheet-likeness', that it was not classed as membrane; similar exudate that did spread, to any more than a slight extent, on to the free surface of the tonsil, so that it became definitely 'sheet-like', was classed as a 'patch', not as a 'spot'.

The way has been paved, in the foregoing description, for definition of those special categories of 'medium and large spots' listed in Appendix table IV. Thus in the two cases listed as having spots of '(?) tough but loose membrane' there was follicular exudate with a very slight degree of spread-over of a (? sheet-like) pellicle (see diagram no. 37) which resembled 'tough but loose membrane' in that it was not adherent (except centrally to/

to its base deep in the crypt) but was coherent (tough). In the two cases listed as having had 'exceptionally large spots of (?) tough but loose membrane', the exudate was situated in those very wide saucer-shaped depressions (? wide-mouthed crypts) mentioned above, and was coherent but not adherent. Owing to the area covered by these spots (see diagram no. 30), doubt arose as to whether they should be classed as such or as 'patches'; the decision as to their classification was eventually made principally on consideration of their site - not covering the free surface of the tonsils, but in depressions below the surface. The three cases listed as having had 'exceptionally large spots of (?) friable membrane' were essentially similar to those mentioned above except that the exudate was friable.

'Specks'

This group consisted of cases in which the only exudate present was in the form of minute specks. (For classification purposes, if there was any doubt as to whether a given deposit should be classed as a 'medium or large spot' or a 'speck', it was considered to be the former). Unlike the other forms of 'spots', specks were not mainly restricted to the tonsillar crypts but also occurred, almost as frequently, on the free surface of the tonsils and, more rarely, elsewhere in the throat. In some cases the lymphoid follicles of the tonsils were enlarged, a small speck of exudate being seen at the mouth of each.

There were 4 cases, of the 34 in this group, in which the specks may not have consisted of exudate at all,/

all, the appearances having perhaps been caused by alteration having taken place, for some unknown reason, in small areas of the mucosa, whereby the superficial layers of the epithelium at these sites became opaque. Support for this hypothesis is derived from two observations: that the specks, in the cases referred to, could only be seen on very close inspection (although white, they did not stand out prominently on inspection); and that they usually remained more or less unaltered for a week or more, or faded in tone so slowly that it was difficult to decide when the throat could be considered to be 'clean' of 'exudate' (especially as the 'abnormality' had from the start been minimal, and was probably insignificant). In these four cases the evidence of throat (or other) disease was minimal. Although the occurrence may well have been a matter of no diagnostic or pathological significance, the cases were not classed in the 'clean throats' group - because only cases in which there was no doubt as to the absence of exudate were so classed.

The appearances of the throat in the cases of the 'specks' exudate-group are exemplified by diagrams nos. 31 to 33.

'Spots of (?) typically diphtheritic membrane'

In the three cases classed as having exudate of this type, there were two or more very small deposits of exudate (e.g. see diagram no. 34) which, in spite of the small area of mucosa covered, may well have been 'sheet-like': for the deposits were situated on the free surface of the/

the tonsils - not in the crypts, as 'spots' usually were - and it could be seen that the surface of each deposit was parallel to, and only very slightly raised above, the level of the surrounding mucosa - not heaped up (see diagram no. 38). The exudate was both tough and adherent - it could neither be broken up or separated from the underlying mucosa. Possibly the pathogenesis of the local lesion in these cases was essentially the same as that operative in the production of 'typically diphtheritic membrane' - in view of which and of the possible 'sheet-likeness' of the deposits, the exudate could perhaps have been classed as 'membrane'; but in consideration of the size of the deposits - smaller than most 'spots' - it seemed misleading to class it as such.

'Semi-confluent Spots' (syn. 'semi-confluent exudate').

The features of the exudate in the cases classed in this group were essentially those of 'medium and large spots' except that there was some confluence of the individual deposits - but not sufficient confluence to lead to the formation of 'patches'. Examples of this type of exudate are represented by diagrams nos. 15 to 22.

The only cases for which it was thought necessary to make a special category - the '(?) tough but loose membrane' sub-group - were four in which the features of the exudate were the same as in the corresponding sub-group of the 'medium and large spots' group except for the occurrence of a degree of confluence between a few of the deposits./

deposits.

'Clean Throats' group of cases.

Classified in this group were cases with no exudate visible in the throat (but with signs of inflammation of the throat).

'Ulcer Group' of cases

There was a considerable number of cases with 'patches' or 'spots' of exudate, in which, while there were no definite signs of ulceration on admission, evidence suggestive of very superficial ulceration, or of recently healed ulceration, became apparent when the throat became clear of exudate. These cases were not classified in the 'ulcer' group, but in accordance with the characteristics of the exudate present earlier. The reason for this procedure was that it was often very difficult to judge, when the patients were first seen, whether there was definite loss of tissue or not.

Only a relatively small number of cases - eight in all - were classified in the 'ulcer' group. In six of these there was very definite evidence of loss of tissue on admission (the ulceration was assessed as 'moderately deep' in three cases, 'deep' in two, and as 'ulcer post-tonsillectomy' in one). The remaining two cases, in which there was evidence of a minimal degree of ulceration only, were classed in this group because no exudate had been present. The appearances in these different types of cases (except in the 'ulcer post-tonsillectomy' case, in which the/

the area denuded by tonsillectomy had become infected with Streptococcus haemolyticus) are represented by diagrams nos. 39 to 41 (p. 43). In the two cases with 'minimal' ulceration, small irregularly-shaped erosions were situated on one or both tonsils (diagram no. 39 A & B). In the three cases with 'moderately deep' ulceration (diagram no. 40 A & B; and see also the diagrams in table 42, p.215) the bases of the ulcers were ragged and irregular, being more or less fully covered by exudate which, although friable, was adherent basally. Regarding the cases with 'deep' ulceration, in one (described in Chapter IX, p. 207) the cause was tuberculosis, in the other, syphilis (the latter is the case represented by diagram no. 41. In this case the ulcer was clean-cut and free from exudate, but there was also tonsillitis - probably not causally related to the syphilitic lesion - with exudate of follicular distribution; this accounts for the appearances represented in the diagram).

'Scum' group of cases.

In the four cases in this group there was evidence of well-marked pharyngitis and stomatitis. The exudate consisted of a thin film of fragile material covering part of the palate and fauces, in two cases, extending, in parts, as far forwards as the gum margin. The film could easily be stripped off with a swab and was seen to be stringy in consistency, only semi-opaque, probably consisting of altered mucus. It was not adherent to the underlying mucous membrane, and the latter, when exposed, was seen to be normal except for an intense degree of congestion which, in/

in these cases, was widespread over the buccal, palatal, faucial and pharyngeal mucosa. As the exudate was 'sheet-like', it should perhaps have been classed as 'membrane'; but, as it was in other ways quite distinct from membrane (especially with regard to its nature and site), it was considered justifiable to class it apart.

(2) <u>On the classification of the cases in which more than one type of exudate was present, and other observations concerning the exudate</u>.

In each case the throat was examined when the patient was admitted to hospital, and thereafter daily until it became clear of exudate. As stated in the section on 'friable membrane', it was not always possible to determine the consistency of the exudate on admission but, as a rule, this was effected either then or on the following morning (the exceptions to this rule are listed on pp. 52 and 53). There were certain cases in which the exudate, after it had been allocated to its appropriate group, underwent change, so that re-allocation became necessary. The rules adopted for the grouping of these cases are described here. They were also applied to the classification of cases in which two different types of exudate were present at the same time.

If both 'patches' and 'spots' were present in the same case - whether concurrently or successively - the case was classed in the former exudate-group. Within the 'patches' group, 'typically diphtheritic membrane with free edge' took precedence, then 'typically diphtheritic membrane without free edge', next 'tough but loose membrane' and/

and 'intimately adherent membrane', and, lastly, 'friable membrane'. Within the 'spots' group, a case in which there were some discrete spots and others partially coalescing was, as stated previously, classed in the 'semi-confluent spots' group. With regard to 'discrete spots' (when these only were present), 'medium and large spots' took precedence over 'specks'.

The reason for the adoption of these rules was that it was considered to be important to give precedence, for classification purposes, to those appearances which most nearly resembled the typical findings in diphtheria. In fact, although the concurrence of 'spots' and 'patches' was quite commonly encountered, further development of the exudate after a patient's admission to hospital (e.g. from 'spots' to 'patches', or from 'friable membrane' to 'typically diphtheritic membrane') was uncommon. The data concerning the latter occurrence are given in tables 22 and 23 (p. 164).

Other observations recorded were: (1), the day of the patient's stay in hospital when the throat became clear of exudate except for 'spots'; (2), the day when the throat became altogether clear of exudate; (3), whether or not any superficial erosion was seen to be present when the throat became clear of exudate; and (4), the day when any such erosion first appeared to be fully healed.

(3) <u>The degree of hyperaemia (or redness) of the fauces</u>.

The cases were classed, according to the degree/

degree of redness of the fauces, in five groups - as to whether there was (1) no appreciable hyperaemia, or hyperaemia of (2) minimal, (3) slight, (4) moderate or (5) extreme degree. For the purposes of subsequent study, however, 'moderate' and 'extreme' changes were referred to collectively as being 'marked'. With regard to 'minimal' changes, cases were classed as showing these when the only evidence of hyperaemia was the presence of one, or a few, small injected vessels, and there were no other signs of inflammation of the fauces. As this appearance is commonly seen in subjects with no signs or symptoms of throat disease (e.g. in the series of 'normal' school-children), it is certainly of no diagnostic significance, and probably of no pathological significance.

While most often the hyperaemia was at its height on the patients' admission to hospital, it occasionally happened that it became more marked during the following few days. For classification purposes, it was the maximum that was recorded.

(4) The degree of oedema.

It probably often happens in cases of tonsillitis that the only evidence of oedema is a temporary enlargement of the tonsils. But as it is frequently difficult to judge whether this is present or not - particularly when patients are only seen for a relatively short time - patients in the series were seldom regarded as having developed oedema unless the other structures of the throat were also involved. The oedema was classed as being 'slight' or 'moderate' in degree, or, if the signs warranted/

warranted it, as being indicative of peri-tonsillar cellulitis or peri-tonsillar abscess. The diagnosis of peri-tonsillar abscess was only made when there was definite evidence of pus formation. Unfortunately, however, in the earlier part of the work, the distinction between peri-tonsillar cellulitis and peri-tonsillar abscess was not always made clear in the case-notes.

As in the case of hyperaemia, it was the maximal degree of oedema which occurred that was recorded for classification purposes - whether this occurred on the patients' admission to hospital (as was usual) or shortly afterwards.

(5) The occurrence of foetor.

Note was made as to the occurrence of oral foetor, and, if present, whether it appeared to be suggestive of any particular disease or not. Unfortunately, the author's sense of smell was only poorly developed, and, during the earlier part of the work, was not practised in the art of differentiating throat lesions; the findings were therefore not taken into account in the studies carried out subsequently. As the work progressed, however, the opinion was formed that the characteristic foetor, so often found in typical cases of diphtheria, is practically pathognomonic of that disease.

(6) Other observations (about the throat).

Two other abnormalities which were encountered remain to be mentioned. Since they are not characteristic/

characteristic of diphtheria or likely to be confused with the signs of that disease, they are only briefly referred to:-

(a) Keratosis.

There were four cases, in all of which there was considerable hyperaemia of the fauces ('moderate' in degree in three, 'extreme' in one), in which the hyperaemic mucosa, which was intact, was speckled with multiple minute bright white dots. It was considered that the whiteness was not due to the presence of exudate, but was probably caused by a change in the superficial cells of the mucosa whereby they became opaque (hence the choice of the term 'keratosis'). If this is the correct explanation, presumably the eventual return of the mucosa to normal was due to the desquamation of these abnormal cells.

The most frequent sites of keratosis were the anterior pillars of the fauces. In three of the cases, peri-tonsillar cellulitis or abscess was present, and it was the anterior pillar on the affected side - already oedematous and hyperaemic - that was the seat of the keratosis. In the fourth case, there was acute inflammation of the pharynx and mouth (without peri-tonsillar cellulitis), and the keratosis affected the buccal mucosa as well as the pillars.

(b) The occurrence of 'vesicles'.

In nine cases, small flat bullae or vesicles were seen to be present; most often there was only one vesicle in each case, usually situated on one of the anterior pillars. A specially note-worthy case was that of a female child, thirteen months old, in which there were two/

two small round vesicles on the right anterior pillar and vesicles at the angles of the mouth; the throat was clean and only very slightly injected. It seems possible that this was a case of herpetic infection. In the other eight cases, in addition to the presence of a 'vesicle', usually on the anterior pillar, exudative tonsillitis was present and there was considerable hyperaemia, and often oedema, of the fauces, and, in two cases, peri-tonsillar cellulitis. Here it seemed that the primary lesion was the tonsillar infection, and that the exudation if fluid in the form of a vesicle was the result of the hyperaemia of the parts.

(B) The Nose.

The information sought for regarding the nose included whether anterior or posterior nasal discharge was present or not; the features of any discharge present (e.g. whether serous or purulent, or if blood-stained); and whether there was excoriation of the nostrils or upper lip or not.

(C) The Cervical Glands.

The upper cervical glands were examined to detect the presence of enlargement, tenderness, or peri-adenitis.

(a) Enlargement.

Originally an attempt was made to class all cases, according to an arbitrary scale, as to whether the upper cervical glands were 'not palpable', 'only just palpable', or 'very slightly', 'slightly', 'moderately' or 'much' enlarged. In fact, however, it was found that the size of/

of these glands varied very greatly, not only in those suffering from throat disease, but also in others not so suffering: for example, in the series of 50 'normal' school-children, all variations in size up to 'slight' enlargement were commonly encountered. There can be no doubt that, in cases of acute throat disease in which the cervical glands are found to be relatively large, the enlargement is not necessarily attributable to the disease they present, but may be the consequence of previous disease. In view of this difficulty, it was decided, for analytical purposes, to take account only of enlargement which was 'moderate' or 'much' in degree - this is, greater in degree than that which occurred in the 'normal' series. With regard, then, to the definition of the terms used in subsequent chapters, 'moderate enlargement' of the upper cervical glands may be defined as being enlargement of a slightly greater degree than that commonly encountered in apparently healthy city school-children, and 'much enlargement' as being enlargement of a still greater degree. These two degrees of enlargement are referred to collectively as 'considerable enlargement'.

(b) Tenderness.

Cases were grouped as to whether there was judged to be, (i), no appreciable tenderness of the upper cervical lymph glands, (ii), slight tenderness or, (iii), marked tenderness. Included were a small number of cases in which, although the glands could not be clearly palpated, there was tenderness at their site. Unlike enlargement, it/

it appears that tenderness invariably indicates the presence of active disease - thus, for example, it did not occur in any of the 'normal' school-children. In the case of very young children it was, of course, sometimes difficult to assess whether there was tenderness or not.

(c) Peri-adenitis.

In two cases in which the upper cervical glands were considerably enlarged ('moderate' in degree in one, 'much' in the other), the outline of the glands was poorly defined; it was considered that this occurrence was due to presence of peri-glandular oedema, and was indicative of a slight degree of peri-adenitis. In neither case were the appearances suggestive of 'bull-neck'.

(D) The Tongue.

The presence or absence of a 'strawberry' tongue (i.e. reddening and, usually, enlargement of the papillae of the tongue) was noted, positive findings being classified as to whether the changes were 'moderate' or 'very marked' in degree. Although, unfortunately, a distinction was not always made in the records between the 'white' and 'red' appearances, a strong impression was formed that nearly all of the 'strawberry' tongues had been 'white' only, and that the subsequent 'red' stage had but seldom developed. For analytical purposes, a few cases, mostly in adults, in which there had been marked redness of the tongue but no enlargement of the papillae, were also classed as having developed 'strawberry' tongues.

(E) The Ears/

(E) The Ears.

The ear drums were examined in all cases because it was thought that it might be of interest to compare the incidence of middle ear disease (latent or otherwise) in the 'diphtheria' group of cases with the incidence in the other cases - in most of which the cause was probably streptococcal infection. Excluded, however, were a small number of patients, not having symptoms of disease of the ears, in whose case, on account of wax in the meati, the drums could not be seen. The results of these examinations, and the method of classification of the findings, are described in chap. VIII.

(F) Other Sites.

Also noted was the presence of other signs which might tend to confirm the diagnosis of diphtheria or to point to some other diagnosis - for example, signs indicative of laryngeal obstruction or of pulmonary disease, the occurrence of enlargement of the spleen or of lymph glands other than those of the cervical group, and the presence of a rash.

SECTION III.

THE SIGNS OF TOXAEMIA AND TOXIC DAMAGE.

(A) The importance of study of the signs of toxaemia in diagnosis.

While assessment of the degree of toxaemia is obviously of importance in the prognosis and treatment of diphtheria, it is also of some value in the diagnosis of the/

the disease. Thus it is clear that the occurrence of such a characteristic feature as, for example, palatal paresis, during convalescence from an attack of membranous tonsillitis, the nature of which had been uncertain, would point strongly to diphtheria. On the other hand, the absence of complications of that nature would be of less value in diagnosis - as they do not always develop in diphtheria.

For diagnosis, as for prognosis and treatment, it is important to distinguish between those indications of toxaemia which, being relatively 'non-specific', are present in most forms of acute disease of the throat, and those others which are particularly suggestive of diphtheritic toxaemia or of its resultant damage (as an example of the former, pyrexia may be cited, and of the latter, the signs of diphtheritic myocarditis). It is not intended to suggest that there are any toxic complications which, considered by themselves, are pathognomonic of diphtheria (for example, there are other causes of palatal paresis as well as diphtheria) but it is suggested that it is important to distinguish between those effects of diphtheritic toxaemia which are indistinguishable from the effects of the majority of acute infections and those other effects - damage of a particular type to the cardio-vascular, nervous and other systems - which are so much more distinctive. In this work, only those cases of diphtheria in which there developed manifestations indicative of the latter type of damage are classed as having developed the 'toxic complications' of the disease. The term 'febrile/

'febrile toxaemia', on the other hand, is used to describe that febrile disturbance, accompanied by tachécardia and occasionally a slight degree of proteinuria, which is commonly seen in many acute infections, including diphtheria, and is sometimes apparently caused by the toxin of C. diphtheriae.

(B) The method of classification of cases of diphtheria, according to the severity of the toxic damage, described by H. M. Leete.

With regard to the investigations performed to detect the occurrence of toxic damage, and to the method of interpreting the pathological significance of the observations made, the procedure followed in the present study was, to a large extent, that recommended by Leete in 1938. Prior to describing the precise methods used, and the results obtained, the points brought out by Leete are briefly summarised.

While Leete did not claim to describe any new clinical signs, he reviewed certain of the signs occurring in a very large series of cases of diphtheria and discussed their pathological and prognostic significance. He first drew attention to the alteration in the pulse rate which may occur in the disease. In very severe, but not fatal, cases, the initial period of tachécardia is followed by a period, usually of about one to three weeks' duration, of marked bradycardia, this being, in turn, followed by a period when the pulse rate rises. If the figures are charted, a fairly/

fairly characteristic curve is seen, termed by Leete 'cup-shaped'. In less severe cases the decline in the pulse rate is more gradual, the bradycardia is not so extreme, and the subsequent rise in the pulse rate is also more gradual - with the result that the pulse-chart is 'saucer-shaped', not cup-shaped. In cases without evidence of myocardial damage, the initial period of (febrile) tachecardia is usually followed by a return to the normal rate - resulting in an 'L-shaped' curve.

Associated with these changes in the pulse rate are alterations in the character of the heart sounds. The first alteration to occur, and the commonest, is a reduction of the intensity of the first sound. For classification purposes, Leete recommended that the relative intensity of the two sounds should be compared. He considered it important that auscultation should be carried out at the apex and that the listener should attempt to assess only the relative loudness, not the 'quality', of the sounds. If there were difficulty in deciding which sound was the louder, they were to be classed as equally loud. It was suggested that cases should be classed as follows: (1) those in which the first heart sound, throughout the illness, is louder than the second (1st > 2nd); (2) those in which the first sound is normally louder than the second, but in which a phase occurs, usually during the second or third week and during the period of bradycardia, in which the first sound approximates to the second (1st = 2nd); (3) cases similar to the previous/

previous group, but with a phase during which the second sound is louder than the first (2nd > 1st). Leete also referred to the occasional occurrence in healthy subjects, usually children, of a second sound which is louder than the first.

Another manifestation of the damage to the cardio-vascular system described was a fall in the blood pressure occurring at the same time as the bradycardia and diminished loudness of the first sound. That being so, it was considered unnecessary to measure the pressure as a routine, provided that examination of the pulse rate and heart sounds is regularly undertaken.

Proteinuria was mentioned as being another relatively early indication of toxic damage. In mild cases proteinuria is absent except that there may be a trace during the initial febrile stage of the illness; in cases with only a slight degree of toxic damage, it is absent or limited to a period of a few days' duration during the second or third week; in more severe cases, it is present throughout the first two or more weeks.

Leete was of the opinion that provided that none of the above-mentioned changes in the pulse rate, heart sounds, and urine had been detectable during the first three weeks of the illness, it could be stated with confidence that later toxic complications would not occur. It requires to be mentioned, however, that his observations were made during an epidemic of particularly severe diphtheria, and that he was of/

of the opinion that myocardial damage was a more prominent feature in the clinical picture than it usually is; he made the proviso that his conclusions were not necessarily generally applicable. With regard to prognosis and treatment, he suggested the following classification:-

(a) Cases of mild or moderate severity without signs of myocardial damage: pulse chart, 'L-shaped' or flat; relative loudness of the heart sounds, the same throughout (usually '1st > 2nd'); no proteinuria. As post-diphtheritic paralysis does not develop in this type of case (Leete maintained), the patients may be allowed up during the fourth week of the disease.

(b) Cases with slight myocardial damage: inconspicuous or shallow 'saucer' type of pulse chart; a phase in which the heart sounds are '1st = 2nd' or '2nd > 1st'; proteinuria either absent or limited to a few days in the second or third week (frequently at the end of the third week). As paralysis is a possibility, patients should be kept in bed until about the sixth week.

(c) Cases with severe myocardial damage: deep 'cup-shaped' pulse chart; a phase in which the heart sounds are '2nd > 1st', and there may also be extrasystoles or reduplication of the second sound; proteinuria present. If recovery takes place from the myocardial damage, severe paralyses will develop; prolonged rest required.

(d) Cases with fatal myocardial damage: these are usually essentially similar to type (c) above; death, which is due to cardiac arrest, most often occurs during the phase of bradycardia.

(C) Description of the investigations carried out to detect the signs of toxaemia and of its resultant damage.

The observations were recorded under the following headings: (1) general appearance, (2) temperature, (3) cardio-vascular system, (4) urine, (5) paralytic complications.

(1) General Appearance./

(1) General Appearance.

In assessing the 'general appearance' (whether particularly suggestive of toxaemia or not) in each case, an attempt was made to discount any bias which knowledge of the other features of the case (e.g. the state of the throat, the temperature, or the presence of, for example, obstructed breathing) might otherwise produce. Allowing for the great individual variation which exists with regard to such matters as complexion (e.g. whether pallor is present or not) and attitude (whether animated or otherwise), the general appearance was only classed as being indicative of toxaemia if no doubt existed as to its being so. In this respect, it is shown in Appendix tables VI and VII that in only a minority of the cases of diphtheria in which the toxaemia was certainly severe - as judged by the extent of the local lesion and the development of toxic complications - was the general appearance on admission indubitably indicative of this. In only one case (case no. 3 in the tables referred to) was there that marked listlessness, pallor, and prostration described by Ker (1909) as occasionally occurring in severe diphtheria.

(2) Temperature.

The axillary temperature was recorded four-hourly until it became settled, thereafter twice daily. For study to assess the value of the temperature readings in differential diagnosis, the highest temperature recorded in each case was specially noted, as also was the duration of/

of the febrile period. For these special records it was the readings taken during the initial illness that were studied, any subsequent rise, which appeared to be due to a new complication or new infection, being ignored. It was assumed as a general rule that an elevation which occurred after an afebrile period of twenty-four hours' duration or longer was due to a new infection; but there were a small number of exceptions to this rule - cases in which the subsequent rise appeared to be due to the original disease, and was classed as such. On the other hand, an elevation occurring after less than twenty-four hours of normal temperature was normally classed as being due to the original illness even if a new complication (e.g. adenitis) had arisen.

(3) Cardio-vascular System.

The pulse was counted four-hourly for the first week - or for longer if this appeared to be indicated - and thereafter twice daily. On each occasion it was counted for a period of thirty seconds - a routine which materially differs from that recommended by Leete who considered that the period should be a full minute and that the pulse should be re-counted if the rate was more than slightly different from the previous rate.

Auscultation of the heart was carried out at weekly intervals, and more frequently in severe cases and in others in which this was thought to be indicated (e.g. when slowness or irregularity of the pulse was reported). The relative loudness of the sounds at the apex was assessed, and/

and any irregularity of rhythm, or other abnormality, noted. In cases in which the diagnosis of diphtheria was not confirmed, if the patient had not been discharged by the end of his third week in hospital, auscultation was not normally carried out after that time. Similarly, there were certain patients, suffering from mild uncomplicated diphtheria, who were detained in hospital for long periods for various other reasons (e.g. waiting accommodation in a welfare home) in whose case auscultation was stopped after six weeks.

Blood pressure readings were not taken as a routine, but only as an aid to the interpretation of difficult cases, in which they were normally taken weekly.

In the interpretation of the findings relative to the cardio-vascular system, with one exception (case no. 11 in Appendix table VII) the presence of a more or less 'saucer-' or 'cup-shaped' pulse chart was not taken as being indicative of toxic damage to the myocardium unless there was other evidence of toxic damage. Such charts were, in fact, not uncommonly encountered in cases in which the diagnosis of diphtheria had been definitely ruled out. Usually it seemed that the first part of the 'cup' or 'saucer' (the period of tachecardia) could be attributed to the effects of 'febrile toxaemia'; the second part (the period of relative bradycardia) to the normal physiological reaction to recumbency (in this respect it requires to be mentioned that patients not suffering from diphtheria were not allowed to sit up in bed until that diagnosis had been finally excluded/

excluded - often not until nearly a week after their admission, and sometimes longer); and the third part (the period when the rate rose to normal) to the physiological reaction to increased activity.

The findings in those cases in which toxic complications were considered to have developed are shown in Appendix table VII, from which it may be seen that myocardial damage was not so much in evidence as it was in Leete's series; there were several cases in which proteinuria and paresis occurred but in which signs of damage to the cardio-vascular system were inconclusive or absent.

(4) The Urine.

The urine was examined for protein on the day after each patient's admission to hospital and thereafter weekly, or more often in severe cases. The examination was carried out by the sister or staff nurse of each ward by the heat test (University Standing Committee, 1944). If more than a 'trace' of protein was found to be present (a 'trace' being defined as an amount so small that the observer knew, as a result of previous experience, that a reading would not be obtained by Esbach's method), an Esbach tube was set up.

Owing to the interval between each examination, and as the work was carried out by several different persons, it was thought possible that the results might not be as accurate as was desirable. For several reasons, however, it is considered most probable that errors were not common. Thus, in the earlier cases the writer personally/

personally corroborated many of the results (both 'positive' and 'negative' for protein), especially when they appeared to conflict with the other observations. In almost all cases his findings were in agreement with those reported. Latterly, as a further check, he independently examined specimens from each patient twice a week; this also confirmed that the tests were, on the whole, being conducted competently by the nursing staff.

(5) Paralytic Complications.

(a) Palatal paresis.

As is shown in Appendix table VII, the commonest form of paresis to occur was that affecting the palatal muscles. The mechanism and diagnosis of this condition are discussed in the standard text-books and in an article by Maher (1948), and are only briefly referred to here.

In the present series of cases, no particular search for the condition was made, as a general rule, provided that the patient's voice, in ordinary conversation, was observed to be normal and that no regurgitation (of fluids through the nose on attempting to swallow) occurred. In some cases the well-known test phrases quoted by Ker (1909) were used. The palate was inspected to confirm the presence of paresis; in most cases the appearances left no room for doubt, the palate being seen to be asymmetrical, or to fail to contract on stimulation. In two cases, however, in which a typical nasal tone/

tone developed, and in one case regurgitation also (this case is no. 8 in Appendix table VII, the other no. 7), it was scarcely possible to be certain, on inspection of the throat, that paresis was present: for the palate was seen to be symmetrical and to contract to a moderate extent on stimulation. The reasons why it was concluded that a degree of paresis was present were that in both cases the attack of diphtheria had been moderately severe, such that the possibility of complications had been anticipated, and that the nasal tone (and regurgitation) was quite typical, had developed at the expected time in convalescence, and in due course cleared up completely. (The difficulty experienced in confirming the presence of paresis on inspection is probably attributable to the fact that there is considerable individual variation in the shape and movements of the palate; so that it is difficult to be sure that an abnormality is present unless it is pronounced in degree, or involves one side more than the other.)

Difficulty is not likely to be encountered in the case of those children who normally speak with a nasal intonation, for this abnormality is likely to be observed on their admission to hospital. There was one similar case, however, in which considerable difficulty arose, which is therefore thought to be note-worthy. This was the case of a boy, aged 14 years, whose speech did seem to be abnormal on admission (although his mother stated at that time that he occasionally 'spoke through his nose') but who, when/

when convalescent from a mild attack of diphtheria, habitually spoke with a typical nasal tone when asked to repeat the test phrases and at other times when he realised that he was being observed by the staff. On account, however, of the complete absence of signs of toxaemia (apart from a slight degree of pyrexia on admission) and of signs suggestive of palatal or other paresis, and of the observation that he spoke quite normally to his fellow patients when he did not realise that he was being overheard by the staff, it was concluded that paresis was not present. In view of the above-mentioned and other circumstances of the case, it was considered that the condition was hysterical in nature.

(b) Loss of tendon reflexes.

Loss of the tendon reflexes is described as being a not uncommon occurrence after severe diphtheria. That this was only rarely encountered in the present series of cases (in 4 out of the 76 cases of diphtheria; cases no. 2, 3, 5, and 6 in Appendix tables VI and VII) is perhaps not surprising in view of the comparative mildness of the disease at the time. On the other hand it must be admitted that the reflexes were not tested in all cases. Since, however, they were tested in all severe cases, and in any others in which difficulty in walking was noted during convalescence, it is probable that few cases were overlooked in which the reflexes would have been found to be absent if they had been tested. In most of the tested cases, only the quadriceps reflexes were studied.

There was no evidence of loss of power of the limb muscles in any case, nor were the plantar reflexes ever found to be absent or abnormal (the latter were tested when the quadriceps reflexes were found to be absent, and in several other relatively severe cases).

In the four cases in which loss of the quadriceps reflexes did occur, this persisted for long periods, the reflexes still being absent when the patients were discharged from hospital.

(c) Multiple pareses.

The muscles affected in the case classed as having developed multiple pareses (case no. 2 in Appendix table no. VII) were the right external rectus, and the palatine and pharyngeal muscles. The diaphragm was also affected for a few days, and there was persistent loss of the tendon reflexes.

(d) Paralysis of accommodation.

Paralysis of the ciliary muscles is described as being one of the commonest complications of diphtheria. Although no symptoms suggestive of this condition were complained of, they may, of course, have been present unrecognised, particularly in the case of the younger patients.

(D) Interpretation of the results of the investigations: Classification of the cases in which toxic complications developed.

In each case, the data relevant to the degree of toxaemia were reviewed and summarised. For this review/

review it was found to be helpful to record the following information diagrammatically: the pulse and temperature readings, the relative loudness of the heart sounds, the blood pressure, the presence or absence of proteinuria, the occurrence of paresis, and any other relevant observations. The method of recording was essentially similar to that used by Leete. The official hospital records were used for the purpose, the pulse and temperature having already been charted by the nursing staff, the other data being added subsequently. It was found that study of these composite charts facilitated the interpretation of the various observations - making it easier to decide whether a given feature (for example, the occurrence of proteinuria at a certain stage in the illness) could be accepted as being a manifestation of the relatively non-specific febrile type of toxaemia, whether it should be taken as a sign of the more specific damage produced by the toxin of C. diphtheriae, or whether it appeared to be attributable to some other factor.

Certain particulars of the cases of diphtheria in which toxic complications were judged to have occurred (including four cases in which there was some doubt about this) are shown in Appendix tables VII and VII. In all of these cases the diagnosis of diphtheria had been made as a result of the clinical and bacteriological observations made during the acute stage of the illness - that is, in none of the cases originally considered not to be diphtheritic was it necessary to change the diagnosis on account of the subsequent/

subsequent occurrence of signs of, for example, diphtheritic myocarditis or paralysis.

It will be recollected that Leete's system of classification of cases of diphtheria was based principally on the degree of myocardial damage - as to whether this appeared to be absent, slight, severe, or fatal. As myocardial damage was a much less prominent feature in the present series of cases, such a system of classification was difficult to apply. Instead, the cases in which toxic complications were considered to have developed were arbitrarily grouped as follows:-

(a) With a fatal degree of toxic damage: 1 case (no. 1 in Appendix tables VI and VII). The patient was severely toxic on admission. The pulse was rapid at first, later very slow (half 'cup-shaped' curve) with concomitant changes in the heart sounds; heavy proteinuria. Death occurred from cardiac arrest during the phase of bradycardia.

(b) With a severe degree of toxic damage: 2 cases (nos. 2 and 3). The relevant features were evidence of marked toxaemia on admission, heavy proteinuria for several weeks, and signs of myocardial damage and, later, of paralysis.

(c) With a moderate degree of toxic damage: 8 cases (nos. 4 to 11). The general appearance of the patients on admission was not particularly suggestive of toxaemia. Except in two cases, two of the following triad of features developed: proteinuria for two or more weeks, myocardial damage, paralysis. Regarding the two exceptions, in one (case no. 7) all three features developed (the main reason why this case was not classed in the 'severe' toxic-damage group was that there was only a slight degree of proteinuria), in the other (case no. 11) signs of myocardial damage only.

(d) Probably with a slight degree of toxic damage: 4 cases (nos. 12 to 15). The only indication of toxaemia, apart from the initial febrile disturbance, was the occurrence of a relatively slight degree of proteinuria during the first two (in one case, three)/

three) weeks of the illness. As no other explanation for this abnormality could be discovered, it was considered that it probably was an effect of diphtheritic toxaemia. In three of the cases 'typically diphtheritic membrane' was present, but in the fourth (case no. 15) there were only signs of a very mild catarrhal pharyngitis, no exudate being present (in this case the illness seemed - apart from the presence of proteinuria - to be exceedingly mild; the patient was playing in the streets, apparently well, when the ambulance called for him three days after the onset of his symptoms).

Apart from the details of the above-mentioned cases shown in Appendix tables VI and VII, they and the other cases of diphtheria in the series are reviewed in Chapter VI.

To conclude this section, it is appropriate to consider whether or not Leete's statement - that toxic complications do not develop in diphtheria if signs of damage are found to be absent during the first three weeks of the disease - was borne out in the series of cases studied. It may be seen from Appendix table VII that the statement was, in fact, found to be valid provided that it is realised that, in certain cases, the only early sign of damage may be the occurrence of (other than febrile) proteinuria. (It is also shown in the table that such proteinuria was present in all but one of the fifteen cases in which toxic complications definitely or probably occurred; in the opinion of the writer, this is one of the most sensitive indications of toxic damage, and careful examination of the urine - preferably at least twice weekly - is of great importance in all cases of diphtheria.)

SECTION IV.

BACTERIOLOGICAL METHODS/

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BACTERIOLOGICAL METHODS.

The bacteriological investigations which were carried out in all suspected diphtheria admissions during the year commencing 1st October 1947 were outlined in the previous chapter. Here a description is given of the method of investigation of the 'main series' of cases (the series which forms the principal basis of the paper) and also of the two control series - the 'scarlet fever' and 'normal' series. The section is divided into eight parts in which the following matters are dealt with:-

(1) Number of swabs taken and method of swabbing.
(2) Cultural methods.
(3) Criteria for the identification of organisms.
(4) Method of assessing the number of colonies of each type present on the blood agar plates.
(5) The examination for Vincent's organisms.
(6) Notes on cases in which the full bacteriological investigations were not carried out.
(7) On the effect which treatment may have had on the bacteriological results.
(8) The bacteriological investigation of the 'scarlet fever' and 'normal' series of cases.

(1) Number of swabs taken and method of swabbing.

For reasons discussed in Chapter II, it was considered to be much more important to examine thoroughly a relatively small number of swabs than to take a large number/

number but only to inoculate them on one type of medium. In each case, a throat swab (and swab of other site if indicated), taken shortly after the patient's admission, was used to inoculate the three types of media used (these are described below), and an additional swab was taken the following morning and sent without delay to Dr. Carter's laboratory. If diphtheria was thought to be the diagnosis, one or more further swabs were sent to both laboratories (for Dr. Carter and the author) and submitted to the same intensive examination (unless the provisional examination of the growth from the first swab after one day's incubation showed the presence of C. diphtheriae). Apart from the foregoing procedure, to conform with the hospital ruling at the time, at least three throat and nose swabs were taken on consecutive days and inoculated on Loeffler's medium.

The swabs were taken in accordance with the methods recommended by a Committee of the London County Council (1936). When taking the throat swab, an attempt was made to remove some of the exudate (and at the same time to 'test' its consistency - see Section II of this chapter); or, if there was no exudate, the surface of both tonsils, the fauces, and the posterior pharyngeal wall were swabbed. The nose swab was passed as far back as possible in both sides.

(2) Cultural methods.

The media used were (1) a modification of Loeffler's serum medium (100% ox serum) inspissated in the form of slopes, (2) blood tellurite agar plates (the type/

type used was Young's modification of Neill's medium, as described by Mackie and McCartney, 1942), and (3) 5% horse blood agar plates. As a routine, the Loeffler slope was inoculated first, then the blood agar plate, and finally the tellurite. For "spreading" the inoculum on the plates, a technique was elaborated which almost always ensured that the colonies were well separated on at least part of each plate. This technique had the disadvantage that it was difficult to assess the number of colonies present (since the density of growth varied on different parts of each plate) but had the advantage of facilitating the study of individual colonies.

The Loeffler slopes were examined after approximately 12-24 hours' incubation, smears being made and stained by Neisser's method. Those slopes in which organisms morphologically resembling C. diphtheriae appeared to be present were kept aside pending the results of the other investigations, the remainder being discarded.

The blood agar plates were examined after approximately 18-24 hours' incubation. Several of each of the predominant types of colonies present were picked off and examined microscopically (stained by Gram's method); particular attention was paid to any colony (however scanty) which resembled C. diphtheriae, Streptococcus haemolyticus, or Staphlococcus aureus. The degree of haemolysis (if any) produced by the various colonies was assessed and graded as follows: as being 'complete' in degree if the colony was/

was surrounded by a relatively wide, clearly defined, colourless zone; or as being 'partial' if there was a narrow zone of more or less incomplete clearness, or a zone of yellowish or greenish discolouration. The degree of haemolysis having been thus assessed, the plates were kept at room temperature for a further 24 hours and then re-examined. In fact, however, it was found that the findings at this second examination did not materially differ from those at the first except that in one case, in which the haemolysis had originally been of doubtful degree, the degree was later seen to be definitely 'complete'. If any doubt remained as to whether a colony should be regarded as being 'completely' or 'partially' haemolytic, it was classed as being the latter; but difficulties in this respect were relatively rare - borderline instances seldom being encountered. It incidentally requires to be stated that in the remainder of this work the term 'haemolytic', as applied to a strain of an organism, implies 'complete' haemolysis unless otherwise qualified.

The tellurite plates were examined after 42-48 hours' incubation. At the beginning of the work, one or more of every type of black colony present on each plate were examined microscopically (stained by Neisser's method or, latterly, Pugh's wet method). Latterly, those colonies which were found to have that characteristic tenacious consistency which, as previous experience had shown, only occurs with colonies of cocci, were not microscopically/

microscopically examined. If the microscopic examination showed that the organisms were cocci, they were not further investigated. Colonies found to be of bacilli were sub-cultured to Loeffler's medium and re-examined after 24 hours' incubation.

(3) Criteria for the identification of organisms.

(a) C. diphtheriae.

As stated in Chapter III, Dr. H. S. Carter was the final arbiter as to the identity of suspected strains of C. diphtheriae. Any such strain isolated in a case in which his investigations had given negative results was sent to him for confirmation of its identity.

(b) Streptococcus haemolyticus.

The criteria for the identification of this organism were (1) the presence of 'complete' haemolysis around the colonies, and (2) that the organisms, as judged by the examination of several representative colonies, were seen to be Gram-positive cocci with a tendency to chain formation. Study of the appearance of the colonies was also helpful - several different types of colony-form being recognised. If there was doubt as to chain formation - as was not uncommonly the case - subcultures were made to glucose broth, in which medium it was found that long chains were formed in all the cases in which subculture was performed.

(c) Staphlococcus aureus.

Typical colonial and microscopic appearances were taken as the criteria for the identification of this/

this organism. Coagulase tests were not performed.

(d) Other organisms.

Apart from those referred to above, various other organisms, e.g. pneumococci, have occasionally been implicated in the pathogenesis of tonsillitis. On account of this, the decision was made to investigate each type of colony present in relatively large numbers in the blood agar plates. Unfortunately, however, it was only found possible to carry out the most elementary investigations - in particular, study of the colony-form on blood agar and of the microscopic appearances when stained by Gram's method.

Among the strains most frequently encountered were those which resembled Neisseria, Streptococcus viridans, and Pneumococcus. For the purposes of analysis, however, as it was found to be scarcely possible, within the limitations of the methods adopted, to differentiate between the two last-mentioned organisms, such differentiation was not attempted, and both organisms were classed together to form the 'S. viridans/pneumococcus' group. Strains were less frequently encountered which resembled the following organisms: Haemophilus influenzae (this group was classified according to the degree of haemolysis produced on blood agar - fully, partially, and non-haemolytic strains all having been seen), Staphlococcus albus, Micrococcus tetragenous, C. Hofmanni (most often recognised on tellurite, but also on blood agar; in addition to study of the colony-form, the morphological appearances after subculture to Loeffler's medium, and the/

the sugar reactions were used in the identification of this organism), yeasts (identified both on blood agar and tellurite), and non-haemolytic streptococci.

Comment on the identification of Vincent's organisms follows later in this section, in part (5).

(4) Method of assessing the number of colonies of each type present on the blood agar plates.

It was previously explained that the method of plating out the inoculum was such that the density of the growth varied in different parts of each plate and that this method had the effect of making it difficult to assess the numbers of each type of colony present. In practice the colonies were counted in that part of the plate in which the growth was of moderate density, by which means an approximate estimate was made of the totals. These totals were notated as follows: if there were estimated to be 1-10 colonies of a particular strain per plate, the colonies were classed as being '1 plus'; if 11-40 colonies, '2 plus'; if 40-80, '3 plus'; if 80-160, '4 plus'; if over 160 colonies per plate, '5 plus'.

(5) The examination for Vincent's organisms.

A direct film was made in each case in which there was exudate of any kind in the throat. The films, which were stained either by Gram's method or by dilute carbol fuchsin, were examined for the presence of fusiform organisms and spirochaetes. The object of this was not only to detect cases of Vincent's angina, but also to review the diagnostic/

diagnostic criteria of that disease. For both types of organisms the following system of classification and notation was used: '0', to denote that none of the particular type was seen during a very thorough search; '1 plus', to denote that not more than approximately 10 organisms were seen during such a search; '2 plus', to denote that the organisms were fairly numerous, and '3 plus', very numerous.

(6) Notes on cases in which the full bacteriological investigations were not carried out.

During the early part of this work, owing to the inexperience of the observer, it was not found possible to carry out in full the bacteriological investigations described above. This being so, effort was, at that time, mainly concentrated on the examination for C. diphtheriae, it being found necessary to postpone temporarily the full search for other organisms. With regard to the results of the examination for Streptococcus haemolyticus, the following cases were excluded: nos. 1-50 and 110-132. The reason for the exclusion of the latter group is that during that part of the work recurrent batches of blood agar medium were unsatisfactory. These two series of cases make up what is described subsequently as the 'incompletely investigated' group. The investigations to detect the presence of other organisms (Staphlococcus aureus, Streptococcus viridans, Pneumococcus, Neisseria, etc.) were fully carried out, by the method described, in the last 180 cases of the series only, (nos. 134-313); the results relative to these organisms in/

in the first 133 cases were therefore discounted.

(7) On the effect which treatment may have had on the bacteriological results.

The administration of penicillin or sulphonamides, and the local application of any antiseptic were postponed until at least the first swabs had been taken - lest such treatment might affect the bacteriological findings.

Inquiry was made about any treatment received by patients before their admission to hospital. It is probable that systemic penicillin in large doses would be the form of therapy most liable to affect the findings (Long, 1947 a and b); however it appeared that penicillin had been given parenterally in only 4 of the 313 cases, and it seemed very unlikely that it had had any significant effect on the results (in one case 1,600,000 units had been given, but in spite of that both C. diphtheriae and Streptococcus haemolyticus were isolated on culture; the most given in any of the other three cases was 400,000 units). Similarly, although penicillin lozenges or sulphonamides had been given to a number of patients, the dosage was, in most cases, very small and the evidence seemed to suggest that it had not affected the bacteriological findings.

(Since this work was carried out, however, there has developed a much greater tendency on the part of practitioners to administer large doses of penicillin, and the possible effect of this on the bacteriological diagnosis of diphtheria must be borne in mind.)

(8) The/

(8) The bacteriological investigation of the 'normal' and 'scarlet fever' series of cases.

A throat and nose swab were taken in each of the cases in these series and were investigated as described above. Swabs were not sent to Dr. Carter.

SECTION V.

IMMUNOLOGICAL AND OTHER INVESTIGATIONS.

(A) Immunological Investigations.

The information sought for bearing on the state of immunity of the patients to diphtheria is described under the following headings: (1), History of inoculation; (2), Shick test; (3), Previous history.

(1) History of Inoculation.

A note was made as to whether inoculation had been performed and, if so, where, when, and how often. In most of the inoculated cases two injections of A.P.T. had been given at a month's interval. Cases were primarily grouped as follows:-

(a) Fully inoculated (the criterion being a history of two or more injections of toxoid at approximately a month's interval).

(b) Fully and re-inoculated (as for 'fully', but with also a history of a 'boosting' dose having been given after an interval of some years).

(c) Said to have been inoculated but details not available.

(d) Partially inoculated (cases in which, for one reason or another, only one injection had been given).

(e) Very recently inoculated (this group consisted of three cases - two being carriers of C. diphtheriae and the third a case of non-diphtheritic tonsillitis - in/

in which inoculation had been performed only a few weeks before the patient's admission to hospital.

(f) Not inoculated.

For the purposes of further study, however, as this classification was found to be unworkable, the cases were divided into two groups only - as to whether there was a history of inoculation (complete, and fully documented, or otherwise) or not. Owing to the relatively small number of cases in the series, it was scarcely possible to test the validity of this procedure; but it may be mentioned that a Committee of the Department of Health for Scotland (1948) concluded that it was justifiable, in their series, to regard any patient with a history of inoculation as being inoculated. The large majority of the cases in the 'inoculated' group - whether cases of diphtheria or not - had apparently been 'fully' inoculated, those in the 'partially' and 'very recently' groups, in particular, being very few in number.

(2) The Shick Test.

Circumstances permitting, patients were submitted to this test on their admission to hospital, the administration of anti-diphtheritic serum then being postponed for at least a further three hours. Patients not so tested were those in whose case this delay in treatment did not seem to be justifiable, and others admitted to hospital at such a time that it was not possible for the author to carry out the test himself.

The test was carried out by the standard method,/

method, approximately 0.2 c.cs. of test solution (the quantity was judged by the size of the resultant wheal) being injected intradermally into one forearm, and the same amount of control solution into the other. Observations of the results were made daily or, in certain cases, every second day, until at least the sixth day. For classification purposes, 'pseudo-negative' results were grouped with 'negative', and 'pseudo-positive' with 'positive'. There was a small number of cases in which only a minute area of erythema developed on the test arm (less than approximately 5 m.ms. in diameter); in accordance with the recommendation of O'Brien (1929), this result was classed as negative.

With regard to the interval between the performance of the test and the subsequent administration of serum, this was usually of either 3, 6, or 12 hours' duration; it was never less than 3 hours. It was found that the length of this interval did not seem to affect the proportion of positive results. None the less, as Harries and Mitman stated in 1951 that with the modern highly refined serum an interval of 12 hours is necessary, a detailed study was made of the present results, as also of the work of Mayfield (1934) on the subject.

Mayfield first studied the effect of various intervals of time - between performing the test and the subsequent intramuscular injection of antitoxin - in definite cases of diphtheria - in which he assumed the result should be positive. He found that the result was positive in 24 (86%)/

(86%) of 28 cases in which the test was performed immediately before the administration of antitoxin, and in all of 42 and 16 cases in which the interval was of one and two hours' duration respectively. But in other experiments, in which the test was performed twice in the same patients, two hours, and then one hour, before giving antitoxin intramuscularly, he observed that the one-hour test was negative in one (only) of 49 cases in which the two-hour test was positive, and that in a number of other cases the positive reaction to the one-hour test was less well-marked than the reaction to the two-hour test. He thus concluded that, with an interval of one hour, the test, although subject to some extent to the nullifying effect of the injected antitoxin, yet possesses a high degree of reliability; and that, with an interval of two hours, it can be assumed that the antitoxin does not interfere with the test. As regards the intravenous injection of antitoxin, he tested 14 definite cases of diphtheria one hour before, and again immediately before, giving this treatment: the result was positive in ten of the one-hour tests, but in only one of the immediate tests.

In view of Mayfield's observations - perhaps particularly those on the effect of intravenous injection of antitoxin on the test - it would seem probable that an interval of three hours should be sufficient to give a reliable result - no matter how rapidly absorbed the modern antitoxin may be, nor even if it is given intravenously - as it often was in the present series. As may be seen from table 1, it was found in the present series that the/

the proportion of positive results, both in the diphtheria cases and the others, was approximately the same whether the interval was of three hours' duration or longer. It was also found that while particularly marked positive reactions were relatively frequent in the diphtheria cases, the length of the interval between test and serum did not appear to have any bearing on their incidence. Admittedly the significance of the data shown in the table is limited, in view of the fact that the cases in the various time-interval groups are not strictly comparable with regard to a number of factors - e.g., age, history of inoculation, and, in the diphtheria cases, the severity of the disease - which may affect the result of the test. The claim that the results were uninfluenced by the subsequent administration of antitoxin is thus based primarily on Mayfield's observations, and only secondarily on the results tabulated.

Table 1. Shick test results in relation to the time-interval between the performance of the test and the subsequent administration of antitoxin (all cases except those in the 'no apparent disease' group).

Final Diagnosis		Time Interval (Hours)					
		3	-6	-12	>12	No serum	Total
Diphtheria	No. Tested	16	27	4	0	1	48
	No. Positive	6	9	1		1	17
	% Positive	37%	33%	25%		100%	35.4%
Other than diphtheria	No. Tested	13	117	45	9	11	195
	No. Positive	2	16	6	2	1	27
	% Positive	15%	14%	13%	22%	9%	13.8%
All cases	No. Tested	29	144	49	9	12	243
	No. Positive	8	25	7	2	2	44
	% Positive	28%	17%	14%	22%	17%	18.1%

(3) Previous History.

The knowledge that a patient had previously suffered from diphtheria would be relevant to the/

the immunological history of the case. It was not uncommonly found, however, that such a history was not confirmed by the official records (thus patients who had been admitted to a diphtheria ward but had not been found to be suffering from that disease were sometimes unaware of the change of diagnosis).

(B) Other Investigations.

The leucocyte count, the Paul-Bunnell reaction, and the Wassermann reaction may be cited as examples of other tests which may be required in the elucidation of the diagnosis in suspected cases of diphtheria. Such tests were carried out when this seemed to be indicated.

SECTION VI.

METHOD OF CLASSIFICATION.

The method of classification of the 'main series' of cases used for analytical purposes was partly described in the preceding chapter. It will be recollected that the cases were divided into four main groups: the '*diphtheria*' group (in all of which a strain of C. diphtheriae, proved or assumed to be virulent*, was isolated from a site which was the seat of an inflammatory lesion); the group of '*carriers*' (in which a virulent strain was isolated from a healthy site); the '*non-virulent*' group (in which a non-virulent strain of C. diphtheriae was isolated); and the '*negative*' group (in/

*As explained on p. 29 , there is reason to believe that all, or practically all, of the strains assumed to be virulent were so.

(in which the bacteriological results were negative for C. diphtheriae). None of the cases in the last three groups was considered to be an instance of diphtheria.

A further method of classification applied depended on the site of the disease (if disease was present), the cases being grouped as follows: in the 'throat' group, if the throat was affected, with or without other sites; in the 'nasal etc.' group, if the throat was not affected, but there was disease elsewhere; or in the 'no apparent disease' group, if there was no clinical evidence of disease (this group consisted of carriers and others admitted as such in whose case that diagnosis was not confirmed).

The result of applying both the methods described above and of taking into consideration a number of other factors is shown in Appendix table II. While most of the various groups and sub-groups in that table are self-explanatory, some require further comment or definition:-

Groups (B), I and (C), I: 'Diphtheria' cases.

While in many of the cases in these groups the typical signs of the disease were present, in others this was not so; it is possible that some may have been carriers suffering from other disease (e.g. streptococcal tonsillitis). This question, and the reason why it was decided to class them all as cases of diphtheria, are considered in the following chapter.

Group (C), II, 1: 'Non-virulent' ('throat') group.

It has recently been suggested in the literature/

literature that infection with a non-virulent strain of C. diphtheriae is a possible cause of diphtheria. This subject in general, and the features of the 'non-virulent' cases of the present series in particular, are discussed in Chapter VII.

Group (C), II, 2 (a): 'Miscellaneous' ('throat') group.

Classified in this group were five cases, one of tuberculous ulceration of the fauces, one of glandular fever, and three of measles.

Comment follows below on certain other cases which might have been included in this group, but were not, and on the reasons for their exclusion:-

(a) Vincent's angina.

The subject of Vincent's angina is discussed in Chapter IX where it is explained that there were three cases with the characteristic signs of that condition, and many cases of diphtheria and other forms of throat disease in which the clinical picture may have been complicated to a minor extent by the action of Vincent's organisms. As, however, there was evidence of infection with Streptococcus haemolyticus in all of the three cases mentioned, and as it was considered probable that that infection had been as much responsible for the pathogenesis of the lesions as the infection with Vincent's organisms, it was decided to class the cases primarily in the 'streptococcal' group (see below), not in the 'miscellaneous' group.

(b) Syphilitic ulceration.

One case of syphilitic ulceration of the palate occurred in the series. The ulcer was deep, clean-cut, and free from exudate (see diagram no. 41, p. 43); it was apparently of several months' duration. The typical signs of follicular tonsillitis were also present; it seemed that it was the subsequent development of this condition that had aroused suspicion as to the possibility of diphtheria. The syphilitic lesion being thus regarded as coincidental, the case was classed according to the findings/

findings relative to the attack of tonsillitis - that is, in the 'non-virulent' group (for a non-virulent strain of C. diphtheriae was found to be present).

(c) Brain abscess.

One case in the series was of brain abscess. There was also a severe degree of stomatitis and pharyngitis, which had led to suspicion as to the possibility of diphtheria. It was apparent that the condition of the throat and mouth was purely secondary to the very severe febrile and toxic state of the patient. After some hesitation, it was decided - for the reason that the infective agent, if any, associated with the condition of the mouth, had not been determined - to class the case in the 'unknown cause' group (see below), not the 'miscellaneous' group.

(d) Post-tonsillectomy sloughs.

Since in the only case of post-tonsillectomy sloughs in the series there was evidence of severe streptococcal infection (of the area exposed by the operation), and as it appeared that it was the occurrence of this infection that had resulted in the patient's admission to hospital, it was decided to classify the case in the 'streptococcal' group.

Group (C), II,2 (b): 'Incompletely investigated' group

Group (C), II, 2 (c): 'Streptococcal' group.

Group (C), II, 2 (d): 'Unknown cause' group.

All 'throat' cases not classified in the categories previously mentioned (the 'diphtheria', 'non-virulent', and 'miscellaneous' groups) were apportioned to the groups listed above, as follows: to the 'incompletely investigated' group, those in the two series in which the findings as to Streptococcus haemolyticus (H.S.) were not considered to be reliable and were discounted (see p.94); to the 'streptococcal' group, those with '2 plus' or more colonies of H.S. (93 cases), those with only '1 plus' colonies of H.S., in which peritonsillar cellulitis had been present (2 cases), and those/

those with '1 plus' or no colonies of the organism but with scarlet fever (there were 2 of the former and 1 of the latter); and to the 'unknown cause' group, the remainder of the cases (in 7 of which there were '1 plus' colonies of H.S., in the remaining 29, none).

The main criterion for the admission of a case to the streptococcal group - that, except in special circumstances, more than 10 colonies of H.S. were isolated on culture - was chosen after consideration of the findings in the 'normal' and 'scarlet fever' series and of the work of Dingle et al. (1944).

It was considered that the findings as to H.S. in the 'normal' series could be taken as giving an approximate estimate of the carrier-rate in Glasgow children at the time; and that the findings in the 'scarlet fever' series could be taken as being indicative of the results to be expected when known streptococcal cases were investigated by the methods employed. It is apparent from Appendix table VIII that if a growth of '2 plus' or more colonies of H.S. were taken as the bacteriological criterion for the diagnosis of streptococcal disease, 9 (18%) of the 'normal' series would have been regarded as being streptococcal, and 5 (10%) of the 'scarlet fever' series as being non-streptococcal; but it is also apparent that if any other criterion were chosen - say, a '1 plus' or '3 plus' growth of H.S. - the error would have been very much greater.

Dingle et al., who, in their study of exudative/

exudative tonsillitis, insisted on serological confirmation of a diagnosis of streptococcal disease, concluded that there were no infallible clinical or bacteriological (or, for that matter, serological) criteria on which the diagnosis could be based with absolute certainty, but that if the growth of H.S. were relatively profuse, the diagnosis was likely to be streptococcal disease.

In view of what has been stated above, it is certainly not claimed that all of the 'streptococcal' cases were indeed instances of that infection and that none of the 'unknown cause' cases were; but it is claimed that a large proportion of the former group were actually streptococcal, and probably only a small proportion of the latter group. The validity of this claim is further considered in Chapter IX.

CHAPTER V.

COMMENTARY ON THE DEFINITION OF DIPHTHERIA ADOPTED FOR CLASSIFICATION PURPOSES.

SECTION I.

OBSERVATIONS ON CERTAIN FACTORS WHICH MIGHT HAVE BEEN, BUT WERE NOT, USED TO DIFFERENTIATE BETWEEN MILD DIPHTHERIA AND OTHER DISEASE OCCURRING IN A CARRIER.

It will be recollected that cases were classed as being instances of diphtheria if C. diphtheriae of virulent strain was isolated from a site (usually the throat) which was the seat of an inflammatory lesion. The possibility was referred to that some of the cases may in fact have been carriers of C. diphtheriae suffering from other (non-diphtheritic) disease. It had been intended to divide the cases into two groups - to separate those which seemed to have been instances of non-diphtheritic disease in carriers from those which appeared to have been definite cases of the disease. In effect, however, it was found that, as the boundary between the two conditions is so extremely tenuous, the differentiation would have had to be based on the most arbitrary grounds. As a result of this it was reluctantly concluded that it would be less misleading to class all the cases as having been instances of diphtheria, even although a proportion - the size of which is debatable but probably small - may not have been. The most important factors on which the differentiation might have been based are these:-

(1) The type of exudate present.

(2) The site of the exudate.

(3) The occurrence of toxic complications.

(4) The/

(4) The Shick test results.

(5) The available epidemiological information.

(6) Evidence of other (non-diphtheritic) disease.

Comment follows below on the findings with regard to these factors, partly to explain why the differentiation (between diphtheria and other disease in carriers) was not carried out, and partly to enable an approximate assessment to be made as to what proportion of the cases were really instances of diphtheria.

(1) Type of Exudate Present.

The type of exudate (if any) present in the 290 'throat' cases (cases in which the throat was involved) is shown in Appendix table IV, from which it may be seen that the only type to occur only in the 'diphtheria' group of cases (those in which C. diphtheriae of virulent strain was isolated) was 'typically diphtheritic membrane'. In view of this and of the characteristic features of such membrane, there seems little doubt that the 33 cases in which it was present were indeed cases of the disease. With regard to the 'diphtheria' cases with other types of exudate the position is less certain: for, as similar exudate also occurred in the 'other than diphtheria' cases, it is at least theoretically possible that some may have been instances of other disease and that the strain of C. diphtheriae isolated was not causally related to the lesion present. None the less, the probability that the diagnosis was correct would seem to be high in all those cases in which 'membrane' of any type was present; apart from/

from those with 'typically diphtheritic membrane', this would seem to apply particularly to the three cases with 'tough but loose membrane' and to the one with 'intimately adherent membrane' - but to a less extent to the five with 'friable membrane'. Other cases in the 'diphtheria' group in which the exudate, while not typical, was suggestive of the disease were one in the 'semi-confluent spots' group and four in the 'discrete spots' group in which the exudate was tough and possibly, but not definitely, 'sheet-like' (that is, 'membranous'); these cases are classed in Appendix table IV in groups B(a), C I(a), C I (b), and C III (in the case in the 'semi-confluent spots' group there was further evidence for the diagnosis of diphtheria in that signs of myocardial damage appeared; further details are given in Appendix tables VI and VII in which the case is no. 11).

(2) The Site of the Exudate.

The occurrence of confluent exudate which has spread beyond the tonsils in a case in which a virulent strain of C. diphtheriae has been isolated could be taken as giving very strong confirmatory evidence to the diagnosis of diphtheria. This feature, however, only occurred in cases in which there was 'typically diphtheritic membrane' - in which, therefore, there was already strong support for the diagnosis.

Another feature supporting the diagnosis in otherwise doubtful cases is the occurrence of croup in addition to a throat lesion: this was observed to be present, although only slight in degree, in one of the 'diphtheria' cases, the/

the case in which 'intimately adherent membrane' was present.

(3) The Occurrence of Toxic Complications.

The subsequent occurrence of, for example, palatal paresis in a case in which the diagnosis had been in doubt would point emphatically to diphtheria. It may be seen from Appendix tables VI and VII that toxic complications definitely developed in 11 cases, in 9 of which 'typically diphtheritic membrane' had been present, and that there was less definite evidence of toxic damage in a further 4 cases, in 3 of which such membrane had been present. In the group of 43 'diphtheria' cases in which 'typically diphtheritic membrane' had not been present, definite toxic complications developed in only 2 cases (nos. 10 and 11 in the tables referred to) and in a third (no. 15) there was less definite evidence of toxic damage. It is apparent, then, that the characteristic toxic complications of the disease were lacking in the large majority of those cases in which the local manifestations were also equivocal.

(4) The Shick Test Results.

The use of the Shick test in the diagnosis of diphtheria was discussed in Chapter II, where reference was made to certain authorities who opine that the finding of a Shick negative reaction in a case of, for example, follicular tonsillitis, in which a virulent strain of C. diphtheriae has been isolated, indicates that the case is not one of diphtheria. On the other hand, it was pointed out that it is known that Shick negative reactors are not necessarily/

necessarily completely immune to diphtheria and that they do occasionally contract the disease, often, but not always, in an atypical form (the form in which confusion with other disease in a carrier is most likely to occur). It was therefore suggested that the finding of a negative Shick reaction in these difficult atypical cases by no means excludes diphtheria. Reference was also made to three cases in the present series in which, although the Shick reaction was positive, the clinical evidence seemed entirely against the diagnosis of diphtheria. The salient features of these cases are briefly described here:-

In two the signs were those of follicular tonsillitis (these cases are classed in Appendix table IV in group C I (d)). The clinical picture in each was thought to be typical of a pyogenic infection - with an acute onset, marked hyperaemia of the fauces, frankly purulent exudate of follicular distribution, and marked tenderness of the upper cervical glands. The findings regarding Streptococcus haemolyticus and Staphlococcus aureus were not available in one case (which was one of the 'incompletely investigated' group); in the other, scanty colonies ('1 plus') of the former organism were present but none of the latter. The patients were uninoculated males, aged 7 and 36 years respectively. The type of C. diphtheriae was gravis in the former case, mitis in the latter; in both cases the virulence of the organism was proved by animal inoculation.

The third case was that of an uninoculated male, aged ten months, who had been feverish and had had a cough for about four days before his admission to hospital. A throat swab taken at that time was found to be positive for C. diphtheriae (gravis type), which was the reason for his admission. The temperature was sharply elevated and there were signs of broncho-pneumonia, but no evidence of laryngitis. The throat was quite normal apart from slight intermittent post-nasal discharge. The case being one of the 'incompletely investigated' group, the bacteriological results, apart from those relating to C. diphtheriae, were not available. With anti-diphtheritic serum (40,000 units intramuscularly) and a course of sulphadiazine, the broncho-pneumonia cleared up satisfactorily. Apart from the initial febrile disturbance, there was a striking lack of any/

any evidence of toxaemia. It is presumably possible that this was a case of diphtheritic broncho-pneumonia but, if that were so, it is surprising that the larynx was not also involved and that the child was not more toxic. Perhaps it is more likely that the case was one of broncho-pneumonia - infective agent undetermined - occurring in a subject who, although Shick positive, was a carrier. (Another explanation, which seems most improbable but cannot be entirely dismissed, is that some error, possibly in labelling, took place, whereby the first swab was erroneously reported as positive; in keeping with this theory is the observation that several swabs taken shortly after the patient's admission to hospital were all negative.)

Further information as to the Shick test results is given in the following chapter.

(5) The Available Epidemiological Information.

Points about the epidemiological background were considered to be of importance in the diagnosis in five cases. One of these was the case of an uninoculated three years old child who was infected with a virulent strain of mitis type and presented clinical signs of a mild attack of follicular tonsillitis. The knowledge that a sibling, who was infected with the same strain and sickened at the same time, developed laryngeal diphtheria was thought to indicate that it was probable that C. diphtheriae had only recently been introduced into the family and that that infection was the cause of the illness in both children (that is, that the case at issue was one of diphtheria, not of other disease in a carrier). The four other cases referred to were infants who were suffering from rhinorrhoea of minimal degree - a very small amount of mucoid discharge being seen from time to time - from which discharge C. diphtheriae of gravis type was isolated. The fact that they were occupants of a children's home/

home, several other members of which presented more definite signs of anterior nasal diphtheria, seemed to suggest that they were suffering from a very mild attack of the disease and were not only carriers.

(6) Evidence of Other (Non-diphtheritic) Disease.

With regard to the 'diphtheria' cases in which the characteristic local and general signs of that disease were lacking, it had been hoped that study of the data about the presence or absence of clinical and bacteriological features particularly suggestive of some other disease (e.g. streptococcal tonsillitis) might assist in the differentiation between diphtheria and other disease occurring in a carrier. In fact, however, as stated earlier, it was found to be virtually impossible to draw up any definite criteria which would permit of this classification. To take streptococcal tonsillitis, for example, (which was by far the most common possible alternative diagnosis to diphtheria) it was most often impossible to decide, with any reasonable degree of certainty, whether C. diphtheriae or Streptococcus haemolyticus (H.S.) (when both these organisms were present in a given case), or both organisms, or neither of them, should be regarded as being causally related to the lesion present.

As illustrative of the difficulties in interpreting the bacteriological findings, it may be mentioned that H.S. were found to be present in fairly large numbers ('2 plus' or more on the blood agar plate) as frequently in/

in the group of 'diphtheria' cases in which there was definite clinical evidence of that disease as in the group without such evidence (in the former group were classed 29 cases with 'typically diphtheritic membrane' and an additional case, without such membrane, in which definite toxic complications developed, of which 30 cases 10 (33%) presented the bacteriological findings referred to; the latter group consisted of 27 other cases, 8 (30%) of which presented these bacteriological findings; cases in the 'incompletely investigated' group were not included in computing these figures as in these the results as to H.S. were discounted). These figures show clearly that the finding of even a fairly profuse growth of H.S. by no means excludes the diagnosis of diphtheria.

With regard to the clinical aspects, three cases were briefly described earlier in this chapter in which the findings seemed to point to a diagnosis other than diphtheria (tonsillitis in two cases, broncho-pneumonia in one) but in which the Shick test was positive and there was thus, on that account, one fairly strong piece of evidence for diphtheria. Apart from these, there were two cases which were almost certainly instances of other (non-diphtheritic) disease. In one of these, the case of an inoculated female aged twelve years who was found to be Shick-negative, the clinical picture was typical of quinsy (with abundant pus formation) and the throat swab revealed numerous colonies of H.S. ('3 plus') and scanty colonies of C. diphtheriae (of virulent/

virulent mitis strain); there seemed to be no doubt that it was the infection with the former organism that had caused the disease. The other was a case of very mild tonsillitis in which only the last of the routine admission swabs - taken on the patient's fourth day in hospital - was positive for C. diphtheriae (gravis type). Swabs taken after as well as before the positive one were all negative; on account of this and the other circumstances of the case, it seemed almost certain that the patient had been a temporary carrier (the infection having been contracted in hospital) and that the strain of C. diphtheriae isolated had not been causally related to the tonsillar infection present on admission.

SECTION II.

CONSIDERATION OF THE QUESTION, "WERE THE 'DIPHTHERIA' CASES, OR, AT ALL EVENTS, THE LARGE MAJORITY OF THEM, REALLY CASES OF THAT DISEASE?"

With regard to the question, how many of the 76 'diphtheria' cases were indeed instances of that disease, the statements made in the previous section of this chapter may be summarised thus:-

(1) In 35 cases there was strong evidence for the diagnosis - on account of the occurrence of characteristic local manifestations in 33 cases and of characteristic general manifestations in a further 2.

(2) In 13 cases the evidence for the diagnosis was fairly definite but not absolutely conclusive - being based principally on the nature of the local manifestations in 13/

13 cases and on the epidemiological circumstances in 5.

(3) In 3 cases the evidence pointed to other disease occurring in a carrier - except that the Shick test was positive.

(4) In 2 cases there was virtually conclusive evidence against the diagnosis.

(5) In the remaining 18 cases the signs were those of an "undifferentiated" acute tonsillitis or pharyngitis and did not point conclusively to diphtheria or to any other particular condition (e.g. streptococcal infection)*.

*To consider further the last-mentioned group, it may be mentioned that the exudate was in the form of 'semi-confluent spots' in four cases, medium-sized 'discrete spots' in two, and 'specks' in seven; no exudate was present in the remaining five cases, but in one of them, classed in the 'ulcer' exudate-group, parts of the tonsillar mucosa were whitish in colour, as if perhaps recently the site of superficial ulceration or of membrane (as against the latter possibility, the patient had been ill for only three days before admission). All the patients except two (aged 20 and 31 years respectively) were between 5 and 16 years old. In nine of the cases there was a history of prophylactic inoculation against diphtheria; in the other nine, which included the two older patients, there was no such history. The Shick test was performed in fourteen of the cases (7 with a history of previous inoculation, 7 without) with negative results in all but two (one inoculated, one not). The distribution of the different types of C. diphtheriae was almost exactly the same in the inoculated and uninoculated patients (in the former, the organism was of gravis strain in 5 instances, mitis virulent in 3, and "type IV" in 1; in the latter, gravis in 5, and mitis virulent in 4). In both of the known Shick-positive cases, the organism was of gravis strain; in five of the Shick-negative cases it was also of that strain, in the other seven, mitis virulent. The duration of illness prior to admission was three days or less in all but two cases. As stated previously, there was considered to be no unequivocal evidence for or against the diagnosis of diphtheria.

CHAPTER VI.

A DESCRIPTION OF THE CLINICAL CHARACTERISTICS OF PRESENT-DAY DIPHTHERIA.

SECTION I.

GENERAL COMMENT ON THE MATERIAL.

While the principal object of study in this chapter consists of the cases of diphtheria encountered in Ruchill Hospital during the year 1947-48, the features of the disease, as manifested by these cases, are also compared with the features it displayed during the years 1942 and 1951 (as described in certain reports to which reference is made later). It is for this reason, and because, as will be shown, the characteristics of the disease appear to have been much the same at each of these periods, that the title of the chapter is considered to be appropriate.

The claim that a description of the cases of diphtheria encountered in Ruchill Hospital during the period mentioned may be taken as depicting, even if only approximately, the disease as it occurred in Glasgow at the time rests on two assumptions: first, that the diagnostic criteria were reasonably adequate and that most of the 'diphtheria' cases were indeed instances of that disease; and, second, that the series can be regarded as being representative of the disease as it occurred in the city at the time. The first of these assumptions was considered in the previous chapter, where it was concluded that only 2 of the 76 'diphtheria' cases of the 'main series' were almost certainly not instances of that disease, but that there were a further 21 cases in which there was some doubt, which could not be resolved, as to the diagnosis. With regard to the second assumption, it is/

is almost certain, owing to the hospital arrangements in Glasgow, that the cases of diphtheria seen in Ruchill Hospital during the year of the study consisted of practically all the recognised cases of the disease occurring in that part of the city which the hospital serves.

It is shown in Appendix table I that there were 109 confirmed cases of the disease during the year, of which 76 were included in the 'main series' which was particularly investigated. An analysis of the total cases was made for the purposes of this chapter; but since it was found that the features of the main series did not differ materially from those of the total cases - except in certain respects referred to later - and since a description of the former group also serves to delineate part of the material on which the subsequent chapter on the diagnosis of diphtheria is based, only the figures for this group are given here - except where the figures for the total cases differ in important respects.

The two other series of cases of diphtheria with which the present series was compared were those cases which occurred in certain areas of Scotland during the year 1942 (the subject of a report by a Committee of the Department of Health for Scotland in 1948) and the cases treated in Belvidere Hospital, Glasgow, during 1951 (reported by Thomson and Clementson in 1952). Subsequently in this chapter, these cases are referred to as the 1942 (D.H.S.) and 1951 (Belvidere) series.

SECTION II.

THE/

THE FINDINGS WITH REGARD TO CERTAIN SPECIFIED FEATURES.

(1) Age.

It is apparent from table 2 that in the present series and, more especially, the 1951 (Belvidere) series, there was a larger proportion of cases in the younger age-groups (in the present series in the under-5-years group, in the Belvidere series in the under-10-years groups) than in the 1942 (D.H.S.) series, and a correspondingly smaller proportion in the over-15-years group. The differences between the two later series and the earlier one are statistically significant. Regarding the present series, the exclusion of certain admissions during the year does not explain its difference from the 1942 series: for the age-distribution of the total cases was virtually identical with that of the main series (which is shown in the table). Nor does it seem that the inclusion in the present series of a number of cases in which there was some doubt as to the diagnosis can be taken as an explanation of the difference: for it is shown in table 3 that atypical cases - without the formation of the characteristic membrane or the occurrence of toxic complications - were most frequent in the older age-groups. Again, the different distribution of the two later series from that of the earlier cannot be explained in terms of a general trend of the disease to affect the younger age-groups relatively more often: for Carter (1952) has shown that, in Glasgow at least, the trend has been in the opposite direction. Perhaps the fact that the 1942 series consisted/

Table 2. Age Distribution of the Three Series of Cases of Diphtheria.

Series	Total Cases	Cases in Age-Groups (Years)							
		0 - 4		5 - 9		10 - 14		15 -	
1942 (D.H.S.)	4272	1145	27%	1276	30%	623	15%	1228	29%
1947-48 ('Main series')	76	29	38%	23	30%	12	16%	12	16%
1951 (Belvidere)	92	77*		84%		13	14%	2	2%

*Of the Belvidere cases in the under-10-years age-groups, 19 (21% of the total Belvidere cases) were in the 1-3 years group, 28 (30%) in the 4-5 years group, and the remaining 30 (33%) in the 6-9 years group.

Table 3. Age in relation to Sex, the Inoculation History, the type of Exudate present (whether 'Typically Diphtheritic Membrane' or not), and the Incidence of Toxic Complications. (The table refers to the 'Diphtheria' cases of the 'main series', as also do the other tables in this chapter except where otherwise stated.)

Age-Group (Years)	Total Cases	C a s e s							
		Female		Inoculated		With 'T.D.M.'*		With T.Cs.ø	
0 -11/12	4	1	25%	0	0%	1	25%	0	0%
1 - 4	25	14	56%	5	20%	16	64%	6	24%
5 - 9	23	12	52%	10	43%	7	30%	3	13%
10 - 14	12	8	67%	8	67%	5	42%	1	8%
15 - 19	4	3	75%	4	100%	1	25%	0	0%
20 -	8	6	75%	0	0%	3	37%	1	12%
All Ages	76	44	58%	27	36%	33	43%	11	14%

* 'T.D.M.' : 'Typically Diphtheritic Membrane'.
ø T.Cs. : Toxic Complications.

consisted of cases from various parts of Scotland, including Glasgow, while the two later ones were made up of Glasgow cases only, may be the explanation: for, as was briefly mentioned in Chapter I, there is evidence that overcrowding - which is particularly prevalent in Glasgow - results in a tendency for infectious diseases to be acquired at a relatively early age.

The association of age with such other matters as the type of exudate, toxic complications, and the inoculation history is discussed subsequently under the latter headings.

(2) Sex.

It is shown in table 3 that 58% of the diphtheria cases occurred in females - the same proportion as in the 1942 (D.H.S.) series. In the latter series it was found that the preponderance of female cases only occurred in the over-5-years age-groups. Although the results in the present series are not dissimilar in this respect, the number of cases is too small to permit of generalisation.

No significant correlation was found between sex and certain other factors such as the type of exudate present and the incidence of toxic complications. On account of this and the small size of the series, the data on these matters are not given here.

(3) Seasonal Distribution.

The seasonal distribution of the diphtheria cases is described in Chapter VIII (p. 159).

(4) Duration/

(4) Duration of Illness on Admission.

The duration of the illness in those diphtheria cases in which the throat was affected is shown in table 20, p. 157. T he distribution was similar to that of the 1942 (D.H.S.) and 1951 (Belvidere) series except that a larger proportion of the Belvidere cases had been admitted late in the illness - included in that series being four cases in which the diagnosis was only made after the development of paralytic complications.

(5) Fatality.

Although there was only one death in the diphtheria cases of the main series (1.3%), there were a further two deaths in the other cases occurring in the hospital during the year - giving an overall fatality rate of 2.8%. The corresponding rate in the 1942 (D.H.S.) cases was 3.0%, and that in the 1951 (Belvidere) cases, 2.2%. There is no significant difference between these proportions.

The three fatalities during the year occurred in young children (aged 8 months, and 1 and 2 years, respectively) who had not been inoculated and who suffered from the nasopharyngeal type of the disease. Although the larynx was also involved in two of the cases (which was the reason for their exclusion from the main series), death in all three was due to toxaemia, not to laryngeal obstruction. The type of the organism in the two cases in which the larynx was affected was mitis (virulent), and in the other case, gravis. Further details of the last-mentioned case (which is included in the /

the main series) are given in Appendix tables VI and VII (in which it is case no. 1).

(6) Toxic Complications.

Details of the cases in the main series in which toxic complications developed are shown in Appendix tables VI and VII. In assessing the toxic complication rate it was decided, in order to obtain a figure which would be directly comparable with the 1942 (D.H.S.) and 1951 (Belvidere) series, to regard only cases nos. 1 to 11 in the tables (the cases in which there was evidence of damage to either or both the cardio-vascular and nervous systems) as having developed toxic complications and to exclude nos. 12 to 15 (in which there was evidence of damage only to the urinary system). The figure thus obtained for the main series was 14.5%, and for the total cases during the year 16.4%. In the 1942 (D.H.S.) and 1951 (Belvidere) series the comparable figures were 11.1% and 20.7% respectively. Apart from the difference between the two last-mentioned proportions, which is 2.3 times the standard error, the differences between these proportions are not significant. The relatively high incidence of toxic complications in the Belvidere series would seem to be attributable to the relatively large proportion both of patients admitted late in the illness and of younger patients.

The association of age with toxic complications is shown in table 3 (p. 120) from which it may be seen that complications were most frequent in the 1-4 years age-group. Although in the 1942 (D.H.S.) series the incidence of complications was slightly higher in the 5-9 years group than/

than in the 0-4 years group, the significance of the present observations is limited by the size of the series.

Correlation of the toxic complication rate with the type of exudate, the inoculation history, the type of C. diphtheriae, and the Shick test results is dealt with subsequently under the latter headings.

(7) The Characteristics of the Local Lesion.

The frequency distribution of the different types of exudate in the main series is shown in Appendix tables III and IV. These tables were discussed in Chapter V, and they require no further comment here.

The extent, or site, of the exudate was also discussed in Chapter V, where it was stated that confluent exudate spreading beyond the tonsils was only encountered in those cases in which the membrane was 'typically diphtheritic' in nature. Such extensive and characteristic membrane occurred in 13 cases: in 3 there was slight spread to the anterior pillars only, in 5 spread to the pharynx, and in the remaining 5, in addition to spread to the pharynx, there were clinical signs of nasal involvement. In 11 of these cases the membrane was classed as being 'typically diphtheritic membrane with free edge', in the other 2 cases, 'typically diphtheritic membrane without free edge'. With regard to the association of toxic complications with the site of the exudate, such complications developed in 7 (54%) of the cases in which the membrane had spread beyond the tonsils, and in 2 (10%) of those other cases with 'typically diphtheritic/

diphtheritic membrane' in which spread beyond the tonsils had not occurred (see table 7, p. 130).

The association of age with the incidence of of 'typically diphtheritic membrane' is shown in table 3 (p. 120) from which it may be seen that this type of exudate occurred most frequently in the age-group 1-4 years (as also did toxic complications).

Correlation of the type and site of the exudate with the inoculation history, the type of C. diphtheriae, and the results of the Shick test is considered in the sections dealing with the latter subjects. Here it remains to comment on the incidence of adenitis and peri-adenitis.

Adenitis and Peri-adenitis.

It was thought that it might be of interest to study the association of signs of cervical adenitis and peri-adenitis with the type of exudate present and the incidence of toxic complications. Although the only statistically significant correlation was that of enlargement of the glands with the presence of 'typically diphtheritic membrane', it is apparent from table 4 that all three features studied - tenderness, enlargement, and peri-adenitis - most commonly occurred in association with that type of membrane. In table 5 it is shown that enlargement and peri-adenitis - but not tenderness - were relatively frequently associated with toxic complications.

As tenderness of the cervical glands is a common feature of streptococcal throat infections, as well as of diphtheria, it was decided to classify the diphtheria cases as /

Table 4. The association of signs relative to the upper cervical glands with 'typically diphtheritic membrane'.

	Total Cases	Cases with Signs					
		Tenderness		Enlargement		Peri-adenitis	
With T.D.M.*	33	14	42.4%	9	27.3%	2	6.1%
Without T.D.M.*	43	12	27.9%	1	2.3%	0	0%

*T.D.M. : 'Typically diphtheritic membrane'.

Note: (1) The tenderness was 'marked' in degree in 3 of the cases with 'T.D.M.' and in 1 of the others.

(2) In this and the following table the glands were only classed as enlarged if they were 'considerably' so (this term is defined on p.68).

Table 5. The association of signs relative to the upper cervical glands with toxic complications.

	Total Cases	Cases with Signs					
		Tenderness		Enlargement		Peri-adenitis	
With T.Cs.*	11	3	27.3%	3	27.3%	1	9.1%
Without T.Cs.*	65	23	35.4%	7	10.8%	1	1.5%

*T.Cs. : Toxic complications.

Note: The tenderness was not 'marked' in degree in any of the cases with toxic complications, but it was marked in 4 of the others.

as to whether there was bacteriological evidence of streptococcal infection or not. After the exclusion of the anterior nasal and 'incompletely investigated' cases, the remainder were divided into two groups: a group of 18 cases in which Streptococcus haemolyticus had been isolated in culture in a density of growth of '2 plus' or more; and a group of 39 cases in 11 of which that organism had been present in a density of growth of '1 plus' only, and in the remainder it had not been isolated. Glandular tenderness had been noted in 10 (56%) of the former group of cases (it had been marked in degree in 2 cases) and in 13 (33%) of the latter (marked in degree in 2 cases). While the difference between these proportions is not very striking, nor is it statistically significant, it is, of course, possible that streptococcal infection may have contributed to, or been the sole cause of, the glandular tenderness in some of the cases.

(8) The Inoculation History.

There was a history of prophylactic inoculation in 27 (36%) of the diphtheria cases. The corresponding proportions in the 1942 (D.H.S.) and 1951 (Belvidere) series were 24% and 43% respectively.

Discussion follows below on the association of inoculation with (a) age, (b) toxic complications, (c) the type of exudate, and (d) the site of the exudate.

(a) The inoculation history in relation to age.

It is shown in table 3 (p. 120) that it was in the case of patients aged between 5 and 19 years that there/

there was most often a history of inoculation.

(b) The inoculation history in relation to toxic complications.

As shown in table 6, toxic complications occurred very much less frequently in the 'inoculated' group of cases than in the 'uninoculated' (3.7% as against 20.4%). This difference is statistically significant. It is also shown that in each age-group the inoculated fared better than the uninoculated with regard to complications; but the small size of the series limits the significance of this observation.

Table 6. The Inoculation History in relation to Age and Toxic Complications.

Age-Group (Years)	Inoculated			Uninoculated		
	Total Cases	Cases with T.Cs.*		Total Cases	Cases with T.Cs.*	
0 - 11/12	0	0		4	0	0%
1 - 4	5	0	0%	20	6	30.0%
5 - 14	18	1	5.6%	17	3	17.6%
15 -	4	0	0%	8	1	12.5%
All ages	27	1	3.7%	49	10	20.4%

*T.Cs. : Toxic complications.

(c) The inoculation history in relation to the type of exudate.

It was thought to be of interest to study the relationship between inoculation and the occurrence of 'typically diphtheritic membrane'. It was found that such membrane occurred in a slightly higher proportion of the/

the 'inoculated' cases than of the 'uninoculated' (51.9% as against 38.8%), but that the difference was not statistically significant. None the less, the finding contrasts strikingly with that regarding toxic complications.

(d) The inoculation history in relation to the site of the exudate.

Table 7, in which is presented the data on this subject, relates only to cases in which 'typically diphtheritic membrane' was present - for it was only in these cases that confluent exudate spreading beyond the tonsils was encountered. It was found that such extensive exudate was present in 3 (21.4%) of the 'inoculated' cases, as against 10 (52.6%) of the 'uninoculated'; and also that toxic complications, which in these groups of cases only occurred in the 'uninoculated', were, as expected, most frequent in the group with relatively extensive exudate.

To conclude this study of the influence of inoculation on diphtheria, the cases with 'typically diphtheritic membrane' were scrutinised more closely; the further analyses carried out are presented in tables 8 to 10. The findings were similar to those of the Committee of the Department of Health for Scotland. Thus it was found that the more favourable outcome of the inoculated - in spite of the presence of the typical local lesion - could not be attributed to the distribution of the different types of C. diphtheriae (for gravis and intermedius strains were more frequent in the inoculated than in the others) but could be partly attributed/

Table 7. Cases with 'Typically Diphtheritic Membrane': The Inoculation History, the Site of the Membrane, and the Incidence of Toxic Complications.

Site of Membrane	Inoculated			Uninoculated			All cases		
	Total Cases	Cases with T.Cs.※		Total Cases	Cases with T.Cs.※		Total Cases	Cases with T.Cs.※	
Tonsils only	11	0	0%	9	2	22.2%	20	2	10.0%
Tonsils plus∅	3	0	0%	10	7	70.0%	13	7	53.8%
Total	14	0	0%	19	9	47.4%	33	9	27.3%

※T.Cs. : Toxic complications.

∅Tonsils plus : Membrane spreading beyond the tonsils

Table 8. Cases with 'Typically Diphtheritic Membrane': The Inoculation History and the Type of C. Diphtheriae.

	Total Cases	Gravis		Intermedius		Mitis (Virulent)	
Inoculated	14	11	78.6%	2	14.3%	1	7.1%
Uninoculated	19	11	57.9%	1	5.3%	7	36.8%
All Cases	33	22	66.7%	3	9.1%	8	24.2%

Table 9. Cases with 'Typically Diphtheritic Membrane': The Inoculation History, the Site of the Membrane, and the Duration of the Illness on admission.

Site of Membrane	Inoculated			Uninoculated		
	Total Cases	Cases ill 3 days or more		Total Cases	Cases ill 3 days or more	
Tonsils only	11	1	9.1%	9	3	33.3%
Tonsils plus*	3	1	33.3%	10	7	70.0%
Total	14	2	14.3%	19	10	52.6%

*Tonsils plus: Membrane spreading beyond the tonsil

Table 10. Cases with 'Typically Diphtheritic Membrane': The Inoculation History, Age, and the Incidence of Toxic Complications.

Age-Group (Years)	Inoculated			Uninoculated		
	Total Cases	Cases with T.Cs.*		Total Cases	Cases with T.Cs.*	
0 - 11/12	0	0		1	0	0%
1 - 4	5	0	0%	11	6	54.5%
5 - 14	8	0	0%	4	2	50.0%
15 -	1	0	0%	3	1	33.3%
All ages	14	0	0%	19	9	47.4%

*T.Cs. : Toxic complications.

attributed to the earlier admission of the patients to hospital. A possible explanation of their earlier admission is that parents who take the trouble to have inoculation performed may, on the whole, be more interested in the welfare of their children than other parents.

As stated above, the present findings are similar to those of the Committee of the Department of Health for Scotland. In the present series, however, information was also available as to the type of the exudate (whether sheet-like or not, and regarding its consistency) as well as to its site. Although the series is small, it seems justifiable to suggest, in view of the similar findings of the Committee referred to, that although the immunity given by previous inoculation may not always be sufficient to prevent the development of diphtheria and the formation of the typical membrane of the disease, it does nearly always lead to a quicker response by the defensive mechanisms of the body whereby extensive spread of the membrane and the development of toxic complications are prevented.

While in the present series 'typically diphtheritic membrane' occurred slightly more frequently in the 'inoculated', it is not proposed to suggest that an inoculated subject developing diphtheria is as likely to develop the typical membrane as an uninoculated subject (indeed, the opposite is almost certainly the case). A possible explanation of the present findings is that there may be a tendency on the part of practitioners to accept a history of inoculation as being/

being evidence against the diagnosis of diphtheria unless the clinical findings are strongly suggestive.

(9) The Type of C. Diphtheriae.

The incidence of the different types of C. diphtheriae in the present series and in the 1942 (D.H.S.) and 1951 (Belvidere) series are shown in table 11. It is apparent that gravis was the predominant strain in all three series and that mitis was more frequent in the present series than in the others, and intermedius correspondingly less frequent.

The correlation of type with a number of other features was studied, but, on account of the small size of the series, the work was of very limited value. Certain of the findings are given in tables 12 and 13.

(10) The Shick Test Results.

The Shick test results, correlated with a number of other features, are shown in tables 14 to 16. The data referring to the cases in the series in which the diagnosis of diphtheria was not confirmed (excepting only the nine cases with 'no apparent disease') are also given in the tables. It was considered important to state the proportion of the 'diphtheria' cases in each group in which the test was performed: for, as the tested patients were those in whose case the delay in treatment occasioned by the test had seemed to be justified, it is possible that, on the average, they possessed a higher degree of immunity to diphtheria than the others./

Table 11. Distribution of the Different Types of C. Diphtheriae in the Three Series of Cases.

Series	Total Cases	Gravis		Intermedius		Mitis		Type IV	
1942 (D.H.S.)	3187	2219	69.6%	640	20.1%	328	10.3%		
1947-48 ('Main Series')	76	48	63.2%	4	5.3%	23	30.3%	1	1.3%
1951 (Belvidere)	84	68	81.0%	12	14.3%	4	4.8%		

Table 12. Percentage Incidence of Toxic Complications in Infection with the Different Types of Organism in the Three Series of Cases.

Series	Gravis	Intermedius	Mitis	Type IV	All Types
1942 (D.H.S.)	13.1	9.1	7.6		11.7
1947-48 ('Main Series')	12.5	25.0	17.4	0	14.5
1951 (Belvidere)	20.6	0	0		16.7

Table 13. Diphtheria Cases of the 'Main Series' except those with 'Typically Diphtheritic Membrane'*: The Type of Organism and the Inoculation History.

	Total Cases	Gravis		Intermedius		Mitis (Virulent)		Type IV	
Inoculated	13	7	53.8%	0	0%	5	38.5%	1	7.7%
Uninoculated	30	19	63.3%	1	3.3%	10	33.3%	0	0%
All cases	43	26	60.5%	1	2.3%	15	34.9%	1	2.3%

*The corresponding figures for the cases with 'typically diphtheritic membrane' are given in table 8.

others.

With regard to age, it is apparent from table 14 that no significant correlation was found between this factor and the results of the test. The finding that the result was negative in a large proportion (80%) of the 'diphtheria' cases in the age-group 1 - 4 years is offset by the fact that only 40% of the cases in that group were tested.

With regard to the inoculation history, it is also shown in table 14 that, as expected, a larger proportion of the 'inoculated' cases was Shick-negative than of the 'uninoculated'. When all the results (in both the 'diphtheria' and 'other' cases) were summated, the difference was found to be one that is significant. As regards the 'diphtheria' cases, it was found that the test had been performed in a larger proportion of the 'inoculated' cases than of the 'uninoculated' (in many of the latter the disease had been thought to be too severe to justify the performance of the test); so it is probable that the difference would have been greater still if the test had been carried out in all of the cases. As regards the 'other than diphtheria' group, it may be seen that while the 'Shick-negative rate' was highest in the 'inoculated' cases (92%) it was also high in the 'uninoculated' (79%); it would seem that this observation may be correlated with the high degree of immunity to diphtheria prevailing at the time of the study (a post-epidemic period).

The relationship between the type of C. diphtheriae/

Table 14. The Shick Test Results, Age, and the Inoculation History (All Cases except the 'No Apparent Disease' Group).

Inoculation History*	Age-Group (Years)	Diphtheria Cases					Other Cases	
		Total Cases (A)	Cases Tested (B)	Cases Negative (C)	Percentages B/A	Percentages C/B	No. tested	% of these negative
IN.	0-11/12	0	0	0	-	-	0	-
	1-4	5	3	3	60	100	16	100
	5-14	18	14	11	78	79	68	88
	15-	4	4	2	100	50	25	96
	All Ages	27	21	16	78	76	109	92
UN.	0-11/12	4	3	2	75	67	4	100
	1-4	20	7	5	35	71	15	67
	5-14	17	12	5	71	42	25	68
	15-	8	5	3	62	60	42	88
	All Ages	49	27	15	55	56	86	79
TOTAL	0-11/12	4	3	2	75	67	4	100
	1-4	25	10	8	40	80	31	84
	5-14	35	26	16	74	62	93	83
	15-	12	9	5	75	56	67	91
	All Ages	76	48	31	63	65	195	86

*IN. : Inoculated.

UN. : Uninoculated.

Table 15. The Shick Test Results, Toxic Complications, and the Type of Organism (Diphtheria Cases only).

Toxic Complications	Type*	Total Cases (A)	Cases Tested (B)	Cases Negative (C)	Percentages B/A	Percentages C/B
Present	Gr.	7	3	2	43	67
	Int.	1	0	0	0	-
	M.V.	3	0	0	0	-
	IV	0	0	0	-	-
	All Types	11	3	2	27	67
Absent	Gr.	41	29	16	71	55
	Int.	3	2	2	67	100
	M.V.	20	14	11	70	79
	IV	1	0	0	0	-
	All Types	65	45	29	69	64
Total	Gr.	48	32	18	67	56
	Int.	4	2	2	50	100
	M.V.	23	14	11	61	79
	IV	1	0	0	0	-
	All Types	76	48	31	63	65

*Type:- Gr.: Gravis. Int.: Intermedius.
M.V.: Mitis (Virulent). IV: Type IV.

Table 16. The Shick Test Results and the Type and Site of the Exudate (Diphtheria Cases only).

Type and Site of Exudate*		Total Cases (A)	Cases Tested (B)	Cases Negative (C)	Percentages B/A	Percentages C/B
T.D.M.	Tonsils only	20	15	10	75	67
	Tonsils plus	13	2	0	15	0
	Total	33	17	10	52	59
Other than T.D.M.		43	31	21	72	68
All Cases		76	48	31	63	65

*T.D.M.: 'Typically diphtheritic membrane'.

Tonsils only: Exudate restricted to the tonsils.
Tonsils plus: Exudate spreading beyond the tonsils.

C. diphtheriae present and the Shick result is shown in table 15; no significant differences were found.

With regard to toxic complications and the characteristics of the exudate, it was stated earlier that one of the reasons why the Shick test result was not used in the differentiation of diphtheria from other disease in a carrier was that it is known that diphtheria may occur in negative reactors, occasionally even in a severe form. In tables 15 and 16 it is shown that the Shick-negative rate was approximately the same whether toxic complications developed or not (but note that only three of the complicated cases were tested) and whether 'typically diphtheritic membrane' was present or not. As against that, however, a much smaller proportion of complicated cases were tested than of those without complications, and a slightly smaller proportion of cases with 'typically diphtheritic membrane' than of those without it. It is also shown that in both of the two cases with membrane spreading beyond the tonsils in which the test was performed, the result was positive.

SECTION III.

SUMMARY OF CHAPTER.

A series of cases of diphtheria occurring in Glasgow in the year 1947-48 is described and compared with two other series, one of cases occurring in parts of Scotland (including Glasgow) during the year 1942, the other of Glasgow cases occurring in 1951. In spite of the very marked decline in the incidence of the disease which took place between 1942/

1942 and 1951, its characteristics, as judged by these series of cases, have not greatly changed. That since about 1942 there has been but little change in the nature of diphtheria, in spite of the striking fall in its incidence, is also borne out by the statistical studies of Dr. H. S. Carter (1952) which were discussed in Chapter I.

The predominant type of C. diphtheriae in each series was gravis. In the two later series there was a larger proportion of cases in the younger age-groups, which may perhaps be attributable to their being made up of Glasgow cases, unlike the earlier series which also included cases from other areas. In the 1951 series, a relatively large proportion of the patients were admitted to hospital late in their illness, and associated with this was a relatively high incidence of toxic complications; as to the explanation of these occurrences, it is probable that, as a result of the low incidence of the disease, practitioners are becoming less alert to its dangers.

With regard to the comparative characteristics of diphtheria in inoculated and uninoculated subjects, the findings in the series of cases described are essentially similar to those in the 1942 (D.H.S.) series. In the present series, however, fuller information is available as to certain clinical particulars, especially those regarding the characteristics of the exudate. It was found that the characteristic membrane of diphtheria occurred slightly more frequently in the 'inoculated' group of cases than in the/

the 'uninoculated', but that in the former group the patients were more often admitted to hospital relatively early in their illness, the membrane was much less often extensive, and toxic complications were very much less frequent.

With regard to the Shick tests which were performed, it was found, as expected, that the result was more often negative in the 'inoculated' cases than in the 'uninoculated', and more often positive in the 'diphtheria' cases than in those in which that diagnosis was not confirmed. None the less, the Shick-negative rate was relatively high in each of these groups; in this respect it is suggested that the high Shick-negative rate found in the group of 'other than diphtheria' cases in which there was no history of inoculation can be taken as being an indication of the high degree of (natural) immunity to diphtheria prevalent at the time of the study.

CHAPTER VII.

ON THE SIGNIFICANCE OF NON-VIRULENT STRAINS OF C. DIPHTHERIAE IN DISEASE OF THE THROAT.

It was stated in Chapter IV that it was decided that none of the 35 cases in the 'non-virulent' sub-group of the 'throat' group should be classed as being instances of diphtheria. It will be recollected that in all of these cases there was evidence of acute inflammatory disease of the throat, and that a non-virulent strain of C. diphtheriae was isolated from swabs of that site. In this chapter, by means of a review of these cases, introduced by a brief commentary on the literature on the subject, it is proposed to examine the validity of this assumption - that these were not cases of diphtheria.

SECTION I. COMMENTARY ON THE LITERATURE.

There are three relatively recent reports in which doubt is expressed as to the correctness of the generally-held view that diphtheria is caused only by infection with a virulent (as tested by guinea-pig inoculation) strain of C. diphtheriae and that non-virulent strains of the organism cannot cause the disease. Of these reports perhaps the most important is the work of Frobisher et al. (1947) who produce evidence which strongly suggests that non-virulent strains contain an endotoxin which resembles the exotoxin of virulent strains in a number of ways. These workers also claim to have isolated non-virulent organisms in a considerable number of clinically typical cases of diphtheria. Unfortunately, however, they give no details about these cases, nor do they state the criteria on which the diagnosis was based; this omission must be regarded as weakening their claim that/

that infection with a non-virulent strain may be capable of causing diphtheria or a diphtheria-like disease.

The second report is the work of Harkness (1945) who described a condition which he termed 'non-virulent diphtheria'. He had encountered two cases in which there was a localised area of chronic atrophic change in the mucosa of the upper respiratory tract, in the subglottic region in one case, on part of one of the nasal turbinates in the other. C. diphtheriae was isolated from the affected area in both cases, in one case in pure culture. In one case the organism was proved to be non-virulent by animal inoculation, in the other it was only assumed to be so on account of the clinical picture. There was no clinical response to anti-diphtheritic serum; as stated above, the lesions were chronic in nature. It seems clear from the description given that the condition encountered was certainly not diphtheria. Further, there was no evidence to show that the strains of C. diphtheriae were causally related to the lesions from which they were isolated. It therefore seems reasonable to conclude that the application of the term 'non-virulent diphtheria' to the syndrome described in the report was unjustifiable, and that the conclusion implicit in the use of the term - that non-virulent strains may cause diphtheria - was not warranted by the evidence produced.

The most recent of the three reports is the work of Edward and Allison (1951) who isolated non-virulent strains from 19 cases in which the diagnosis of diphtheria had been/

been made on clinical grounds. But since the particularly characteristic clinical features which may occur in diphtheria did not occur in any of the cases (toxic complications did not develop; the exudate was always limited to the tonsils and was not extensive in any of the cases; its consistency was not described) it would seem that the diagnosis was not firmly established. As the authors themselves indicate, no conclusions can be drawn as to the aetiology in these cases.

It would not seem that the evidence produced in the above-mentioned reports makes a convincing case that non-virulent strains may cause diphtheria - particularly when considered in light of the generally-held view, based on many years of clinical and bacteriological work, that they do not.* But as the question has been raised, and as there was a considerable number of 'non-virulent' cases in the present series, it was considered that a study of them might be of interest.

SECTION II. STUDY OF THE 'NON-VIRULENT' GROUP OF CASES.

The 35 'non-virulent' ('throat') cases were scrutinised to determine if there was any evidence to show that a non-virulent strain of C. diphtheriae could cause,/

*The case for the orthodox view is well stated by Andrewes et al. (1923). As more recent exponents of this view, Thomson and Clementson (1952) may be cited: in their series of suspected-diphtheria admissions, they did not consider that the evidence warranted the diagnosis of diphtheria in any of the 26 cases in which non-virulent strains were isolated.

cause, first, typical diphtheria (i.e. the characteristic local and systemic manifestations of the disease) or, if not, second, the local manifestations of the disease without the toxic complications, or, third, any disease of the throat. In the event of a positive answer to any but the first question, it would then be necessary to consider, fourth, should the disease produced by such infection be termed diphtheria or not.

The first question proposed can readily be answered by the statement that the characteristic toxic complications of diphtheria did not occur in any of the cases.

With regard to the second question, the frequency distribution of the different types of exudate in the 'diphtheria', 'non-virulent', and 'negative' groups of cases is shown in Appendix table V. It is apparent that the exudate occurring in the 'non-virulent' cases was similar in type to that in the 'negative' cases and in those atypical 'diphtheria' cases in which the characteristic local feature of the disease ('typically diphtheritic membrane') did not develop. There was thus no evidence to show that infection with a non-virulent strain can cause the characteristic local manifestations of diphtheria.

It is not possible to give a definite answer to the third question propounded. Although there was nothing particularly distinctive about the clinical features of the 'non-virulent' cases (except in two cases, one a case of scarlet fever, the other of peri-tonsillar cellulitis, in/

in both of which Streptococcus haemolyticus was isolated on culture; that organism was certainly the causative agent in the former case, and probably in the latter), this does not exclude the possibility that a 'non-virulent' infection may be one of the agents which are capable of causing the ordinary clinical types of tonsillitis. A finding which seems to suggest that this may indeed be so is that the common pathogenic organisms (Streptococcus haemolyticus, Staphlococcus aureus, and certain others) were present in a much smaller proportion of the 'non-virulent' cases than of the 'negative' cases (see Appendix tables VIII and IX) and that the difference was statistically significant. In interpreting the aetiological significance of this finding it must be borne in mind that the presence of C. diphtheriae in the one group, but not in the other, was not the only difference between the two groups of cases which may have been related to the apparent deficiency of streptococcal (and other) infections in the one group: thus the exudate-distribution was dissimilar, a lesser proportion of the 'non-virulent' cases having had the more extensive forms of exudate which are relatively frequently associated with streptococcal infection; and there were differences in age-distribution and in other ways*. Even/

*It is interesting and perhaps significant, although not considered relevant to the point at issue here, that there was a history of inoculation in a much larger proportion of the 'non-virulent' cases than of the others: thus of the 35 'non-virulent' cases, 27 (77.1%) were inoculated, of the 76 'diphtheria' cases, 27 (35.5%), and of the 193 'negative' cases 99 (51.3%). Similarly Edward and Allison, while they do not say how many of their 'non-virulent' cases of diphtheria were inoculated, found that the antitoxin titre in these cases was usually relatively high.

Even when allowances were made, as far as possible, for these different factors (by means of rather complicated analyses and calculations, which are not presented here) it still seemed that there was a deficiency of streptococcal (and other) infections in the 'non-virulent' group which was unlikely to have occurred by chance, and could not be satisfactorily explained. The finding suggests, but by no means proves, that infection with a non-virulent strain of C. diphtheriae is a possible cause of tonsillitis.

The fourth question proposed was if it should be considered that infection with a non-virulent strain of C. diphtheriae was the causative agent in a case of tonsillitis (in which the characteristic signs of diphtheria were lacking), then should the case be classed as one of diphtheria. In support of this suggestion might be cited the observation that infection with a virulent strain of the organism occasionally produces clinically similar lesions which are classed as being diphtheritic. But, on the other hand, while infection with a virulent strain is capable, under certain circumstances, of producing the well-known clinical picture of diphtheria, it has not been adequately proved that a 'non-virulent' infection can do so. It is therefore suggested that while cases of tonsillitis presumed to be due to infection with a virulent strain may be regarded as being atypical cases of diphtheria, clinically identical cases presumed to be due to infection with a non-virulent strain should be regarded as being typical cases of/

of a different disease altogether.

SECTION III. SUMMARY OF CHAPTER.

As a result of study of the literature and of the series of cases reported here, it is concluded that it has not been proved that infection with a non-virulent strain of C. diphtheriae can cause diphtheria. Such strains were, however, isolated from a number of cases of tonsillitis, and it may be that infection with this organism is one of the possible causes of that condition.

CHAPTER VIII.

ON THE DIAGNOSIS OF DIPHTHERIA

IN PRESENT-DAY CIRCUMSTANCES.

Introductory Comment.

In this chapter a comparison is made between the features of those cases in which the notified diagnosis of diphtheria was confirmed and of those others in which this was not so - the object of the study being to determine whether the classical diagnostic criteria, described fully by Bretonneau (1826 and 1855), Ker (1909), and others, are still valid in times when a large proportion of the child population has received prophylactic inoculation, and when the prevalence of the disease is low.

As the large majority of the cases studied were of faucial infection (diphtheritic or otherwise), attention is mainly directed to the diagnosis of this type of case; but, in the first instance, brief comment is made on the other cases in the series.

SECTION I. THE DIAGNOSIS IN CASES IN WHICH THE THROAT IS NOT AFFECTED.

It will be recollected that the size of this group was reduced in that patients admitted to the 'croup' ward were not included in the series. The group consisted of 14 cases, of which only 4 were diphtheritic (being cases of the anterior nasal type of the disease). The features of these four cases were discussed in Chapter V (p.112) where it was stated that the patients contracted the disease during a localised epidemic in a children's home. Of the remaining - non-diphtheritic - cases, 6 were suffering from one or more of the following conditions: rhinitis, laryngitis, bronchitis./

bronchitis. In the other 4 cases, the respective diagnosis was: abscess of cervical gland, fracture of nasal cartilage and bronchitis, dermatitis, and acute suppurative otitis media. There were no signs particularly suggestive of diphtheria in the non-diphtheritic cases (e.g. in those admitted with rhinorrhoea, there was no evidence of fibrinous or membranous rhinitis), nor had any bacteriological investigations been carried out prior to their admission (i.e. the certified diagnosis of diphtheria had been made solely on the strength of the clinical findings). Under these circumstances, it was often difficult to understand why the provisional diagnosis of diphtheria had been made.

One deduction which can be drawn from these findings, but which is almost self-evident, is that it can be assumed that the chances are small of a case of, for example, rhinorrhoea being due to diphtheria when it is known that the prevalence of that disease is low. Yet two occurrences were encountered which indicated that such a possibility cannot be entirely dismissed without danger. The first occurrence was that of the four cases of anterior nasal diphtheria referred to above and described in Chapter V; this emphasised that it remains possible that a trivial degree of nasal discharge may be the only manifestation of diphtheria. While it may be that little harm would have come to these patients if the true nature of the disease had been overlooked, accurate diagnosis of this type of case is also important to prevent the spread of infection. The other occurrence served as a/

a reminder of the possibility of a still more serious diagnostic error - the possibility of overlooking an attack of diphtheria of nasopharyngeal type when occurring in an infant. The case which drew attention to this danger was an admission to the 'croup' ward, and it is therefore not included in the series now under review; but owing to its importance and relevance, a description of it is given:-

The patient was an uninoculated male, aged eight months, who was admitted to hospital on approximately the 21st day of his illness. The illness began with nasal discharge, which became steadily more profuse. Three practitioners who saw the patient during that period (these different doctors were called in by the parents as they were not satisfied with the advice previously given) diagnosed coryza. On the day before his admission to hospital, breathlessness and a croupy cough developed - which led a fourth practitioner to have the patient admitted. On admission he was seen to be extremely toxic, and the first heart sound was diminished in intensity. The pulse rate was 150; the temperature was not elevated. There was very profuse, thin, muco-purulent, anterior and posterior nasal discharge. In addition, four patches of whiter and more solid exudate were seen in the oro-pharynx; this exudate could not be adequately 'tested' during the patient's life, but examination of it shortly after death showed that it was friable and not adherent. The underlying mucosa was seen to be normal - intact and not inflamed. The cervical lymph glands were not appreciably enlarged. There was only a slight degree of laryngeal obstruction; signs of bronchitis were also present.

The administration of a large dose of antitoxin (80,000 units, half of which was given intramuscularly, half intraperitoneally), and of penicillin, was of no avail, and the patient's condition deteriorated rapidly. On several occasions, each lasting for a few minutes only, there developed extreme pallor, slight cyanosis of the lips, and marked weakness of the pulse. On the last of these occasions, about eleven hours after the patient's admission, the heart rate was found to be 60; at that point, death took place.

Bacteriological examination revealed the presence of a (virulent) mitis strain of C. diphtheriae. Although permission for a post-mortem examination was refused, there is no doubt that the case was one of diphtheria of the naso-pharyngeal type, and that death was due to the effects of/

of toxic damage on all the organs of the body, but especially the heart.

It is also note-worthy that three others in the immediate neighbourhood contracted diphtheria within three weeks of the patient's admission: one, aged twenty months, a purely laryngeal case, required tracheotomy; the other two, aged 7 and 8 years respectively, were cases of very mild faucial infection. None of these patients had been inoculated; in their case, also, the organism was of mitis (virulent) strain. It is apparent, then, that the case described was the first of a small localised outbreak.

The danger of mistaking a case of nasopharyngeal diphtheria for simple coryza (which error certainly contributed to the fatal outcome in the case described above) was most clearly described by Bretonneau as long ago as 1855. That author's work was previously mentioned in Chapter II, but is again referred to here as the present writer was unable to find such a clear exposition of the danger in any of the more recent text-books. Bretonneau pointed out how the apparently simple nature of the illness, often exactly simulating coryza until the disease is well advanced, is liable to deceive alike the patient, the relatives, and the doctor, and to give rise to a false and treacherous sense of security. He stressed the importance of palpating to detect the presence of enlargement of the cervical glands, for he considered that that finding is extremely suggestive of diphtheria; as also is the presence of unilateral excoriation of the upper lip. But he realised that these signs were not invariably present in the disease (neither was present in the case described here).

An important feature about the case described here is that it occurred at a time when the prevalence of diphtheria was relatively low. It would appear, then, that the/

the occurrence of it, and of the other cases described, indicates that Bretonneau's warning (as to the danger of confusing diphtheria with coryza) not only applies (as he applied it) to times when severe diphtheria is prevalent, but that it must also be borne in mind even when the incidence and severity of the disease are low.

SECTION II. THE DIAGNOSIS IN CASES IN WHICH THE THROAT IS AFFECTED.

Studied in this section are the 290 'throat' cases, a comparison being made between the features of those 72 cases in which the provisional diagnosis of diphtheria (made by the practitioners who notified the cases) was more or less definitely confirmed (i.e. cases of inflammation of the throat in which a virulent strain of C. diphtheriae was isolated from that site; the question as to whether all these cases were indeed instances of diphtheria was considered in Chapter V) and the features of the remaining 218 cases. The order of this study follows the same lines as the material in Chapter IV, the clinical history being considered first, then the 'local signs', the signs indicative of toxaemia, the bacteriological findings, and, lastly, the immunological data.

(A) The Clinical History.

(1) The Basis of Notification.

It was explained in Chapter IV that the cases could be divided into two groups: first, 'notified clinical', in which the provisional diagnosis of diphtheria was based solely on the clinical observations of the notifying/

notifying practitioner; and, second, 'notified positive', in which the notification had been made only after the receipt of a provisionally positive bacteriological report. This distinction is considered to be important, particularly for the purposes of this chapter, because it would seem that the 'notified clinical' cases more nearly constituted an unbiased sample of the similar cases occurring in the city at the time than did the 'notified positive' cases or both groups considered together. The reason for this assumption is that, in the 'notified positive' group, the chances of the diagnosis being diphtheria were weighted by the bacteriological findings; for there can be no doubt that an unknown number of similar cases occurred which, in view of the negative bacteriological findings, did not reach hospital.

The association of the basis of notification with the final diagnosis (whether diphtheria or not) and the findings regarding C. diphtheriae is shown in tables 17 and 18. While the diagnosis of diphtheria was confirmed in a larger proportion of the 'notified positive' cases than of the 'notified clinical', even in the former group the diagnosis-confirmation rate was only 58%. Later in this chapter, it is shown that in certain types of case - for example, with exudate of a particular type or with a history of prophylactic inoculation - only a minority of the 'notified positive' cases was found to be diphtheritic. It is apparent, then, that, under present circumstances, the isolation of an organism morphologically resembling C. diphtheriae from an inflamed/

Table 17. Basis of Notification and Final Diagnosis (whether diphtheria or not).

Basis of Notification	Total cases[ø]	Final Diagnosis			
		Diph.[※]		Other than diph.	
'Clinical'	221	32	14.5%	189	85.5%
'Positive'	69	40	58.0%	29	42.0%
Total	290	72	24.8%	218	75.2%

[※]In this and the subsequent tables, Diph. = Diphtheria.

[ø]This and the subsequent tables in this section refer only to the 'throat' cases.

Table 18. Bacteriological Findings (with regard to C. diphtheriae) and Basis of Notification: 'Other than diphtheria' cases only.

Basis of Notification	Total cases	C.D. present (non-virulent)		C.D. absent	
'Clinical'	189	11	5.8%	178	94.2%
'Positive'	29	24	82.8%	5	17.2%
Total	218	35	16.1%	183	83.9%

C.D. = C. diphtheriae.

inflamed throat by no means necessarily indicates that diphtheria is even the most probable diagnosis.

(2) Age and Sex.

The association between age and sex and the diagnosis-confirmation rate (the proportion of cases in which the diagnosis of diphtheria was confirmed) is shown in table 19. While no significant association was found between sex and the rate, the rate was found to be significantly higher in the younger age-groups (especially the 1-4 years group) than in the older groups. Not only was the diagnosis of diphtheria most often confirmed in the case of the younger patients, but, as pointed out in Chapter VI, it was in these that the disease was most often severe (those in the age-group 1-4 years were particularly vulnerable in both respects).

Table 19. Age and Sex and the Final Diagnosis.

Age-group (years)	MALE			FEMALE			BOTH SEXES		
	Total cases	Diph. cases		Total cases	Diph. cases		Total cases	Diph. cases	
0-11/12	5	2	40.0%	1	0	0%	6	2	33.3%
1 - 4	25	11	44.0%	30	12	40.0%	55	23	41.8%
5 - 9	35	11	31.4%	39	12	30.8%	74	23	31.1%
10 - 14	29	4	13.8%	37	8	21.6%	66	12	18.2%
15 - 19	10	1	10.0%	22	3	13.6%	32	4	12.5%
20 -	20	2	10.0%	37	6	16.2%	57	8	14.0%
All ages	124	31	25.0%	166	41	24.7%	290	72	24.8%

While the above-mentioned association between age and the diagnosis-confirmation rate was found to apply to all the 'throat' cases considered together, it is important to/

to note that, when further analysis of the material was carried out, the cases being classified as to the type of exudate present, it was found that the association was still more marked in the group of cases in which 'patches' of exudate had been present, but was not operative in the group without such exudate - that is, it was found that a young child in whose (inflamed) throat 'patches' of exudate were present was very much more likely to be suffering from diphtheria than was an adult with exudate of the same type, but that a child in whose throat 'patches' of exudate were not present (there being other forms of exudate, such as 'spots', or no exudate) was no more likely to be suffering from diphtheria than was an adult with a comparable throat lesion. (The data on which this conclusion is based are shown in table 25, p. 167.)

With regard to the correlation of the basis of notification of the cases with age and the diagnosis-confirmation rate, it was found, in both the 'notified clinical' and 'notified positive' groups, that the proportion of cases in which the diagnosis of diphtheria was confirmed decreased with increasing age, but that this trend was less pronounced in the latter group than in the former. The explanation of the difference seemed to be that 'patches' of exudate were less frequently present in the cases in the latter group than in the former.

(3) The Duration of Illness on Admission.

A clinical impression was formed that if a/

a patient had been ill for only a relatively short time, the chances of the infection being diphtheritic were less than otherwise. On analysis, however, it was found that the differences in this respect were very slight and not significant. The data are shown in table 20.

Table 20. The Duration of Illness on Admission in relation to the Final Diagnosis (whether diphtheria or not) and, in the diphtheria cases, the Type of Exudate (whether in the form of 'patches' or not).

Final Diagnosis	Type of Exudate	Patients ill for no. of days						
		-1	2	3	4	5	6-	Total
Diph.	Patches	13 31%	14 33%	7 17%	4 10%	2 5%	2 5%	42 100%
	Other	9 30%	7 23%	9 30%	2 7%	1 3%	2 7%	30 100%
	Total	22 31%	21 29%	16 22%	6 8%	3 4%	4 6%	72 100%
Other	Any or none	77 35%	67 31%	31 14%	20 9%	7 3%	16 7%	218 100%

(4) History of Previous Attacks of Diphtheria.

As previous hospital records are seldom available when patients are first seen, it was thought to be more useful to analyse the figures in such a way as to show the effect of a previous history of diphtheria, as reported by the patients or relatives, on the diagnosis-confirmation rate - instead of studying the effect on the rate of a confirmed (by the records) history of the disease. It was found that such a history was obtained in 10% (7) of the diphtheria/

diphtheria cases and in 14% (30) of the others - a difference which might easily have occurred by chance. While it might perhaps be regarded as surprising that there was a history of a previous attack in as many as 10% of the diphtheria cases, it must be borne in mind that in some cases the history was found, on study of the records, to be false (patients who had previously been admitted to a diphtheria ward, but had been found to be suffering from some other disease, were not always aware of the change of diagnosis). In some other cases the previous diagnosis of diphtheria had not been bacteriologically confirmed, and there was other evidence which seemed to leave room for doubt as to its accuracy.

With regard to a history of two or more attacks of diphtheria (as reported by the patient or relatives), this was forthcoming in four of the non-diphtheritic cases, but in none of the cases of diphtheria. In the cases with such a history, the evidence of the records showed that there was considerable doubt as to whether any of the previous illnesses had really been diphtheria. It seemed that the history in these cases pointed to a liability to repeated attacks of tonsillitis (of a clinically diphtheria-simulating type) but not to diphtheria.

(5a) History of Contact with Diphtheria.

6 (8.6%) of the patients found to be suffering from diphtheria and 5 (2.3%) of the others were reported to have been in contact, at a material time, with patients who had been notified as suffering from diphtheria. In the/

the cases in which the diagnosis was not confirmed, neither had the contacts been found to be suffering from the disease.

While it is generally held, and with good reason, that the occurrence of any form of inflammation of the throat or nose in a subject who has been in contact with a patient suffering from diphtheria should be regarded with suspicion as possibly being a manifestation of that disease, it requires to be stressed that, under present circumstances, in view of the high altered-diagnosis rate in diphtheria-suspects admitted to hospital, it is very desirable, prior to having the secondary case removed, to find out, if possible, whether or not the diagnosis in the original case has been confirmed - otherwise there may be needless disturbance of patients and wastage of hospital facilities.

(5b) History of Contact with Scarlet Fever.

As expected, a history of contact with scarlet fever was more frequently obtained in the cases in which the diagnosis of diphtheria was not confirmed than in those in which it was - such a history having been forthcoming in six (2.8%) of the former group of cases and in one (1.4%) of the latter. In most of the cases with that history, there was evidence suggestive of streptococcal tonsillitis.

(6) Seasonal Distribution of Cases.

The seasonal distribution of the total suspected-diphtheria admissions during the year (which include those of the series now under review) is shown in table 21.

With regard to those cases in which the diagnosis/

Table 21. Seasonal Distribution of Suspected-Diphtheria Admissions during the year 1947-48 classified as to Type of Case (whether admitted to the 'croup' ward or not) and Final Diagnosis (whether diphtheria or not).

Month	All except 'croup' admissions			'Croup' admissions	
	Diph.	Other	(% diph.)	Diph.	Other
Sept.	8	30	(21)		5
Oct.	4	37	(10)	1	9
Nov.	6	30	(17)	1	4
Dec.	9	38	(19)		5
	27	135	(17)		
Jan.	13	38	(25)		7
Feb.	10	24	(29)		16
Mar.	8	22	(27)	1	3
Apr.	13	18	(42)	1	8
	44	102	(30)		
May	6	26	(19)	1	7
June	13	29	(31)		2
July	11	19	(37)	2	7
Aug.	5	20	(20)		6
	35	94	(27)		
Total	106	331	(24)	7	79

Note: (1) Unlike the other tables in this section, which refer only to the 'throat' cases of the 'main series', the above table refers to all suspected-diphtheria admissions during the year.

(2) Included in the table as cases of diphtheria are four carriers.

diagnosis was confirmed, it is apparent that, contrary to the usual experience in Glasgow (that the incidence of diphtheria is highest in the last quarter of the year), the incidence was found to be highest during the months of January to July inclusive. The proportion of cases with relatively extensive membrane, and with toxic complications, was also found to be significantly higher during that period. The reason for this increase (which was only temporary) of the prevalence and severity of the disease is uncertain.

With regard to the other admissions, in which the diagnosis of diphtheria was not confirmed, apart from the cases in the 'croup' group there was a gradual downward trend in the numbers during the period of study. The numbers of non-diphtheritic croup cases fluctuated throughout the period; the most striking feature was the large number of admissions during the month of February.

(B) The 'Local Signs'.

(1) The Type of Exudate.

(a) General Comment.

The proportion of cases in each of the various exudate-groups in which the diagnosis of diphtheria was confirmed is shown in Appendix tables III and IV. As pointed out in Chapter V, the only groups in which the diagnosis was confirmed in all the cases were the two 'typically diphtheritic membrane' groups. It may be seen that the diagnosis-confirmation rate was low in the other numerically large groups, and that the rate was 42% in the/

the group of cases in which membrane, of one type or another, had been present (that is, group (A) in Appendix table III).

The method of classification of exudate employed in the analyses carried out in this chapter is the relatively simple method used in Appendix table III (for most purposes the last five groups in that table are classed together and compared with the first group - the group with 'patches' of exudate), not the more complicated method used in Appendix table IV. Apart from its greater simplicity, it is considered that the former method has other advantages for the purposes of the chapter: first, although based on the findings when the local lesions were fully developed, it very nearly approximates (more closely so than the other, more complicated, method) to the position at the time when the patients were admitted; and, second, it is based on the visual appearances only, not also (as is the other method) on the findings as to the consistency of the exudate. As to why these advantages are considered to be such, the main object of this chapter is to supply data which, it is hoped, will be of value in the management of suspected cases of diphtheria - in deciding what the chances are that a given case may be one of the disease and what administrative and therapeutic steps should be taken. Because a decision (at least, a provisional decision) as to the procedure to adopt has to be made when a patient is first seen is one of the reasons why the more simple of the two methods of classification, which closely approximates to the findings when the patients were admitted, is considered to be the most useful. Similarly, as explained /

explained in Chapter IV, it is often not possible to determine the consistency of the exudate at the first examination; yet it is necessary, at that time, to make at least a provisional assessment of the case; consequently the advantage again lies with the more simple method of classification, based solely on the visual appearances.

The difference between the findings (as to the type of exudate) when the patients were admitted and when the local lesions were fully developed is shown in tables 22 and 23. With regard to the relatively simple method of classification used in Appendix table III and in this chapter (by which the cases were classed in 'exudate-groups' only, not also in 'exudate sub-groups'), it is shown in table 22 that further development of the exudate after admission, in such a way that change of exudate-group became necessary, only occurred in 3 cases; therefore, with the exception of these cases, the data given in Appendix table III, and the other tables based on the same method, are true of the time when the patients were admitted as well as of the time when the local lesions were fully developed. On the other hand, the more complicated method used in Appendix table IV (by which cases were classed in 'exudate-sub-groups' as well as 'exudate-groups') reflects to a considerably less extent the findings on admission - for in addition to the 3 cases listed in table 22 there were a further 7 cases (listed in table 23) in which alteration of exudate-sub-group became necessary after admission.

(b)/

Table 22. Cases in which the exudate changed in character in such a way that allocation to a different exudate-group - as well as to different exudate-sub-group - became indicated.

Original exudate-group (and sub-group)	Final exudate-group (and sub-group)	Total cases	
		Diph.	Other
'Discrete spots' ('medium and large')	'Patches' ('typically diphtheritic membrane without free edge')	1	
'Clean throats'	'Discrete spots' ('medium and large')		2
	Total cases	1	2

Table 23. Cases in which the exudate changed in character in such a way that allocation to a different exudate-sub-group - but not to a different exudate-group - became indicated.

Exudate-Group	Exudate-sub-group		Total cases	
	Original	Final	Diph.	Other
'Patches'	'Friable membrane'	'Typically diphtheritic membrane with free edge'	1	
"	" "	'Tough but loose membrane'	1	1
"	" "	'Intimately adherent membrane'		1
"	'Tough but loose membrane'	'Typically diphtheritic membrane with free edge'	1	
'Discrete spots'	'Specks'	'Medium and large spots'		2
		Total cases	3	4

(b) The type of exudate and the basis of notification.

It is shown in table 24 that in each of the exudate-groups the diagnosis of diphtheria was confirmed in a higher proportion of the 'notified positive' cases than of the 'notified clinical'. With regard to the 'notified positive' cases, the diagnosis was confirmed in all but one of those in the 'patches' exudate-group, but in a lesser proportion of those in the other groups. As to the 'notified clinical' cases, the diagnosis was confirmed in 27% of those in the 'patches' group, in a lesser proportion of those in the 'semi-confluent' and 'discrete spots' groups, and in none of the others.

Regarding the 'notified clinical' cases in the 'clean throats' group, if it is so that diphtheria, while it may occur in the form of catarrhal tonsillitis or pharyngitis (without exudate formation), is a relatively rare cause of these conditions, then it would be expected that one might have to examine many such cases before finding one which was diphtheritic, and it would not be surprising if none was found to be so in a series of cases of the size of the 'notified clinical' 'clean throats' group (which consisted of 24 cases).

(c) The type of exudate and age.

The association between these factors and the diagnosis-confirmation rate was discussed on p.156 where it was pointed out that in the group of cases with 'patches' of exudate there was marked correlation between advancing age (from the group 1-4 years upwards) and diminishing/

Table 24. The Type of Exudate, the Basis of Notification, and the Final Diagnosis.

Exudate-group	'Notified Clinical'			'Notified Positive'			Percentage diph. of total cases
	Total cases	Diph. Cases		Total cases	Diph. Cases		
'Patches'	80	22	27.5%	21	20	95.2%	41.6%
'Semi-confluent Spots'	47	3	6.4%	4	3	75.0%	11.8%
'Discrete Spots'	60	7	11.7%	27	11	40.7%	20.7%
'Clean Throats'	24	0	0%	15	5	33.3%	12.8%
'Ulcer' group	6	0	0%	2	1	50.0%	12.5%
'Scum' group	4	0	0%	0			0%
All groups	221	32	14.5%	69	40	58.0%	24.8%
All except the 'Patches' group	141	10	7.1%	48	20	41.7%	15.9%

Table 25. Type of Exudate, Age, and the Final Diagnosis.

Exudate-Group		Cases in age-groups (years)						
		0-11/12	1-4	5-9	10-14	15-19	20-	All Ages
'Patches'	Total no.	4	24	19	19	9	26	101
	Diph. no.	1	20	9	6	2	4	42
	" %	25%	83%	47%	32%	22%	15%	42%
'Semi-confluent Spots'	Total no.	1	8	12	13	10	7	51
	Diph. no.	0	0	2	2	0	2	6
	" %	0%	0%	17%	15%	0%	29%	12%
'Discrete Spots'	Total no.	0	12	30	25	7	13	87
	Diph. no.	0	3	9	2	2	2	18
	" %		25%	30%	8%	29%	15%	21%
'Clean Throats'	Total no.	1	11	10	9	3	5	39
	Diph. no.	1	0	2	2	0	0	5
	" %	100%	0%	20%	22%	0%	0%	13%
'Ulcer' group	Total no.	0	0	3	0	3	2	8
	Diph. no.	0	0	1	0	0	0	1
	" %			33%		0%	0%	12%
'Scum' group	Total no.	0	0	0	0	0	4	4
	Diph. no.	0	0	0	0	0	0	0
	" %						0%	0%
All groups	Total no.	6	55	74	66	32	57	290
	Diph. no.	2	23	23	12	4	8	72
	" %	33%	42%	31%	18%	12%	14%	25%
All except the 'Patches' group	Total no.	2	31	55	47	23	31	189
	Diph. no.	1	3	14	6	2	4	30
	" %	50%	10%	25%	13%	9%	13%	16%

diminishing proportional incidence of cases in which the diagnosis (of diphtheria) was confirmed, but that this was not so of cases with other forms of exudate or with none. The data on which these conclusions are based are given in table 25.

It is considered to be worthy of comment that many of the patients under the age of ten years were found to be suffering from non-diphtheritic and non-scarlatinal forms of follicular tonsillitis; for this finding was thought to be unexpected in view of Ker's statement (1909) that follicular tonsillitis is uncommon in children and his conclusion that "it really almost amounts to this, that, if we can exclude scarlatina and thrush in these young patients, any visible patching or speckling of the throat must be regarded as suspicious, and in any case should be treated as diphtheria". Of the 63 cases of follicular tonsillitis in children under the age of ten years in the present series (in 42 of which the exudate had had the form of 'discrete spots'; in the remainder it was essentially similar but, as there had been slight coalescence of the individual deposits, it was classed as 'semi-confluent spots'), in only 14 was there evidence of diphtheria, in 2 of scarlet fever, and in none of thrush. Regarding the diagnosis in the remaining 47 cases: 1 was a case of glandular fever; in 8, a non-virulent strain of C. diphtheriae was cultured from the throat swab (that organism may not, of course, have been causally related to the inflammation present); in 22, there was evidence/

evidence suggestive of streptococcal infection (these cases are included in the 'streptococcal' group in Appendix table II); in 9, there was no bacteriological or other evidence of any particular infection (these cases are classed in Appendix table II in the 'unknown cause' group); and in 7, which were classed in table II in the 'incompletely investigated' group, the bacteriological investigations were incomplete.

It was also found, as expected, that if only the less selected 'notified clinical' cases were considered, the incidence of the infections which Ker indicted was still less: for of the 48 cases (of children under ten years suffering from follicular tonsillitis) of this type, only 5 were diphtheritic, 2 scarlatinal, and none a case of thrush. In addition, however, there was one other case, a case of diphtheria, which, although the clinical picture on admission was that of follicular tonsillitis, was not so classed because 'typically diphtheritic membrane' developed subsequently (on the patient's second day in hospital) (see table 22, p. 164). While, as a result of recent epidemiological changes, the chances are now only small that a child presenting the clinical picture of follicular tonsillitis will be found to be suffering from diphtheria, the possibility of this should always be borne in mind - lest an atypical case of the disease or, more important, a typical case at an early stage, should be missed.

(2) <u>The Site of the Exudate</u>.

(a) <u>Regarding cases in which there was exudate</u>

both/

both on the tonsils and elsewhere in the throat.

The occurrence of 'spots' of exudate elsewhere than on the tonsils or tonsillar beds requires only brief consideration. This was encountered in five cases, in four of which the tonsillar exudate had also the form of 'spots', in the other, 'patches' (of 'friable membrane'). None was a case of diphtheria, nor was the clinical picture particularly suggestive of that disease. It appeared that the exudate had been formed in small follicles in the pharyngeal wall, and that this had been brought about by that process which so much more commonly and characteristically affects the follicles in the tonsils.

Similarly, the cases of tonsillitis in which there was also stomatitis, of a type characterised by the formation of a thin film of altered mucus over the surface of the palate and, in some cases, the fauces, can be dismissed with the statement that none was diphtheritic nor were the clinical appearances particularly suggestive of that disease. It will be recollected that four such cases were described as forming the 'scum' exudate-group; but there were also three other cases in which the clinical picture was similar which were not classified in that group as 'semi-confluent spots' were present on the tonsils.

A matter of greater diagnostic significance is the site of membranous exudate ('patches' of exudate). As is in accordance with the findings of Ker (1909) and others, it/

it was found that membranous exudate sited both on the tonsils and elsewhere (i.e. spreading from the tonsils to the anterior pillars or other parts of the pharynx or palate; or sited both on the tonsils and uvula) was very much more frequently encountered in diphtheria than in other disease; it occurred in 13 (31%) of the 42 cases of diphtheria with 'patches' of exudate, as against 1 (2%) of the 59 non-diphtheritic cases with that type of exudate. This difference is statistically significant.

The diphtheria cases with exudate spreading beyond the tonsils were discussed in Chapter VI. As regards the non-diphtheritic case, in this there was a 'patch' of 'friable membrane' covering about half of the one tonsil, 'semi-confluent spots' on the other, and a further 'patch' of 'friable membrane' covering about half of the uvula. Although the case is one of the 'incompletely investigated' group, and therefore the results as to Streptococcus haemolyticus were discounted, it is known that a practically pure growth of that organism was obtained on culture.

(b) Regarding cases in which there were 'patches' of exudate restricted to the tonsils.

Since it was found that membranous exudate which was so extensive that it had spread beyond the tonsils was almost always diphtheritic, it was thought that it might be interesting to correlate the extent of the exudate in cases in which membrane was present but was restricted to the tonsils with the proportional incidence of diphtheria. As /

Table 26. The Extent of the Membrane and the Final Diagnosis - cases with 'patches' of exudate, except those in which the membrane had spread beyond the tonsils and those in which 'spots' of exudate were present as well as 'patches'.

Extent of Membrane*	With Unilateral Membrane		With Bilateral Membrane		All Cases	
	Total cases	Diph. cases	Total cases	Diph. cases	Total cases	Diph. cases
Less than 1/3 tonsil	5	1 20.0%			5	1 20.0%
1/3 - 2/3	10	3 30.0%	1	0 0%	11	3 27.3%
2/3 - 1 1/3	6	3 50.0%	13	5 38.5%	19	8 42.1%
More than 1 1/3 tonsil			29	14 48.3%	29	14 48.3%
All groups	21	7 33.3%	43	19 44.2%	64	26 40.6%

*Extent of membrane: the figures in this column refer to the approximate proportion of the total tonsillar surface covered by membrane: thus both a case with unilateral membrane in which approximately 2/3 of the affected tonsil was covered, and one with bilateral membrane in which 1/3 of each tonsil was covered, were classed as having 2/3 of a tonsil covered.

As shown in table 26, it was found that the more extensive the membrane (i.e. the greater the proportion of tonsillar surface covered by it), the more likely it became that a given case would be found to be one of diphtheria. The differences, however, are not very marked, nor are they statistically significant; and it is important to note that even when both tonsils were completely, or nearly completely, covered with membrane, there was still only about an even chance (other factors such as age, the consistency of the exudate, and the basis of notification being ignored) that the case would be found to be one of diphtheria.

With further regard to table 26, it is also shown that the chances of the diagnosis being diphtheria were less if the membrane was unilateral than if it was bilateral. This finding is considered to be surprising, for Ker (1909) stated that, while diphtheria commonly affects either or both tonsils, the conditions simulating it usually affect both sides to an equal degree; he therefore opined that, other things being equal, the presence of a unilateral lesion was a point in favour of a diagnosis of diphtheria. The explanation of the difference between the findings described here and Ker's findings is uncertain; but the small size of the present series must be borne in mind.

(c) <u>The significance of the occurrence of both 'spots' and 'patches' of exudate in the same case</u>.

An impression was formed that, in cases with/

with 'patches' of exudate, the chances of the diagnosis being diphtheria were much less if 'spots' were also present. On analysis this impression proved to be correct: for it was found that the diagnosis of diphtheria was confirmed in only 5 (21%) of the 24 cases in which both 'patches' and 'spots' were present, as against 37 (48%) of the 77 cases with 'patches' only; the difference between these proportions is significant. If the cases in which the exudate had spread beyond the tonsils were excluded (for the reason that that occurrence in itself was found to be practically pathognomonic of diphtheria), a similar difference was observed - 3 (14%) of 22 cases with both 'patches' and 'spots' being diphtheritic, as against 26 (40%) of 65 with 'patches' only; as also if only the 'notified clinical' cases were considered (cases with exudate spreading beyond the tonsils being again excluded) - 1 (5%) diphtheritic out of 20 cases with both types of exudate, as against 15 (28%) of 53 cases with 'patches' only.

(3) The Persistence of the Exudate.

It was thought that it might be interesting to compare the length of time the exudate persisted in the diphtheria and other cases. In this respect, it was frequently noted that the throat relatively early became clear of 'patches' of exudate, but that small 'spots', situated in the crypts, tended to persist for longer, or to disappear, only to reappear again. For this reason, it was decided, for the purposes of this study, to regard previously patched throats as being 'clean' when they became free from/

from 'patches', whether 'spots' were still present or not.

It is apparent from table 27 that the exudate tended to persist for considerably longer in diphtheria than in the other conditions simulating it.

Table 27. The Persistence of the Exudate and the Final Diagnosis - Cases with 'Patches' of Exudate only.

Final Diagnosis	Persistence of the exudate in days*					
	2	3	4	5	6-	Total
Diph.	2 4.8%	2 4.8%	5 11.9%	4 9.6%	29 69.0%	42 100%
Other	9 15.3%	14 23.7%	10 16.9%	11 18.6%	15 25.4%	59 100%

*From the onset of the illness (as reported by the patient or relatives) to the time when the throat was first seen to be 'clean' in the sense defined in the text.

(4) The Degree of Hyperaemia.

It was pointed out by Bretonneau (1826) and many others since his time, and was found to be true of the present series of cases, that marked hyperaemia of the fauces occurs less frequently in diphtheria than in the other diseases which may simulate it. For it was found that a marked (i.e. 'moderate' or 'extreme') degree of hyperaemia occurred in only 16 (22%) of the 72 diphtheria cases, as compared with 91 (42%) of the 218 others - a difference which is statistically significant. When the cases were grouped as to whether membrane ('patches') had been present or not, it/

it was found that the difference was still more striking in the 'patches' group - marked hyperaemia having been present in 11 (26%) of the 42 diphtheria cases, as against 37 (63%) of the 59 others - but less so in the 'other than patches' group - 5 (17%) of 30 cases, as against 54 (34%) of 159.

It was stated in Chapter IV that in some cases the hyperaemia increased in degree after the patients were admitted, and that the degree recorded for classification purposes was the maximum in each case. From the point of view of differential diagnosis, however, it is perhaps more important to consider the position relatively early in the illness when the patients were admitted. In this respect, it was found that in only 50% of the diphtheria cases in which marked hyperaemia occurred had it been marked on admission, but that this was so of 74% of the other cases with marked hyperaemia. It is apparent, then, that the difference between the incidence of marked hyperaemia in the two series of cases was greatest relatively early in the illness.

It is commonly stated that while hyperaemia in diphtheria is relatively marked in a narrow areola surrounding the membrane, in other conditions, particularly streptococcal infection, it tends to be widespread over the fauces. Although the impression was formed that such an areola of relatively intense congestion was infrequent in the diphtheria cases of the present series, it must be admitted that no note was made as to its occurrence unless it was particularly striking. For classification purposes it was the degree of/

of hyperaemia of the fauces generally that was recorded.

(5) The Degree of Oedema.

Contrary to position with hyperaemia, it was found that a relatively marked degree of oedema of the fauces was more frequent in the cases in which the diagnosis of diphtheria was confirmed than in the others. Apart from the cases with peri-tonsillar cellulitis and abscess, which are considered separately, the oedema was not judged to be more than 'moderate' in degree in any; it was classed as being of that degree in 11 (15%) of the 72 diphtheria cases, and in 13 (6%) of the 218 other cases. The difference between these proportions is significant. As regards the type of exudate, it was found that the difference only occurred in the 'patches' group of cases, in which the oedema was 'moderate' in degree in 10 (24%) of the 42 diphtheria cases and in 8 (14%) of the 59 other cases, not in the group of cases with other types of exudate or with none, in which the rate for both the diphtheria and other cases was 3%.

Since an appearance resembling quinsy (except that pus is not formed) is known to occur in very severe diphtheria, it was thought that it might be interesting to compare the incidence of peri-tonsillar cellulitis in the diphtheria cases with that in the other cases. Unfortunately, however, as stated in Chapter IV, in the earlier part of the work the distinction between peri-tonsillar cellulitis and abscess was not always clearly brought out in the notes; so the comparison could not be made. But it may be mentioned/

mentioned that peri-tonsillar cellulitis or abscess occurred in 2 (3%) of the diphtheria cases and in 11 (5%) of the others. Of the two diphtheria cases referred to, one was the case of peri-tonsillar abscess described on p.114 (where it was stated that it was considered that the lesion was the result of streptococcal infection and that the strain of C. diphtheriae present was almost certainly not implicated in the pathogenesis); in the other, peri-tonsillar cellulitis (not abscess) occurred, and it seemed that this was due to the severity of the attack of diphtheria, not to any other infection. The rarity of cases of diphtheria with very marked oedema (simulating quinsy) is no doubt attributable to the relative mildness of the disease at the time of the investigation.

(6) Other Abnormalities of the Throat.

(a) Keratosis.

Only brief mention requires to be made of the diagnostic significance of the change described on p.66 as keratosis. It will be recollected that multiple white specks were seen on the anterior pillars in four cases, in all of which there was very marked hyperaemia of the fauces and, in three, peri-tonsillar cellulitis or abscess on the side of the throat in which the white specks were seen. None of the cases was diphtheritic. It seems that keratosis may be regarded as being an accompaniment of extreme hyperaemia of the mucosa; it is therefore unlikely to be/

be encountered in diphtheria.

(b) The occurrence of 'vesicles'.

Reference was made on p. 66 to the occurrence, in certain cases, of one or, more rarely, more, small bullae or vesicles, usually situated on one of the anterior pillars. It was suggested that, except in one case, which was probably herpetic, the feature could be regarded as being a non-specific accompaniment of hyperaemia of the surrounding parts. Although hyperaemia of the fauces was present in the affected cases, it was not always of an extreme degree, as it was in the cases with keratosis. As the proportional incidence of the feature was the same in the diphtheria cases as in the others (it occurred in 2 of the former, and 7 of the latter - that is, in 3% of both groups), it would appear that its occurrence is of no particular significance as regards the diagnosis of diphtheria.

(7) Nasal Symptoms.

For the purposes of analysis, 'throat' cases which had presented signs of nasal disease were divided into three main categories, as described in table 28. In assessing the amount of the discharge, if there was any doubt as to whether this was 'slight' or 'profuse', it was classed as being the latter.

It is apparent from the table that while profuse discharge was more frequent in the diphtheria cases than in the others, and the other signs slightly less frequent, the differences were not very marked; nor are they statistically/

Table 28. The Occurrence of Nasal Signs, and the Final Diagnosis.

Group of Cases	Final Diagnosis	Total Cases	Cases with Signs of Category*			
			I	II	III	Total with signs
All 'Throat' Cases	Diph.	72 100%	14 19.4%	8 11.1%	3 4.2%	25 34.7%
	Other	218 100%	48 22.2%	39 17.9%	3 1.4%	90 41.3%
Cases with 'Patches' limited to the tonsils	Diph.	29 100%	5 17.2%	3 10.3%	0 0%	8 27.6%
	Other	58 100%	9 15.5%	7 12.1%	3 5.2%	19 32.8%

*The categories into which 'Throat' cases with nasal signs were divided were as follows:

I: Cases in which the only indication of nasal disease was the presence of post-nasal discharge, or nasal obstruction, or both these abnormalities. (Often the discharge was only intermittent, or only seen when the patient retched; the obstruction was also often chronic in nature, as from enlarged adenoids. It is probable that the nasal condition in many of the cases in this category was of long standing, and had no direct bearing on the acute throat disease which had aroused suspicion as to the possibility of diphtheria.)

II: Cases in which there was a slight amount only of mucoid or muco-purulent (anterior) nasal discharge, with or without post-nasal discharge and signs of obstruction. (In a few of these cases, too, the condition was apparently chronic, and was probably not directly associated with the coincidental acute throat condition.)

III: Cases in which there was moderately, or very, profuse (anterior) nasal discharge, with or without post-nasal discharge and obstruction. (Here it seemed that the nasal and throat conditions were directly associated with each other.)

It may also be mentioned that in no case was membrane present in the anterior part of the nose. Nor did epistaxis occur except of a very slight degree, and very temporarily, in a few cases; in these there was often doubt as to whether the cause was not trauma inflicted accidentally while taking a swab. In 2 of the diphtheria cases and 3 of the others, all classed in category III above, there was very profuse yellowish-brown discharge, the colour of which may have been due to the presence of altered blood.

statistically significant. With regard to the three diphtheria cases with profuse discharge, the disease in these was of naso-pharyngeal distribution; the faucial signs were quite characteristic, there being 'typically diphtheritic membrane' spreading beyond the tonsils.

It was thought interesting to determine if the occurrence of nasal signs in cases with membrane ('patches') limited to the tonsils could be taken as indicating that the diagnosis of diphtheria was more or less probable. In fact, however, as such signs occurred in approximately the same proportion of both the diphtheria and the other cases of that type (except that profuse discharge only occurred in the non-diphtheritic cases; but this may be due to chance), it would seem that their occurrence is of no particular significance as regards the differential diagnosis.

(8) Cervical Adenitis.

(a) Peri-adenitis.

The presence of peri-adenitis was suspected in 2 of the 72 diphtheria cases (2.8%), but in none of the 218 other cases. While this difference is significant, in the cases of diphtheria affected, the diagnosis had been self-evident, apart from the presence of peri-adenitis, on account of the occurrence of 'typically diphtheritic membrane with free edge' of tonsillo-pharyngeal distribution.

(b) Enlargement of the cervical glands.

It was found that a 'considerable' degree of enlargement of the cervical glands occurred significantly more/

more often in the diphtheria cases in which there were 'patches' of exudate than in the corresponding group of the non-diphtheria cases, but that the incidence of this feature was approximately the same in the two groups of cases without 'patches'. The relevant data are shown in table 29. As in the case of peri-adenitis, so with considerable glandular enlargement, when this feature occurred in diphtheria the other clinical signs were usually such as to leave but little doubt as to the diagnosis.

(c) Tenderness of the cervical glands.

It was found, as shown in table 30, that tenderness of the cervical glands was most common in those cases, whether diphtheritic or not, in which relatively extensive exudate (that is, 'patches') was present. Although it was more frequent in the non-diphtheritic cases with a given type of exudate than in the corresponding group of the diphtheria cases, the difference was not very marked, nor is it statistically significant.

(9) The Tongue.

With regard to the possible significance of a 'strawberry' tongue in the differential diagnosis of acute sore throat, it is proposed, in the first case, to refer briefly to Ker's (1909) views on the subject. Discussing scarlet fever, Ker stated that while the 'white strawberry' tongue, which appears first in that disease, also occurs not infrequently in other conditions such as diphtheria, the 'red' type, which develops subsequently, seldom occurs in any other/

Table 29. Enlargement of the Cervical Glands, the Type of Exudate, and the Final Diagnosis.

Type of Exudate	Diph. cases			Other cases		
	Total cases	Cases with Enlargement*		Total cases	Cases with Enlargement*	
'Patches'	42	9	21.4%	59	4	6.8%
'Other-than-patches'	30	1	3.3%	159	7	4.4%
Total	72	10	13.9%	218	11	5.0%

*The glands were only classed as being enlarged if they were 'considerably' so; this term is defined on p. 68.

Table 30. Tenderness of the Cervical Glands, the Type of Exudate, and the Final Diagnosis.

Type of Exudate	Diph. cases				Other cases			
	Total cases	Cases with*			Total cases	Cases with*		
		t/T		T		t/T		T
'Patches'	42	19	45.2%	4 9.5%	59	32	54.2%	10 16.9%
'Other-than-patches'	30	7	23.3%	0 0%	159	42	26.4%	7 4.4%
Total	72	26	36.2%	4 5.6%	218	74	33.9%	17 7.8%

*t/T = cases with 'slight' or 'marked' tenderness of the glands.

T = cases with 'marked' tenderness of the glands.

other condition. As to the pathogenesis of the tongue changes, Ker considered it probable that they were associated with the rash, not primarily with the local lesion in the throat (or elsewhere). (The well-known fact that the typical tongue may occur in surgical scarlet fever is corroborative of this theory.) This view may be otherwise stated thus: that the 'red strawberry' tongue is almost always caused by the erythrogenic toxin of scarlet fever, but that the 'white strawberry' is also produced by other factors.

Referring to the appearance of the tongue as a factor in the differential diagnosis of throat conditions other than those associated with scarlet fever - for example, in the differentiation of non-scarlatinal forms of streptococcal tonsillitis from diphtheria - it might be expected, on account of the view expressed above, that a 'red strawberry' tongue would not appear in either of the two diseases specified and therefore could not be of any diagnostic value; but although the diagnostic significance of a 'white strawberry' tongue would be limited (for it is known to occur in both diseases), it would not necessarily be entirely valueless (for experience might perhaps show that it occurred more often in the one disease than the other). In view of this possibility, it was decided to analyse the date bearing on this subject obtained in the present series of cases. The findings in the 'throat' cases, and also in the 'scarlet fever' (control) series, are shown in tables 31 to 33.

It was pointed out in Chapter IV that a record/

Table 31. The Incidence of 'Strawberry Tongue', the Type of Exudate, and the Final Diagnosis.

Type of Exudate	Diph. cases					Other cases				
	Total Cases	Cases with*				Total Cases	Cases with*			
		s/S		S			s/S		S	
'Patches'	42	25	59.5%	2	4.8%	59	37	62.7%	5	8.5%
Other than 'patches'	30	13	43.3%	0	0%	159	72	45.3%	9	5.7%
Total	72	38	52.8%	2	2.8%	218	109	50.0%	14	6.4%

*In this and the following tables,

s/S = 'strawberry' tongue of 'moderate' or 'very marked degree.

S = 'strawberry' tongue of 'very marked' degree.

Table 32. Scarlet Fever (Control) Series of Cases - the Incidence of 'Strawberry Tongue' and the Type of Exudate.

Type of Exudate	Total Cases	Cases with			
		s/S		S	
'Patches'	1	1	100%	0	0%
'Other than patches'	49	46	93.9%	25	51.0%
Total	50	47	94.0%	25	50.0%

Table 33. The Incidence of 'Strawberry Tongue', the Bacteriological Findings as to Streptococcus haemolyticus (H.S.), the Type of Exudate, and the Final Diagnosis.

Final Diagnosis	Type of Exudate	'H.S. Plus' Cases*				'H.S. Neg.' Cases*			
		Total Cases	Cases with			Total Cases	Cases with		
			s/S		S		s/S		S
Diph.	'Patches'	13	9	69.2%	1 7.7%	16	9	56.2%	0 0%
	'Other than patches'	5	1	20.0%	0 0%	12	6	50.0%	0 0%
Other than Diph.	'Patches'	34	22	64.7%	3 8.8%	10	5	50.0%	0 0%
	'Other than patches'	76	34	44.7%	1 1.3%	35	14	40.0%	5 14.3%

*Classification as to bacteriological results:

The 'H.S. Plus' group in the above table consists of those 'negative' (for C. diphtheriae) cases which were classed in the 'streptococcal' group, and of the 'diphtheria' and 'non-virulent' cases in which H.S. was isolated in culture in a density of growth of '2 plus' or more.

The 'H.S. Neg.' group consists of the cases in which H.S. was not isolated.

Excluded from the table are those (diphtheria and other) cases classed in the 'incompletely investigated' group (in which the results as to H.S. were discounted) and those in which a scanty growth only ('1 plus') of H.S. was obtained.

record was not always made as to whether a given 'strawberry' tongue was 'white' or 'red', but that a strong impression was formed that in nearly all of the cases of the 'main series' with this abnormality, it was of the 'white' type and did not later develop into the 'red'; in the 'scarlet fever' series, on the other hand, development from the 'white' type to the 'red' occurred commonly. Turning to the data tabulated, it is clear that the most striking difference was between the incidence of 'strawberry tongue' in the 'scarlet fever' series (which was almost 100%) and the incidence in the 'main series' (which was approximately 50%). With regard to the latter series, it is shown that a 'strawberry' tongue was most commonly present when the exudate was relatively extensive (in the form of 'patches'), but that the frequency of the feature was much the same whether there was bacteriological evidence suggestive of streptococcal infection or not, and whether diphtheria was the diagnosis or not. It would appear then that while, as is well known, the occurrence of a 'strawberry' tongue may be a feature of considerable value in the diagnosis of scarlet fever, it is of no value in the differential diagnosis of non-scarlatinal throat disease. (Further support to this conclusion may perhaps be taken from the work of Dingle et al. (1947) in that these investigators, who discuss fully the features which may assist in the differentiation of streptococcal from other forms of throat disease, make no mention of the appearance of the tongue as being of diagnostic value.)

(10) The Ears.

As also with regard to tenderness of the cervical glands and the appearance of the tongue, it was anticipated that signs of inflammation of the middle ear might be found to occur more frequently in the non-diphtheritic cases - most of which appeared to be instances of streptococcal infection - than in the cases of diphtheria; but here again, as the figures quoted below show, such differences as did occur might easily have happened by chance.

Well-established acute catarrhal otitis media (with inflammation and bulging of the drum, but without perforation) and acute suppurative otitis media (with purulent otorrhoea) did not occur in any of the diphtheria cases, but the former occurred in 2 (0.9%), and the latter in 1 (0.5%), of the other cases. Radial injection of the vessels of the drum, without any other abnormal signs and without symptoms, (which should perhaps be regarded as being indicative of a minor degree of catarrhal otitis) occurred in 2 (2.8%) of the diphtheria cases and in 5 (2.3%) of the others. Chronic suppurative otitis media (of much longer duration than the acute throat condition which had led to the patients' admission to hospital) was present in 2 (2.8%) of the diphtheria cases (C. diphtheriae was isolated from the discharge in one of these cases) and in 3 (1.4%) of the others.

An 'abnormality' which was so often seen that it appeared that it should be regarded as 'normal' was the occurrence of a slight degree of injection localised to the part of the drum where the handle of the malleus is inserted;/

inserted; in some cases one or more minute vessels were injected at that site; in others there was slight reddening of the drum in the immediate vicinity. It must be stressed that these changes were usually of minimal degree only, and could only be appreciated on very close inspection of the drums. During the earlier part of the work, no particular attention was paid to this minimal 'abnormality', and otherwise healthy-looking drums were classed as normal whether it was present or not. Later, as it was thought that it might be of interest to study the incidence of the feature in relation to the final diagnosis, a record was made of its occurrence. It was found that the feature occurred in a higher proportion of the diphtheria cases than of the others (in 18, or 42.9%, of the 42 diphtheria cases studied from this point of view, and in 28, or 27.2%, of the 103 other cases studied) but that the difference was not significant.

To summarise, it was found that the incidence of definite otitis media, as also of minimal injection, probably of no pathological significance, restricted to the immediate vicinity of the insertion of the ossicles, was much the same in the diphtheria cases as in the others. It would appear, then, that the occurrence of these features in a case of acute sore throat does not signify that diphtheria is any more or less likely to be the diagnosis.

(C) The Signs of Toxaemia.

(1) General Appearance.

As described on p.76 , in assessing the/

the general appearance (with regard to toxaemia) in each case on admission, an attempt was made to discount any bias which knowledge as to such features as the state of the throat might give. It is shown in table 34 that in only a very small proportion of the cases (whether of diphtheria or otherwise) was the general appearance judged to be indubitably indicative of more than a slight degree of toxaemia. It was especially

Table 34. 'General Appearance' on Admission and the Final Diagnosis.

Final Diagnosis	Total cases	'General Appearance'			
		'Moderately Severe'		'Severe'	
Diph.	72	2	2.8%	1	1.4%
Other	218	4	1.8%	2	0.9%

striking that in a considerable number of cases of diphtheria in which toxic complications subsequently developed, the general appearance on admission was not particularly, or at all, suggestive of toxaemia (see Appendix table VII). In only one case (a case of diphtheria; no. 3 in the table referred to) was there that marked listlessness, pallor, and prostration described by Ker (1909) as being a characteristic feature of really severe diphtheria.

(2) Temperature.

It was found in both the diphtheria and other cases that the temperature was most often relatively high in cases in which 'patches' of exudate were present. The type/

type of exudate was therefore taken into account in table 35 in which is presented the data on this subject. It is apparent from the table that the differences as to maximum temperature in the two series of cases (diphtheria and other) were not marked. In the following table it is shown that in the diphtheria cases there was no striking correlation between the presence or otherwise of Streptococcus haemolyticus and the maximum temperature.

Regarding the literature on the subject, Ker (1909) observed that the temperature was often normal or only slightly elevated in severe cases of diphtheria and considered that this was a point of some diagnostic importance. Bamberger (1947), however, found in a very large series of cases of diphtheria that in the more severe cases (severe as judged by the subsequent progress) the temperature, although occasionally normal or only slightly elevated, was usually relatively high.

While the finding of a normal or only slightly raised temperature in a severe case of membranous inflammation of the throat could perhaps be taken as a point in favour of the diagnosis of diphtheria, it is probable that in cases of such severity there would be other clinical features pointing more strongly to the diagnosis.

(3) The Pulse Rate.

The importance of study of the pulse, as also of the heart sounds and urine, in the diagnosis of diphtheritic toxic damage was discussed in Chapter IV. In this section,/

Table 35. The Maximum Temperature (during the acute stage of the illness), the Type of Exudate, and the Final Diagnosis.

Type of Exudate	Final Diagnosis	Total Cases	Cases with Maximum Temperature							
			-98.8°		99°-		101°-		103°-	
'Patches'	Diph.	42	8	19%	21	50%	11	26%	2	5%
	Other	59	7	12%	27	46%	23	39%	2	3%
'Other-than -patches'	Diph.	30	13	43%	11	37%	6	20%	0	0%
	Other	159	34	22%	73	46%	47	30%	5	3%
Total	Diph.	72	21	29%	32	44%	17	24%	2	3%
	Other	218	41	19%	100	46%	70	32%	7	3%

Table 36. The Maximum Temperature, the Findings as to Streptococcus haemolyticus (H.S.), and the Type of Exudate - Diphtheria cases only.*

Type of Exudate	Growth of H.S.	Total Cases	Cases with Maximum Temperature							
			-98.8°		99°-		101°-		103°-	
'Patches'	'2 plus' or more	13	0	0%	11	85%	2	15%	0	0%
	'1 plus'	8	2	25%	2	25%	3	37%	1	12%
	nil	16	4	25%	7	44%	5	31%	0	0%
'Other-than - patches'	'2 plus' or more	5	3	60%	2	40%	0	0%	0	0%
	'1 plus'	3	2	67%	0	0%	1	33%	0	0%
	nil	12	5	42%	4	33%	3	25%	0	0%

*Except those classed as 'incompletely investigated' (in which the findings as to H.S. were discounted).

section, brief comment is made on the significance of the pulse rate in the differential diagnosis of the early stage of the disease from other conditions in which a similar local lesion may occur in the throat. In this respect, Ker, Bamberger, and others have stated that in diphtheria, but not particularly in most other inflammations of the throat, the pulse tends to be disproportionately rapid as compared with the degree of pyrexia. In the present series it was found to be practically impossible to test the validity of this assertion: for the pulse rate is known to be affected by so many diverse factors (e.g. age, personal idiosyncrasy, the effects of different diseases, the effect of such psychological factors as the stress which may follow hospitalisation) which it is difficult to make allowance for, that it was considered that statistical analysis of the material would not serve any useful purpose. In view of the large number of variables, the impression was formed that, in general, the pulse rate is not a factor of much value in the diagnosis of the early stage of diphtheria.

(D) The Bacteriological Findings (with regard to organisms other than C. diphtheriae).

The bacteriological findings with regard to Streptococcus haemolyticus (H.S.) and certain other organisms (other than C. diphtheriae) are of obvious importance in the differential diagnosis of those cases of suspected diphtheria in which that diagnosis is not confirmed. But since the investigations to detect the presence of these organisms/

organisms are often less time-consuming than is the full investigation for C. diphtheriae, and for other reasons, it was thought that it might be of interest to study the relative incidence of these organisms in the 'diphtheria' and 'other' groups of cases - to determine, for example, whether it seemed likely that the isolation in a given case of a heavy growth of H.S. could be taken as indicating that the diagnosis of diphtheria would be less likely to be confirmed.

With regard to H.S., it is apparent from table 37 that if that organism was present, but only in the form of a scanty growth ('1 plus'), the chances of a given case being one of diphtheria were not less than they would have been if it had not been isolated; but that the chances were less if the growth was more profuse, and that they progressively lessened, the heavier the growth. None the less, there was a number, although small, of typical cases of diphtheria (bacteriologically confirmed) in which a fairly heavy growth ('2 plus' to '4 plus') of H.S. was obtained.

With regard to Vincent's organisms, the warning is given in most text-books that diphtheria and Vincent's angina may co-exist and that, in a given case, bacteriological evidence of the latter disease must not be taken as excluding the former. None the less, if Vincent's angina occurs relatively frequently as an idiopathic disease, as well as as a complicating feature of other diseases such as diphtheria, then it would perhaps be expected that bacteriological evidence of that disease would be found less commonly in/

Table 37. Findings as to H.S., Final Diagnosis (whether diphtheria or not), and Type of Exudate: All 'throat' cases except those in the 'incompletely investigated' group.

No. of colonies of H.S.	Type of Exudate					
	'Patches'		'Other than Patches'		All Types	
	Total Cases	Diph. Cases	Total Cases	Diph. Cases	Total Cases	Diph. Cases
Nil	26	16 61.5%	49	12 24.5%	75	28 37.3%
'1 plus'	8	8 100.0%	16	3 18.7%	24	11 45.8%
'2 plus'	14	7 50.0%	19	2 10.5%	33	9 27.3%
'3 plus'	15	5 33.3%	24	1 4.2%	39	6 15.4%
'4 plus'	13	1 7.7%	24	2 8.3%	37	3 8.1%
'5 plus'	5	0 0%	8	0 0%	13	0 0%

Table 38. Findings as to Vincent's Organisms, Final Diagnosis, and Type of Exudate: All 'throat' cases except the 39 in the 'clean throats' group and 12 other cases (in most of which there was minimal exudate only) in which direct films were not made.

	Type of Exudate and Final Diagnosis					
	Patches		Other than Patches		All Types	
	Diph.	Other	Diph.	Other	Diph.	Other
Total Cases	42 100%	57 100%	22 100%	118 100%	64 100%	175 100%
Cases with F.※ in any no., with or without S.ø	40 95.2%	55 96.5%	17 77.3%	106 89.8%	57 89.1%	161 92.0%
Cases with F. '2 plus' or more, with or without S.	32 76.2%	36 63.2%	8 36.4%	59 50.0%	40 62.5%	95 54.3%
Cases with F. '3 plus', with or without S.	19 45.2%	22 38.6%	5 22.7%	30 25.4%	24 37.5%	52 29.7%
Cases with both F. & S., each in any no.	22 52.4%	33 57.9%	7 31.8%	47 39.8%	29 45.3%	80 45.7%
Cases with F. & S., both '2 plus' or more	9 21.4%	8 14.0%	1 4.5%	12 10.2%	10 15.6%	20 11.4%
Cases with F. & S., both '3 plus'	2 4.8%	3 5.3%	0 0%	7 5.9%	2 31.2%	10 5.7%

※F. = Fusiform organisms. ø S. = Spirochaetes.

Note: Spirochaetes were only seen in cases in which fusiform organisms were also present.

in diphtheria than in cases of other disease of less certain origin (in that an appreciable number of the latter cases might be instances of the disease); but, as is shown in table 38, this was not found to occur in the series of cases studied. As the possible significance of this finding is discussed fully in Chapter IX, it is sufficient here to summarise by stating that, with regard to the diagnosis of diphtheria, it appears that the finding, in a given case, of fusiform organisms and spirochaetes in the direct film - even if both are present in large numbers - does not lessen, in any way, the degree of probability that the case may be one of diphtheria.

Regarding organisms other than Vincent's, C. diphtheriae, and H.S., it will be recollected that only the findings in the last 180 cases in the series were accepted as being uniformly reliable. Of these cases, 165 were classed in the 'throat' group (48 were cases of diphtheria, 117 were not) and it is on the basis of the observations made in these that the following comments are founded. In general, the results were such as to justify the conclusion that the findings with regard to the organisms referred to are of little or no value in the diagnosis of diphtheria. With regard to Neisseriae and the 'Streptococcus viridans/pneumococcus' group, for example, these organisms occurred in the great majority of both the diphtheria and other cases (in approximately 90% of both groups of cases) and, in both groups, the growth was often profuse. While Staphlococcus/

Staphlococcus aureus, Haemophilus influenzae, and yeasts were slightly more often isolated from the 'other' cases than from the cases of 'diphtheria' (the incidence rates are shown in Appendix table IX), they were but seldom isolated in either group of cases, and the differences between the incidence rates in the two groups are not significant.

To summarise this section, it was found that if more than a scanty growth of Streptococcus haemolyticus was isolated in the culture from a suspected case of diphtheria, then the heavier the growth, the less the chances became that the diagnosis of diphtheria would be confirmed; but that the results as to Vincent's organisms, Neisseriae, the 'Streptococcus viridans/pneumococcus' group, Staphlococcus aureus, Haemophilus influenzae, and yeasts seemed to have little or no bearing on the problem as to whether a given suspected case was likely to be one of diphtheria or not.

(E) The Immunological Data.

(1) The Inoculation History.

As is shown in tables 39 and 40, it was found that the suspected diagnosis of diphtheria was confirmed in a lesser proportion of the cases in which there was a history of prophylactic inoculation than of those without such a history; the difference is one that is significant. On further analysis it was found that the difference was particularly marked in respect of the cases without 'patches' of exudate (in most of which the clinical signs were those of follicular or catarrhal tonsillitis). With regard to those/

Table 39. The Inoculation History, the Basis of Notification, the Type of Exudate, and the Final Diagnosis.

Type of Exudate	Basis of Notification	Inoculated			Uninoculated		
		Total Cases	Diph. Cases		Total Cases	Diph. Cases	
'Patches'	'Clinical'	37	10	27.0%	43	12	27.9%
	'Positive'	6	5	83.3%	15	15	100.0%
'Other than Patches'	'Clinical'	81	4	4.9%	60	6	10.0%
	'Positive'	26	8	30.8%	22	12	54.5%
All types	'Clinical'	118	14	11.9%	103	18	17.5%
	'Positive'	32	13	40.6%	37	27	73.0%
All Cases		150	27	18.0%	140	45	32.1%

Table 40. The Inoculation History, Age, the Type of Exudate, and the Final Diagnosis.

Type of Exudate	Age-Group (Years)	Inoculated			Uninoculated		
		Total Cases	Diph. Cases		Total Cases	Diph. Cases	
'Patches'	0-11/12	0	0		4	1	25.0%
	1 - 4	7	5	71.4%	17	15	88.2%
	5 -14	24	8	33.3%	14	7	50.0%
	15 -	12	2	16.7%	23	4	17.4%
	All Ages	43	15	34.9%	58	27	46.6%
'Other than Patches'	0-11/12	0	0		2	1	50.0%
	1 - 4	16	0	0%	15	3	20.0%
	5 -14	69	10	14.5%	33	10	30.3%
	15 -	22	2	9.1%	32	4	12.5%
	All Ages	107	12	11.2%	82	18	22.0%

those with 'patches' of exudate, it was found that, when allowance was made for the 'basis of notification' of the cases, the diagnosis of diphtheria had been confirmed in approximately the same proportion of both the 'inoculated' and the 'uninoculated' cases.

With further regard to table 40, it is apparent that the influence of age, the type of exudate, and the inoculation history on the diagnosis-confirmation rate was much as would have been anticipated by making allowances for each of these factors considered separately (the slightly higher rate in the 'uninoculated' groups of cases with 'patches' of exudate than in the corresponding 'inoculated' groups can be attributed to an excess of 'notified positive' cases in the former groups).

It is considered to be particularly interesting that the diagnosis of diphtheria was confirmed in a much smaller proportion of the cases of follicular or catarrhal tonsillitis (or of other throat affection in which 'patches' of exudate are not formed) in which there was a history of inoculation than of the similar cases without such a history and that this was true of both the 'notified positive' and the 'notified clinical' groups of cases. This finding accords with the suggestion made on p.24 that atypical attacks of diphtheria are far from being peculiar to previously inoculated subjects.

(2) <u>The Shick Test Results</u>.

The data regarding the Shick test results are/

are quoted and discussed in Chapter VI (p. 133 ff.) where it is shown that there was a considerably higher Shick-negative rate in the 'other' cases than in the cases of diphtheria; this difference is one that is statistically significant. In view of the observations of others - mentioned in Chapter II - it is probable that a Shick negative reactor (whether the reaction is negative because of artificial immunisation or otherwise) is very much less likely to contract diphtheria than a positive reactor and is very unlikely to suffer a severe attack. None the less, both these eventualities are possible; regarding the latter eventuality, it is shown in table 15 (p. 137) that while the test was performed in only three of the cases in the present series in which toxic complications later developed, the result was negative in two.

The value and limitations of the test in the differentiation of mild diphtheria from other disease occurring in a carrier are discussed in Chapter II.

SECTION III. SUMMARY OF THE FACTORS WHICH ARE OF MOST IMPORTANCE IN THE DIAGNOSIS OF DIPHTHERIA.

As the preceding sections of this chapter contain the most important parts of the present work but are somewhat lengthy, a brief summary is given here of the main points which are brought out.

Attention is first directed to certain cases which indicate that the danger, clearly described by Bretonneau (1855), of confusing diphtheria with coryza still exists even/

even in times when the prevalence of the former disease is low. This warning applies to both the anterior nasal and the more sinister naso-pharyngeal types of the disease (in the latter type, it is, of course, in the case of infants that confusion is most likely to occur).

The principal part of the chapter (Section II) deals with cases in which the throat is affected. Certain points about the clinical history are considered first. With regard to the 'basis of notification' of the cases, it was found that the diagnosis of diphtheria was confirmed more frequently in the 'notified positive' group of cases (those in which a provisionally positive bacteriological report - regarding C. diphtheriae - had been received) than in the 'notified clinical' group; but that even in the former group the diagnosis-confirmation rate was only 58%. In this respect it may be mentioned that, as a result of the continuing decline in the incidence of diphtheria, the proportion of 'notified positive' cases in which the diagnosis is confirmed is now considerably less than it was at the time when the clinical observations described here were made.

With regard to sex and age, it was not possible to demonstrate any correlation between the former factor and the diagnosis-confirmation rate. Age was shown to be of importance, but only in the group of cases in which 'patches' of exudate were present - in which group there was a striking correlation between increasing age (from the 1-4 years group upwards) and decreasing proportional incidence of cases in/

in which the diagnosis was confirmed. Not only were the chances high that a young child with 'patches' of exudate would be found to be suffering from diphtheria, but it was also found that the incidence of toxic complications in the disease was greatest in early childhood. In the cases in which 'patches' were not present, the diagnosis was confirmed only relatively rarely - irrespective of the age of the patient.

To consider the remaining points about the clinical history, it was found that the average duration of illness prior to admission was approximately the same in both the diphtheria and other groups of cases. It was concluded that the previous medical history - particularly as to attacks, or suspected attacks, of diphtheria - and a history of contact with cases, or suspected cases, of diphtheria or scarlet fever were, if interpreted with caution, of some help in diagnosis.

With regard to the features classed in the 'local signs' category, the characteristics of the exudate present (if any) were found to be of paramount importance. To consider first the type of exudate, the diagnosis of diphtheria was confirmed in 42% of the cases with 'patches' of exudate, but in only a much smaller proportion of those in the other main exudate-groups (see Appendix table III); of all the cases without 'patches' of exudate, the diagnosis was confirmed in only 16%. On further analysis of the cases with 'patches' (see Appendix table IV), it was found that 100% of those with 'typically diphtheritic membrane' ('tough' and 'adherent' 'sheet-like' exudate which is not 'intimately/

'intimately adherent') were diphtheritic*, but that this was so of only 9% of the only other numerically large group of cases - those with 'friable membrane'. The importance of considering the age of the patient in assessing the diagnostic significance of 'patches' of exudate was previously mentioned in this summary.

With regard to the site of the exudate, all but 1 of the 14 cases in which 'patches' were present on the tonsils and elsewhere were diphtheritic. In the cases with 'patches' limited to the tonsils, the presence of 'spots' as well as 'patches' was found to indicate that diphtheria was much less likely to be the diagnosis than if 'patches' only were present. In the cases with 'patches' only (not also with 'spots'), limited to the tonsils, the diagnosis of diphtheria was most frequently confirmed in the cases in which the 'patches' were relatively extensive. As to the persistence of the exudate, it was concluded that relatively rapid clearing of the throat indicates that diphtheria is less likely to be the diagnosis.

To consider the other 'local signs', it was found that marked hyperaemia occurred significantly more often in the 'other' cases than in the cases of diphtheria, and that the opposite was true of oedema of moderate degree. These differences were particularly marked in the groups of cases/

*The author has subsequently encountered two cases of glandular fever in which what he regarded as 'typically diphtheritic membrane' was present (see p.210).

cases (diphtheria and 'other') in which 'patches' of exudate were present - the cases in which the clinical picture was most suggestive of diphtheria. Regarding hyperaemia, the difference was greatest relatively early in the illness when the patients were first admitted to hospital.

It was found that signs of nasal disease occurred in approximately the same proportion of the diphtheria and 'other' cases. With regard to the cervical glands, it was concluded that the occurrence of peri-adenitis, or of a considerable degree of enlargement of the glands, favoured the diagnosis of diphtheria, and indicated that the case, if one of that disease, might well be severe. On the other hand, however, 'typically diphtheritic membrane' spreading beyond the tonsils was present in most of the cases in which these features occurred, and this in itself pointed strongly to diphtheria. As the incidence of tenderness of the glands was approximately the same in both the diphtheria and 'other' cases (in both groups it was most frequent when relatively extensive exudate - viz. 'patches' - was present), it was concluded that its occurrence is not of itself a point for or against the diagnosis of diphtheria.

Other 'local signs' which, it appeared, are not of much assistance in the differentiation of diphtheria from other forms of throat infection are those relative to the state of the tongue and middle ears.

With regard to the signs indicative of toxaemia, it was concluded that knowledge as to the pulse and temperature/

temperature during the acute stage of the illness is only of very limited value in the differentiation of diphtheria from other disease. (Referring to the signs which may develop during the first three weeks of the illness, the importance was stressed in Chapter IV of continued observation, to detect the early signs of toxic damage, in cases of diphtheria and in other cases in which that diagnosis cannot be entirely ruled out.)

With regard to the bacteriological investigations to detect the presence of organisms other than C. diphtheriae, it was found that if more than a scanty ('1 plus') growth of Streptococcus haemolyticus was obtained, then the heavier the growth, the less likely it became that the diagnosis of diphtheria would be confirmed. It was concluded that knowledge as to the occurrence of Vincent's organisms, and certain other organisms, is of little or no value in the differentiation of diphtheria from other disease.

In considering the diagnostic significance of a history of prophylactic inoculation, it is necessary to take into account the type of exudate present: the diagnosis of diphtheria was confirmed in a much smaller proportion of the 'inoculated' cases in which the signs were those of follicular or catarrhal tonsillitis (or of other throat affection in which 'patches' of exudate are not formed) than of the corresponding group of 'uninoculated' cases; but it was confirmed in much the same proportion of both the 'inoculated' and 'uninoculated' cases with 'patches' of exudate.

Reference is also made to the Shick test results./

results. Other points about the value and limitations of this test in diagnosis are discussed in Chapter II.

SECTION IV. CONSIDERATION OF THE QUESTION, "HAVE THE CLINICAL CRITERIA FOR THE DIAGNOSIS OF DIPHTHERIA CHANGED FUNDAMENTALLY IN RECENT YEARS?"

In view of what is stated in the foregoing pages, it is suggested that it is largely true that the criteria for the clinical diagnosis of diphtheria laid down in such classic accounts as those of Bretonneau and Ker are still valid. Thus, for example, it is still so that the occurrence of membrane of a particular type (sheet-like, tough, and adherent, and perhaps spreading beyond the tonsils) is strongly suggestive of diphtheria, while the occurrence of signs of follicular tonsillitis is not particularly so. In so far as the classical rules now require revision, this would seem to be due not so much to any fundamental change in the features of the disease (when it occurs) but more to access of knowledge about it (the realisation that it may commonly occur in clinically atypical forms) and to the recent extraordinary decline in its incidence. As the practical implications of these factors are discussed in Chapter I (p. 6 ff.), no further comment on the subject is considered to be necessary here.

CHAPTER IX.

ON CERTAIN DISEASES WHICH MAY SIMULATE DIPHTHERIA AND ON THE PROBABLE INCIDENCE OF THESE DISEASES IN THE SERIES OF CASES STUDIED.

Of the many diseases which might, under certain circumstances, be confused with diphtheria, only certain of those which were encountered in the present series (those which occurred relatively frequently, and others of particular interest) are considered here - namely, (1) tuberculosis, (2) syphilis, (3) glandular fever, (4) Vincent's angina, (5) staphlococcal and certain other throat infections, and (6) haemolytic streptococcal throat infections.

(1) Tuberculosis.

A brief description of the case of tuberculous ulceration of the fauces which occurred in the series is given below:

The patient was a female, aged 19 years. The history was of feverishness, loss of weight, and cough and spit for several weeks, and of sore throat for a shorter period. There were clinical and radiological signs of tuberculous bronchopneumonia, and this diagnosis was confirmed by the finding of M. tuberculosis in the sputum (and by post-mortem examination).

As regards the condition of the fauces, which had led the patient to seek medical advice and to the notification of diphtheria, there were multiple irregularly-shaped ulcers, with poorly defined edges, situated on the tonsils, the anterior pillars, the uvula, and the posterior part of the palate. The ulcers were fairly deep centrally, but shallower at their edges; their base was covered with whitish-coloured purulent exudate. M. tuberculosis was isolated from swabbings of the ulcers. Although Vincent's organisms were also seen to be present (in the direct film there were '2 plus' fusiform bacilli, and '1 plus' spirochaetes), it was concluded, in view of the other circumstances of the case, and especially the findings on histological examination of the fauces (carried out post-mortem), that they had not played a significant part in the pathogenesis of the lesions. The presence of diphtheria, syphilis, and agranulocytosis was excluded by appropriate tests.

The patient's condition steadily deteriorated, and she died seven weeks after admission to hospital.

It is clear from the work of Rubin (1927) that/

that the case of tuberculous ulceration of the fauces described above was a typical one in every respect. If, in such cases, due consideration is given to all the circumstances - especially the presence of advanced pulmonary tuberculosis and the characteristics of the faucial lesions - confusion with diphtheria is not likely to arise.

(2) Syphilis.

The case of syphilitic ulceration of the fauces which was encountered in the series was mentioned on p.103, where it was explained that the lesion was a manifestation of the tertiary stage of the disease and that the clinical picture did not at all resemble that of diphtheria. Certain secondary, and more rarely primary, lesions may more closely mimic diphtheria; but as these were not encountered in the series they are not discussed here.

(3) Glandular fever.

As at least one important point in the differential diagnosis of acute throat conditions arose from consideration of the case of glandular fever encountered in the series, a brief description is given of its salient features:

The patient was a boy, aged five years. He was admitted to hospital on the fourth day of his illness, the complaint being of feverishness, sore throat, swelling of the glands in the neck (which had apparently been more affected on the third day of the illness and were already subsiding by the time he was admitted), and also of long-standing nasal obstruction. His temperature was found to reach a maximum of 100.6°, and fever lasted intermittently until his third day in hospital. The tonsils were hypertrophied. There were 'spots' of white exudate, friable in consistency, in the tonsillar crypts, the appearances being typical of follicular tonsillitis; but since there was some confluence of a few of the individual spots, the exudate was classed as 'semi-confluent'. The fauces (and tonsils) were only very slightly/

slightly injected. There was considerable nasal obstruction, intermittent post-nasal discharge, and thin mucoid anterior discharge, slight in degree. Streptococcus haemolyticus was isolated from both the throat and nose, the growth from the former site being '2 plus', from the latter '1 plus'. Fusiform bacilli ('3 plus') were seen in a direct smear from the throat, but not spirochaetes.

The degree of enlargement of the cervical glands was estimated as being 'slight' (i.e. no more than is commonly encountered in Glasgow school-children); although also palpable, the axillary and inguinal glands were not thought to be significantly enlarged. The finding which evoked suspicion as to the possibility of glandular fever was that the spleen and liver were palpable (both extending to about one inch below the costal margin). Other investigations were therefore carried out, with the following results: white blood count, 12,000 per cu. m.m. (polymorphs 23%, mononuclear cells 77%); Paul-Bunnell reaction (Davidsohn's method, as described by Whitby and Britton, 1950), positive to a titre of 1/2,800.

Although the patient felt and looked well after his temperature had returned to normal (on his third day in hospital), the spleen and liver remained palpable for several weeks. His convalescence was otherwise uneventful.

It would seem that in apparently straightforward cases of tonsillitis (as also in certain other types of case) the possibility of glandular fever should always be borne in mind. Thus in the case described above, had it not been for the observation that the spleen and liver were enlarged (occurrences which are, incidentally, by no means invariable in glandular fever), the diagnosis of tonsillitis, query streptococcal, would have been made with confidence (which diagnosis would, in fact, have been correct so far as it went).

With regard to the diagnosis of diphtheria in particular, Tidy (1950) and Librach (1951) have pointed out that in the anginose type of glandular fever a membrane may form on the tonsil which may be quite indistinguishable from the characteristic appearance in diphtheria. Although no/

no such cases were encountered in the series of cases described here, the writer has subsequently observed two cases of glandular fever in which he regarded the membrane as being definitely classifiable as 'typically diphtheritic' - there being a tough and coherent sheet-like membrane which, although adherent, could be separated to some extent from the underlying mucosa. It may incidentally be mentioned that he has not yet encountered such an appearance - membrane that he has had no hesitation in classing as 'typically diphtheritic' - in any other diseases than diphtheria and glandular fever.

(4) Vincent's angina.

As useful material was obtained in the present investigation for a study of the incidence of Vincent's organisms in various types of acute sore throat, and as the results of this study are interesting and in some ways unexpected, the subject is dealt with in considerable detail. In the first case the history of Vincent's angina is briefly discussed.

Vincent, who first described the disease which is associated with his name (1896 and 1899), considered that it could be classified into two main types. The first, or 'diphtheroid', type, which he found to be relatively uncommon, was characterised by the presence of a coherent false-membrane similar to that occurring in diphtheria. At the affected site there was usually very superficial erosion of the mucosa, but no true ulceration; bacteriological examination revealed the presence of large numbers of fusiform organisms, but not/

not of spirochaetes. The second, or 'ulcero-membranous', type, which he encountered more frequently, was characterised by relatively deep ulceration, the base of the ulcers being covered by more or less friable exudate. In cases of this type, the bacteriological examination revealed the presence of both fusiform organisms and spirochaetes. As to the pathogenesis of the disease, Vincent considered that the fusiform organisms and spirochaetes were the specific agents in this respect, but that a predisposing cause other than infection with the organisms - for example, some other infection or gross malnutrition - was necessary before the specific organisms could produce their effect.

After the time of Vincent's work, his views as to the existence of the disease as a specific entity, and as to its pathogenesis, appear to have been generally accepted. But from time to time, and more particularly recently, doubts have been expressed as to the pathogenicity of the organisms described. In this respect, Vincent was the first of many to describe the finding of the organisms in a large percentage of apparently normal mouths and of throat lesions other than those occurring in Vincent's angina (e.g. diphtheritic lesions); but this finding does not, of course, exclude the possibility that, under certain circumstances, the organisms may become pathogenic. Similarly, although the failure to reproduce the disease experimentally in man (Committee of the American Dental Association on Vincent's infection, 1945, and Wilkie, 1945) or in animals (Black, 1938, and Rosebury et al., 1950)/

1950) weakens the claim that infection with the organisms is the principal cause of the disease, it does not necessarily refute the possibility that their presence is one of the essential causal factors. With regard to those who have expressed doubt as to the aetiology of Vincent's angina, who include the authorities referred to above, the views of Black (1938) are briefly quoted: he suggested that infection with other organisms (for example, certain strains of streptococci or staphlococci) was probably the essential cause of Vincent's angina and that, as a rule, the proliferation of Vincent's organisms in the lesions did little more than cause the characteristic foetor of the disease.

As regards the present series of cases, it is shown in table 38, p.195 , that Vincent's organisms were more often found to be present, whether in relatively large numbers or not, in cases in which the exudate was relatively extensive (i.e. in the form of 'patches') than in other cases. That they were more often present in relatively large numbers in the diphtheria group of cases than in the non-diphtheria group would seem to be attributable to the occurrence in the former group of a larger proportion of cases with 'patches' of exudate. In view of the opinions referred to in the preceding paragraph, it seemed a possible explanation of these findings that Vincent's organisms are saprophytes which flourish in septic discharges without necessarily causing disease. It was thought that it might assist in determining whether this explanation was probably correct or not to/

to analyse the data in such a way as to show whether or not there was any particular association between the presence of ulceration (which is the most constant feature in Vincent's angina) and the presence of relatively large numbers of Vincent's organisms.

In conducting this analysis it was decided to exclude from consideration the two cases with 'deep ulceration' (one a case of syphilitic ulceration, the other tuberculous) and the case of 'ulcer, post-tonsillectomy', in all of which the cause of the ulceration was obviously not Vincent's infection; also excluded were the cases in which direct films were not made, that is the 39 cases classed in the 'clean throats' group, and 9 other cases in most of which there had been only relatively little exudate. In classifying the remaining cases, regarded as having shown evidence of ulceration were not only the cases in which this was well-marked (the 3 cases with 'moderately deep ulceration') but also 47 others in which there were the less well-marked changes referred to on pp. 49 and 60 , changes which often involved only a very localised area of the mucosa, usually only became apparent after the throat had become clear of exudate, and were thought to be indicative of superficial erosion of the mucosa or of very recently healed erosion or ulceration (included in the 47 cases were the 6 classed as having 'intimately adherent membrane').

It is apparent from table 41 that there was indeed a definite correlation between the occurrence of ulceration and the presence of Vincent's organisms. This correlation was particularly striking, and statistically significant, if the presence of relatively large numbers of both fusiform organisms and spirochaetes was chosen as the criterion for the bacteriological diagnosis of Vincent's infection. This finding does not, of course, necessarily indicate that the infection with Vincent's organisms played a contributory part in the development of the ulceration. In fact, even in the cases in which the organisms were most numerous there was usually clinical and bacteriological evidence of a disease/

Table 41. Findings as to Vincent's Organisms, Type of Exudate, and the Incidence of Ulceration*: all 'throat' cases except the 51 listed in the text, in most of which there was little or no exudate and direct films were not made.

	With 'Patches' of Exudate		With Other Types of Exudate		With Any Type of Exudate	
	With Ulc.	Without Ulc.	With Ulc.	Without Ulc.	With Ulc.	Without Ulc.
Total Cases	34 100%	65 100%	16 100%	124 100%	50 100%	189 100%
Cases with F. in any no., with or without S.	34 100%	61 93.8%	15 93.7%	108 87.1%	49 98.0%	169 89.4%
Cases with F. '2 plus' or more, with or without S.	27 79.4%	41 63.1%	9 56.2%	58 46.8%	36 72.0%	99 52.4%
Cases with F. '3 plus', with or without S.	19 55.9%	22 33.8%	5 31.2%	30 24.2%	24 48.0%	52 27.5%
Cases with both F. & S., each in any no.	21 61.8%	34 52.3%	8 50.0%	46 37.1%	29 58.0%	80 42.3%
Cases with F. & S., both '2 plus' or more	10 29.4%	7 10.8%	4 25.0%	9 7.3%	14 28.0%	16 8.5%
Cases with F. & S., both '3 plus'	4 11.8%	1 1.5%	3 18.7%	4 3.2%	7 14.0%	5 2.6%

F : Fusiform organisms

S : Spirochaetes

Ulc : Ulceration

*Note: As explained in the text, the degree of ulceration was only slight, or the evidence of its presence doubtful, in all but 3 cases. Data on these 3 cases, in which the ulceration was classed as being 'moderately deep', are given in the following table.

Table 42. Particulars of the 3 Cases with 'Moderately Deep' Ulceration.

Case No.	Age (Years)	Sex	Site of Lesion*	Main Bacteriological Findings			Other Points
				F	S	Other	
1	29	F.		'2 plus'	'2 plus'	H.S. '3 plus'	Marked Gingivitis
2	19	M.		'3 plus'	'3 plus'	H.S. '3 plus' Staph. Aureus '1 plus'	
3	8	M.		'2 plus'	'1 plus'	(H.S.ø '5 plus'	Scarlet Fever

F. : Fusiform organisms. S. : Spirochaetes. H.S. : Streptococcus haemolyticus.

*The depth of the ulcers in these cases is represented in diagram No. 40A, p. 43.

øAlthough case No. 3 was one of the 'incompletely investigated' group, and therefore the results as to H.S. were discounted for statistical purposes, it is known that there was a nearly pure culture of that organism.

disease other than Vincent's angina (most often diphtheria or haemolytic streptococcal infection) which could be regarded as being a sufficient explanation for the minimal degree of ulceration present. Similarly, in the three cases with 'moderately deep ulceration' - the only cases in the series in which the clinical picture was that of Vincent's angina as it is described in most modern text-books (i.e. corresponding to Vincent's ulcero-membranous type) - there was definite evidence of haemolytic streptococcal infection; certain particulars of these cases are given in table 42.

The findings in the present series do not permit of the formulation of any conclusion as to whether Vincent's organisms are mere saprophytes which flourish in necrotic tissue or whether they play a contributory role in the necrotizing of the tissue. If they are potentially pathogenic, it would seem clear that, in view of their near-ubiquity, it must be other factors than their presence - other infection, or other general or local disease - that principally determine whether Vincent's angina will develop or not. The necessity of looking for other causes was well brought out in the present series: with regard to diphtheria in particular, it will be recollected that it was found that the presence of large numbers of Vincent's organisms does not signify that, other things being equal, that diagnosis (diphtheria) is any the less probable.

(5) Staphlococcal and certain other throat infections.

Attention is directed to Appendix table IX, in/

in which are shown the findings as to the incidence of certain organisms (other than C. diphtheriae, Streptococcus haemolyticus, and Vincent's organisms) in the 'throat' and 'normal' series of cases.

With regard to Neisseria and the 'Streptococcus viridans/pneumococcus' group, the finding that these organisms were present - usually in large numbers - in the large majority of the different groups of cases is in accordance with the observations of others that they are part of the normal flora of the throat. It may be that they are capable of causing disease of the throat when the resistance of the host is low, but it is not possible to prove or disprove this from the present work.

While Staphlococcus aureus, H. influenzae, and yeasts were more often encountered in the 'other than diphtheria' group of cases, and particularly in the 'unknown cause' sub-group, than in the 'diphtheria' or 'normal' groups, the differences between the incidence rates in these various groups are not significant. In view of this, and as there were no distinctive clinical features in the cases in which the organisms were present, it was concluded that it was not possible to decide, with any reasonable degree of certainty, whether the organisms, when isolated from diseased throats, should be regarded as being causatively related to the disease present. At any rate, as these infections were only encountered relatively rarely, it would seem that they cannot have been the causative agents in more than a small/

small proportion of the cases.

It may be mentioned that Dingle et al. (1947), who made an intensive study of exudative tonsillitis as it occurred in young American soldiers, found that various of the common aerobic organisms, including pneumococci, staphlococci, and H. influenzae, occurred no more frequently in cases of tonsillitis than in healthy controls. They concluded that it was unlikely that any more than a very small proportion of their cases arose from infection with these organisms.

(6) Haemolytic streptococcal throat infections.

It is considered that the majority of the 'throat' cases in which the diagnosis of diphtheria was not confirmed were instances of haemolytic streptococcal (H.S.) infection. Thus it is shown in Appendix table VIII that the bacteriological findings were suggestive of streptococcal disease (that is, there was a growth of H.S. of a density of '2 plus' or more; the reasons for the adoption of this criterion were discussed on p.105) in 63% of the 'other than diphtheria' cases in which appropriate investigations were carried out. While, on account of the difficulties discussed on p.105 , this figure can only be taken as a very rough estimate of the actual incidence of streptococcal disease in the series, it is not considered to be surprising that the incidence should be high as compared with that reported in certain other series. Landsman et al. (1951), for example, considered that only about 46% of a series of 100 cases of/

of acute sore throat encountered in general practice in Glasgow could be regarded as being streptococcal in origin. But, as pointed out by Dingle et al. (1947), one would expect to encounter a relatively large proportion of the more severe cases, and therefore to find a relatively high incidence of streptococcal infection, in hospital practice. This would seem to apply particularly to suspected-diphtheria admissions, for Dingle found that a relatively large proportion of the cases with more extensive exudate (the type of case in which confusion with diphtheria is most likely to arise) was streptococcal.

Although the estimate given above of the incidence of streptococcal disease in the series was based on the bacteriological findings, it is considered that the clinical findings were such as would be expected on the assumption that the estimate is approximately correct. It had been hoped that a comparison of the presumed streptococcal cases with those of which the cause was uncertain might give evidence in support of, or against, the view that most of the former group were indeed streptococcal. In fact, however, on account of the small size of the series, particularly the size of the group of cases of which the cause was uncertain, such differences as were brought out were seldom of significance; but the findings, while they did not give much support to the view that most of the cases were streptococcal in origin, at least did not conflict with it.

Although the comparison of the presumed strepto-/

streptococcal cases with those of uncertain origin was only of limited value for the purpose for which it was originally intended, some interesting points were brought out; the results are therefore briefly described here. For the purposes of the comparison, not only the 'diphtheria' and 'incompletely investigated' groups of cases were discounted, but also the 'miscellaneous' group (which consisted of cases of which the cause - which was not streptococcal infection - was known) and the 'non-virulent' group (cases in which there was a possibility that infection with C. diphtheriae may have been the causative agent). The remaining cases were classed, by a method, based principally on the bacteriological findings, which was described on p. 104 , into two groups - the (presumed) 'streptococcal' group and the 'unknown cause' group. While the features of the cases in these groups are shown in some detail in table 43, only the more interesting and significant findings are discussed in the text.

With regard to age, it was found that a significantly large proportion of the cases in the under-5-years group were classifiable in the 'unknown cause' group. These cases were similar to the other 'unknown cause' cases, most of them being very mild, and with little or no exudate. A possible explanation of this occurrence is that practitioners, being aware of the particular susceptibility of young children to diphtheria, may tend to make a provisional diagnosis of that disease more readily in their case than in the case of older patients; the result of this tendency would be that an unduly large proportion of the under-5-years/

Table 43. Features of the 'Streptococcal' and 'Unknown Cause' Groups of Cases.

	'Streptococcal' Number	'Streptococcal' Per Cent	'Unknown Cause' Number	'Unknown Cause' Per Cent
Total Cases	98	100.0	36	100.0
Age-Group (Years)				
0 - 11/12	1	1.0	3	8.3
1 - 4	9	9.2	12	33.3
5 - 9	23	23.5	4	11.1
10 - 14	23	23.5	6	16.7
15 - 19	17	17.3	2	5.6
20 -	25	25.5	9	25.0
Sex (Age-Group Over-20-years)				
Male	7	7.1	5	13.9
Female	18	18.4	4	11.1
Duration of Illness on Admission				
Up to 2 days	75	76.5	20	55.6
3 or 4 days	17	17.3	8	22.2
Over 4 days	6	6.1	8	22.2
History of Contact With Scarlet Fever	3	3.1	0	0.0
Exudate-group				
'Patches'	32	32.7	7	19.4
'Semi-confluent Spots'	24	24.5	8	22.2
'Discrete Spots (Medium & Large)'	19	19.4	5	13.9
'Discrete Spots (Specks)'	10	10.2	6	16.7
'Clean Throats' group	10	10.2	7	19.4
'Ulcer' group	3*	3.1	0	0.0
'Scum' group	0	0.0	3ø	8.3

TABLE CONTINUED ON NEXT PAGE

*In the 3 cases in the 'ulcer' exudate-group, the ulceration was classed as being 'moderately deep'. The cases could be regarded as being instances of streptococcal infection and Vincent's angina; they are discussed in the section dealing with the latter disease.

øRe the 'scum' exudate-group, see discussion in text regarding sex.

Table 43 (Features of the 'Streptococcal' and 'Unknown Cause' Groups of Cases) continued.

	'Streptococcal'		'Unknown Cause'	
	Number	Per Cent	Number	Per Cent
Total Cases	98	100.0	36	100.0
Hyperaemia of Fauces, 'Marked' in degree	46	46.9	12	33.3
Oedema of Fauces, 'Moderate' in degree	7	7.1	1	2.8
Peri-tonsillar Cellulitis or Abscess	7	7.1	3	8.3
Stomatitis, marked in degree	2	2.0	5*	13.9
Nasal Symptoms				
Obstruction or P.N.D. (usually only intermittent)	22	22.5	2	5.6
(Anterior) Nasal Discharge	16	16.3	10	27.8
Upper Cervical Glands				
Peri-adenitis	0	0.0	0	0.0
Enlargement to a 'Considerable' extent	1	1.0	4	11.1
Tenderness				
Present	41	41.8	16	44.4
'Marked'	11	11.2	3	8.3
'Strawberry' Tongue				
Present	52	53.1	18	50.0
'Very Marked'	3	3.1	4	11.1
Acute Otitis Media	5	5.1	1	2.8
Maximum Temperature				
- 99°	18	18.4	8	22.2
99.2° - 100.8°	38	38.8	18	50.0
101° -	42	42.9	10	27.8

*Referred to in the discussion in the text on sex.

under-5-years admissions were relatively mild and, as such, less likely to be streptococcal in origin. But as the findings of Landsman et al. in their less selected series (composed of cases occurring in general practice) were similar to those reported here, the apparent excess of mild, non-streptococcal, cases in early childhood may be real.

Although no significant differences were found with regard to sex, the findings in this respect in the over-20-years age-group are of interest. As shown in the table, streptococcal infections were relatively common in females of this age, but non-streptococcal infections were predominant in males. In four of the five male 'unknown cause' cases of this age the clinical picture was distinctive and unusual, there being marked inflammation widespread over the mouth and pharynx, and, in three of the cases, that semi-opaque stringy film, perhaps consisting of altered mucus, which was described earlier as 'scum'. Although the initial febrile disturbance in these cases cleared up quite quickly (except in one case in which the local condition was secondary to a brain abscess), the hyperaemia of the affected parts was very slow to resolve. While the cause of the stomatitis and pharyngitis present in these cases could not be determined (except, perhaps, in the case of brain abscess), the condition is thought worthy of mention on account of its fairly characteristic features, particularly its almost complete limitation to one age- and sex-group.

In general, the findings were similar to those/

those reported by Dingle et al. (1947) in their study of exudative tonsillitis. Thus in the 'streptococcal' group the onset of the illness tended to be more acute (i.e. the duration of the illness on admission was relatively short), and extensive exudate, marked hyperaemia and oedema of the fauces, and a pronounced elevation of temperature were more frequently encountered. Anomalous findings were that the incidence of tenderness of the upper cervical glands was approximately the same in the two groups, and that a more than slight degree of enlargement of these glands occurred significantly more often in the 'unknown cause' group. In the four 'unknown cause' cases with 'considerable' glandular enlargement there was nothing else particularly distinctive about the clinical picture, which was that of tonsillitis of mild or moderate severity; the glandular enlargement was only transitory, and convalescence was rapid and uneventful.*

As regards the tongue, the incidence of the 'strawberry' changes was approximately the same in both groups of cases. This subject is discussed in Chapter VIII (p. 182) where it is suggested that observation of the tongue may well be of assistance in the diagnosis of scarlet fever, but is unlikely to be so in the diagnosis of non-scarlatinal streptococcal infections.

To conclude this chapter, it is considered/

*In retrospect the thought occurs that some of these cases may perhaps have been mild instances of glandular fever. In this respect, see p. 209.

considered interesting to note that the same opinion was formed in this study as was formed by Bretonneau as long ago as 1826 - that streptococcal tonsillitis (that is, scarlatinal angina, with or without the presence of a rash) is the condition which is most commonly mistaken for diphtheria.

CHAPTER X.

SUMMARY AND DISCUSSION.

SECTION I. SUMMARY.

(1) It is concluded that while the unprecedented extent of the recent decline in the incidence of diphtheria is attributable to large-scale prophylactic inoculation, the decline in the severity of the disease, which continued over many years but has not been well-marked since the introduction of mass inoculation, must be mainly attributed to other factors - such as improvement in the hygienic and nutritional state of the community, more early diagnosis (and thus more effective treatment), and more accurate diagnosis (the result of the realisation that diphtheria may occur in clinically atypical forms, and of the availability of bacteriological facilities for the diagnosis of such cases).

(2) A series of cases of diphtheria occurring during the year 1947-48 is described and compared with two other series, the others consisting of cases occurring during the years 1942 and 1951 respectively. In spite of the very marked decline in the incidence of diphtheria which took place between 1942 and 1951, the features of the disease were much the same in each of the three series.

(3) With regard to the comparative characteristics of diphtheria in inoculated and uninoculated subjects, it was found that the typical membrane of the disease occurred slightly more frequently in the 'inoculated' group of cases than in the 'uninoculated', but that in the former group the patients were more often admitted to hospital relatively early in their illness, the membrane was much less often extensive,/

extensive, and toxic complications were very much less frequent.

(4) Attention is directed to certain factors which have been shown to, or might be thought to, play a part in determining whether an individual infected with C. diphtheriae will develop symptoms or not and, if so, whether the diagnosis of diphtheria will be made or not. With regard to 'atypical' attacks of diphtheria (without the formation of the typical membrane of the disease, but with signs of follicular or catarrhal tonsillitis or pharyngitis), it is suggested that it is virtually impossible to determine the true incidence of such attacks, but that it is probably not so that, as is sometimes implied, they seldom occur except in previously inoculated subjects (and in those who have had previous attacks of diphtheria). In fact, in the present series of cases it was found, as stated above, that typical membrane formation occurred more frequently in the inoculated than in the uninoculated, and that atypical attacks were correspondingly less frequent in the former group. Further, regarding the total suspected-diphtheria admissions with signs of follicular or catarrhal tonsillitis, the diagnosis was confirmed in only half as many of the cases with a history of inoculation as of those without.

(5) It is pointed out that it is often impossible to differentiate, with any reasonable degree of assurance, between atypical diphtheria (with signs of, for example, follicular tonsillitis) and other disease occurring in a/

a carrier. While consideration of the epidemiological circumstances may assist in the diagnosis, the Shick test is only of limited value. The difficulties which may arise in the treatment of such cases are briefly referred to: while toxic complications are most unlikely to occur, that possibility cannot be entirely dismissed.

(6) The factors which are of importance in the diagnosis of diphtheria are considered in detail (they are summarised on p. 200 ff.). It is concluded that the criteria laid down in such classic accounts as those of Bretonneau and Ker are still, to a large extent, valid. In applying these criteria in present-day circumstances, however, it is necessary to bear in mind, first, that it is now realised that diphtheria may occur relatively commonly in clinically atypical forms, and, second, the implications of the recent extraordinary decline in the incidence of the disease.

(7) The following conclusions were formed regarding the cases in which the diagnosis of diphtheria was not confirmed:-

(a) Streptococcal tonsillitis was the condition most frequently mistaken for diphtheria.

(b) Infection with staphlococci, or with certain of the other common aerobic organisms, is probably not a frequent cause of tonsillitis.

(c) Vincent's organisms were present in large numbers in a considerable proportion of both the diphtheria and other cases. The significance of this bacteriological/

bacteriological finding is discussed in some detail. It is stressed that the finding does not indicate that the presence of some other disease, for example, diphtheria or streptococcal tonsillitis, is any the less likely.

(d) The possibility is entertained that infection with a non-virulent strain of C. diphtheriae may be capable of causing tonsillitis. There is no evidence to show that this infection can cause diphtheria.

(e) Of the other diseases which may simulate diphtheria, glandular fever, tuberculosis, and syphilis are briefly considered. Although this was not so of the case of glandular fever encountered in the series, that disease may mimic diphtheria particularly closely.

(8) With further regard to the Shick test, it is concluded that, even with the modern highly refined antitoxin, an interval of three hours between the performance of the test and the subsequent administration of antitoxin is sufficient to give a reliable result.

(9) With regard to the diagnosis of diphtheritic toxic complications, the finding of H. M. Leete that it is possible, by means of observations made during the first three weeks of the illness, to forecast whether late complications will definitely, may perhaps, or will definitely not occur was confirmed. In the present series, however, myocardial damage was a less prominent feature than in Leete's series. The importance of careful examination of the urine is stressed.

SECTION II. DISCUSSION ON THE PRACTICAL IMPLICATIONS OF THE POINTS BROUGHT OUT IN THE WORK.

In considering the many administrative and other problems relative to the care of diphtheria-suspects, attention would have to be paid to many different aspects - for example, the facilities available at home or in hospital, the danger of spread of infection to others, and, of course, the question of what would be best for the patients' physical and psychological welfare. While a comprehensive discussion on these matters is considered to be quite outwith the scope of this work, it is proposed to refer briefly to certain of the points which arise directly from the work:-

(1) As the diagnosis of diphtheria is confirmed in only a small proportion of the cases in which the clinical or bacteriological signs are suggestive of the disease, it is clearly necessary that the patients, if admitted to hospital, should be nursed in separate cubicles until it is definitely known what they are suffering from.

(2) It appeared that in a number of the cases in the series the notification of diphtheria had been made not because the possibility of the occurrence of that disease had been seriously entertained, but because it had been virtually the only way in which the admission of the patients to hospital could be arranged. It is obviously desirable that hospital accommodation should be made available for those patients, suffering from acute infections of the upper respiratory tract, whose condition and home circumstances/

circumstances necessitate it - whether they are suffering from one of the notifiable infectious diseases or not.

(3) In view of the rarity of diphtheria, and of the relative prevalence of infections with non-virulent strains of C. diphtheriae, it is highly desirable that the type and virulence of all strains of the organism isolated should be determined. Unless this is done, there is probably little or nothing to be gained, and perhaps much to be lost, by carrying out any bacteriological investigations.

(4) It was mentioned on p. 8 that it was stated authoritatively in 1947 that it was a sound plan to take a swab for C. diphtheriae as a matter of routine in all cases of follicular tonsillitis. It is suggested here that it is very doubtful whether this procedure is still to be recommended. There can be no doubt that only a very small minority of the swabs will be found to be positive, and that in only a small proportion of the positive cases will the organism be found to be virulent. On the other hand, the possibility of the occurrence of diphtheritic tonsillitis cannot be entirely dismissed as long as there is any diphtheria in the community at all. Cases of tonsillitis should certainly be swabbed if there is any special reason to do so - for example, if the patient is known to have been exposed to infection with C. diphtheriae, and perhaps if he is an inmate of an institution. And whether swabs are taken or not, it must not be forgotten that in apparently simple cases of tonsillitis the typical signs of diphtheria may develop subsequently.

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APPENDIX TABLES.

Table I. Classification of all admissions to Ruchill Hospital with the notified diagnosis of diphtheria during the year commencing 1st September 1947.

Table II. Classification of cases as to final diagnosis (this and the subsequent tables refer only to the cases of the 'Main Series').

Table III. Primary classification of the 'Throat' cases as to the type of exudate and final diagnosis (whether diphtheria or not).

Table IV. Detailed classification of the 'Throat' cases as to the type of exudate and final diagnosis (whether diphtheria or not); containing also a summary of certain of the features of the different types of exudate.

Table V. Detailed classification of the 'Throat' cases as to the type of exudate and bacteriological findings with regard to C. diphtheriae.

Table VI. Diphtheria cases in which toxic complications developed: general data.

Table VII. Diphtheria cases in which toxic complications developed: particulars of the signs of toxic damage which appeared.

Table VIII. Findings as to Streptococcus haemolyticus: 'Throat', 'Normal', and 'Scarlet Fever' series.

Table IX. Findings as to various organisms: 'Throat' and 'Normal' series.

Table I. Classification of all admissions to Ruchill Hospital with the notified diagnosis of diphtheria during the year commencing 1st September 1947.

Series		Total Cases	Cases with Final Diagnosis 'Diphtheria'		Cases with Final Diagnosis not Diphtheria				
					'Carriers'	'Non-virulent' cases	'Negative' Cases	Total Cases	
'Main Series'		313	76	24.3%	4	36	197	237	75.7%
Other Cases	with croup	86	7	8.1%	0	1	78	79	91.9%
	without croup	124	26	21.0%	0	3	95	98	79.0%
All Cases		523	109	20.8%	4	40	370	414	79.2%

Note: The method of classification used in the above table is described in Chapter III (p. 28 ff.).

Table II. Classification of cases as to Final Diagnosis (Note: This and the subsequent tables refer only to the cases of the 'Main Series').

FINAL DIAGNOSIS	NUMBER OF CASES.		
(A) 'No Apparent Disease' Group.			
I. Carriers (of virulent strain of C. diphtheriae).		4	
II. Other cases.			
1. Carriers of non-virulent strain of C. diphtheriae.	1		
2. Others without apparent disease.	4	5	9
(B) 'Nasal etc.' Group.			
I. Cases of Anterior Nasal Diphtheria		4	
II. Cases of (non-diphtheritic) rhinitis, otitis, bronchitis etc.		10	14
(C) 'Throat' Group. (cases in which there was was clinical evidence of disease of the throat, with or without disease elsewhere)			
I. 'Diphtheria' Group (in which the throat swab was positive for a virulent strain of C. diphtheriae).		72	
II. 'Other than diphtheria' Group.			
1. 'Non-virulent' group (in which the throat swab was positive for a non-virulent strain of C. diphtheriae)	35		
2. 'Negative' group (in which the throat swab was negative for C. diphtheriae)			
(a) 'Miscellaneous' group	5		
(b) 'Incompletely Investigated' group	44		
(c) 'Streptococcal' group	98		
(d) 'Unknown Cause' group	36	183 218	290
TOTAL CASES (ALL GROUPS)			313

Note: The terms used in the above table, and the method of classification, are defined and discussed on p. 101 ff.

Table III. Primary Classification of the 'Throat' Cases as to the Type of Exudate and Final Diagnosis (whether diphtheria or not).

EXUDATE-GROUP	TOTAL CASES	CASES IN WHICH THE DIAGNOSIS OF DIPHTHERIA WAS CONFIRMED	
(A) 'Patches' (syn. 'membrane', 'confluent exudate')	101	42	41.6%
(B) 'Semi-confluent Spots' (syn. 'semi-confluent exudate')	51	6	11.8%
(C) 'Discrete Spots'	87	18	20.7%
(D) 'Clean Throats' group	39	5	12.8%
(E) 'Ulcer' group	8	1	12.5%
(F) 'Scum' group	4	0	0%
All groups	290	72	24.8%

Note: The method of classifying the cases into the main 'exudate-groups' listed above is described on p. 38 ff.

Table IV. Detailed Classification of the 'Throat' Cases as to the Type of Exudate and Final Diagnosis (whether diphtheria or not); containing also a summary of certain of the features of the different types of exudate.

EXUDATE-GROUP	EXUDATE SUB-GROUP	PRESENCE (+) OR ABSENCE (-) OF			TOTAL CASES	DIPHTHERIA CASES	
		'SHEET-LIKENESS'	'ADHERENCE'	'COHERENCE' ('TOUGHNESS')			
(A) 'Patches'	I, 'Typically diphtheritic membrane'						
	(a) 'With free edge'	+	+	+	26	26	100.0%
	(b) 'Without free edge'	+	+	+	7	7	100.0%
	II, 'Tough but loose membrane'	+	-	+	7	3	42.9%
	III, 'Intimately adherent membrane'	+	(++)	+	6	1	16.7%
	IV, 'Friable membrane'						
	(a) Not adherent	+	-	-	51	5	9.8%
	(b) Adherent	+	+	-	4	0	0%
(B) (Semi-confluent Spots'	(a) '(?) Tough but loose membrane'	?	-	+	4	1	25.0%
	(b) Other cases	-			47	5	10.6%
(C) 'Discrete Spots'	I, 'Medium and large spots'						
	(a) '(?) Tough but loose membrane'	?	-	+	2	1	50.0%
	(b) 'Exceptionally large spots of (?) tough but loose membrane'	?	-	+	2	1	50.0%
	(c) 'Exceptionally large spots of (?) friable membrane'	?	-	-	3	0	0%
	(d) Other cases	-			43	6	14.0%
	II, 'Specks'	-			34	8	23.5%

TABLE CONTINUED OVERLEAF

Table IV, continued.

EXUDATE-GROUP	EXUDATE SUB-GROUP	PRESENCE (?) OR ABSENCE (-) OF 'SHEET-LIKENESS'	'ADHERENCE'	'COHERENCE' ('TOUGHNESS')	TOTAL CASES	DIPHTHERIA CASES	
	III, 'Spots of (?) typically diphtheritic membrane'	?	+	+	3	2	66.7%
(D) 'Clean Throats'	(no exudate)				39	5	12.8%
(E) 'Ulcer Group'	(a) Deep ulceration				2	0	0%
	(b) Moderately deep ulceration				3	0	0%
	(c) Post-tonsillectomy sloughs				1	0	0%
	(d) Minimal ulceration				2	1	50.0%
(F) 'Scum Group'	(cases with stomatitis)				4	0	0%
	All Groups				290	72	24.8%

Note: The terms 'sheet-likeness', 'adherence', and 'coherence', as applied to exudate, are defined on pp. 38 and 40; the detailed method of classification of the cases as to the type of exudate, as used in the above table, is described on p. 45 ff.

Table V. Detailed Classification of the 'Throat' Cases as to the type of Exudate and Bacteriological Findings with regard to C. Diphtheriae.

EXUDATE-GROUP	EXUDATE SUB-GROUP	'VIRULENT' CASES		'NON-VIRULENT' CASES		'NEGATIVE' CASES	
		No.	Per Cent.	No.	Per Cent.	No.	Per Cent.
	All groups	72	100.0	35	100.0	183	100.0
(A) 'Patches'	I, 'Typically diphtheritic membrane'	33	45.8	0	0	0	0
	II, 'Tough but loose membrane'	3	4.2	1	2.9	3	1.6
	III, 'Intimately adherent membrane'	1	1.4	0	0	5	2.7
	IV, 'Friable membrane'						
	(a) Not adherent	5	6.9	5	14.3	41	22.4
	(b) Adherent	0	0	1	2.9	3	1.6
(B) 'Semi-confluent Spots'	(a) '(?) Tough but loose membrane'	1	1.4	0	0	3	1.6
	(b) Other cases	5	6.9	2	5.7	40	21.9
(C) 'Discrete Spots'	I, 'Medium and large spots'						
	(a) '(?) Tough but loose membrane'	1	1.4	0	0	1	0.5
	(b) 'Exceptionally large spots of (?) tough but loose membrane'	1	1.4	0	0	1	0.5
	(c) 'Exceptionally large spots of (?) friable membrane'	0	0	1	2.9	2	1.1
	(d) Other cases	6	8.3	8	22.9	29	15.8
	II, 'Specks'	8	11.1	7	20.0	19	10.4
	III, 'Spots of (?) typically diphtheritic membrane'	2	2.8	1	2.9	0	0

TABLE CONTINUED OVERLEAF

Table V, continued.

EXUDATE-GROUP	EXUDATE SUB-GROUP	'VIRULENT' CASES		'NON-VIRULENT' CASES		'NEGATIVE' CASES	
		No.	Per Cent.	No.	Per Cent.	No.	Per Cent.
	All groups	72	100.0	35	100.0	183	100.0
(D) 'Clean Throats'	(no exudate)	5	6.9	7	20.0	27	14.8
(E) 'Ulcer Group'	(a) Deep ulceration	0	0	1*	2.9	1	0.5
	(b) Moderately deep ulceration	0	0	0	0	3	1.6
	(c) Post-tonsillectomy sloughs	0	0	0	0	1	0.5
	(d) Minimal ulceration	1	1.4	1	2.9	0	0
(F) 'Scum Group'	(cases with stomatitis)	0	0	0	0	4	2.2

*As explained on p. 103, this case (a case of syphilitic ulceration with a coincidental attack of follicular tonsillitis) could alternatively have been classed in the 'discrete spots' exudate-group.

Note: In all cases there was evidence of inflammation of the throat. In the 'virulent' group, the throat swab was positive for a virulent strain of C. diphtheriae and the patients were classed as suffering from diphtheria. In the 'non-virulent' group, the swab was positive for a non-virulent strain of C. diphtheriae; in the 'negative' group that organism was not isolated; none of the patients in these two groups was thought to be suffering from diphtheria.

Table VI. Diphtheria Cases in which Toxic Complications developed: General Data.

Case no.	Age in Years	Sex	If Inoc.	Shick Test	Exudate		Type of C.D.	Day of illness on admission	Serum given	Toxic Complications		Stay in hospital (days)
					Site	Type			I.M. I.V.	Severity	Systems clinically affected	
1	2	F	No		N-Ph.	T.D.Memb. F.E.+	Gr.	5th	48,000 40,000	Fatal	C.V.S., U.S.	Died 6th day
2	4	M	No		T.	T.D.Memb. F.E.+	Gr.	2nd	48,000 40,000	Severe	C.V.S., U.S., N.S.	113
3	6	F	No		N-Ph.	T.D.Memb. F.E.+	M.V.	4th	48,000 80,000	Severe	C.V.S., U.S., N.S.	128(C.C.)
4	1	F	No		N-Ph.	T.D.Memb. F.E.+	Gr.	6th	48,000 20,000	Moderate	C.V.S., U.S.	48
5	4	M	No		T-Ph.	T.D.Memb. F.E.+	Gr.	3rd	28,000 40,000	Moderate	U.S., N.S.	89
6	4	M	No		N-Ph.	T.D.Memb. F.E.-	Int.	4th	38,000 30,000	Moderate	U.S., N.S.	69
7	3	F	No		T-Ph.	T.D.Memb. F.E.+	M.V.	4th	48,000 40,000	Moderate	C.V.S., U.S., N.S.	80(C.C.)
8	22	F	No	Neg. (3)	T.	T.D.Memb. F.E.+	Gr.	3rd	8,000 28,000	Moderate	U.S., N.S.	85(O.R.)
9	6	M	No		T-Ph.	T.D.Memb. F.E.+	M.V.	3rd	38,000 30,000	Moderate	C.V.S. U.S.	62(C.C.)
10	13	M	Yes*	Neg. (6)	T.	Semi-confluent	Gr.	2nd	8,000	Moderate	C.V.S., U.S.	67(O.R.)

*Said to have been inoculated; details not known.

TABLE CONTINUED OVERLEAF

Table VI, continued

Case no.	Age in Years	Sex	If Inoc.	Shick Test	Exudate		Type of C.D.	Day of illness on admission	Serum given	Toxic Complications		Stay in hospital (days)
					Site	Type			I.M. I.V.	Severity	Systems clinically affected	
11	8	M	No	pos. (3)	T.	Semi-confluent	Gr.	3rd	28,000 20,000	Moderate	C.V.S.	56
12	5	M	No	pos. (3)	T.	T.D.Memb. F.E.+	Gr.	2nd	40,000	Probable (slight)	U.S.	42
13	33	M	No	neg. (3)	T.	T.D.Memb. F.E.+	M.V.	4th	28,000	Probable (slight)	U.S.	38
14	3	M	No		T.	T.D.Memb. F.E.+	M.V.	4th	28,000 28,000	Probable (slight)	U.S.	47(O.R.)
15	8	M	No	neg. (6)	O.	-	M.V.	4th	8,000	Probable (slight)	U.S.	42

Abbreviations and Explanatory Notes (working from the left of the table to the right:

If Inoc. : Whether patient had been inoculated against diphtheria or not.

Shick Test : neg. = negative, pos. = positive. The figure in brackets represents the time (in hours) between performing the test and the subsequent administration of serum.

Site of Exudate : N-Ph. = naso-pharyngeal. T-Ph. = tonsillo-pharyngeal. T. = tonsillar. O = no exudate present.

Type of Exudate :

T.D.Memb. F.E.+ = 'typically diphtheritic membrane with free edge' (for definition of this term see p. 45).

T.D.Memb. F.E.- = 'typically diphtheritic membrane without free edge' (for definition, see p. 45).

TABLE CONTINUED OVERLEAF

Table VI, continued.

Type of Exudate, continued:

Semi-confluent exudate : For definition of this term see p. 39. In case no. 10 in the table, the exudate was friable, but in case no. 11 it consisted of '(?) tough but loose membrane'. The former case was therefore classed in Appendix table IV in group B(b), the latter in group B(a).

Type of C.D. = Type of C. diphtheriae.

Gr. = gravis. M.V. = mitis (virulent strain). Int. = intermedius.

Severity of Toxic Complications : The method of classification used is explained on p. 85.

Systems Clinically Affected (by toxic damage) :

C.V.S. = cardiovascular system. U.S. = urinary system. N.S. = nervous system.

Note: Certain details of the signs of toxic damage which appeared are shown in the following table (table VII).

Stay in Hospital (days) :

(C.C.) : indicates that the stay was prolonged by the patient being a convalescent carrier.

(O.R.) : indicates that the stay was prolonged for some reason other than the attack of diphtheria - e.g. intercurrent infection.

Table VII. Diphtheria Cases with Toxic Complications : particulars of the signs of toxic damage which appeared.

Case no.	General appearance	Max. temp.	Strep. haem.	Cardio-vascular system				Proteinuria		Paresis
				Pulse chart	Heart sounds	Blood pressure	Other	Maximum	from to	
1	Moderately severe	102.6	0	'½ cup'	Affected		(Death)	++	A-	
2	Moderately severe	103.8	?	(inconspicuous S.S.)	-	Suggestive	E.S. wks.6-8	4 pts.	A-31	Multiple K.J.
3	Extremely severe	99.2	?	(inconspicuous S.S.)	Affected	(inconclusive)	E.S. wks.4-8	2 pts.	A-42	Palatal K.J.
4	Equivocal	99.2	1 plus	(inconspicuous S.S.)	Affected			1½ ptd.	A-31	-
5	Equivocal	101.8	0	-	-			¾ pt.	A-42	Palatal K.J.
6	Equivocal	101.6	0	-	-	-		½ pt.	A-16	Palatal K.J.
7	Nil appreciable	101.0	3 plus	-	Affected			Trace	11-25	Palatal
8	Equivocal	98.8	0	(bradycardia weeks 1-3)	-	-		Trace	A-16	Palatal
9	Nil appreciable	100.6	1 plus	S.S.	-	Suggestive		Ft.Tr.	9-17	-
10	Nil appreciable	99.2	?	(bradycardia throughout)	Affected	Suggestive		Ft.Tr.	A-24	-

TABLE CONTINUED OVERLEAF

Table VII, continued.

Case no.	General appearance	Max. temp.	Strep. haem.	Cardio-vascular system				Proteinuria		Paresis
				Pulse chart	Heart sounds	Blood pressure	Other	Maximum	from to	
11	Equivocal	98.4	1 plus	Marked brady. weeks 1-4.	-	(incon-clusive)		-		-
12	Slightly febrile	103.6	1 plus	-	-			Trace	A-18	-
13	Nil appreciable	99.2	0	-	-	-		¼ pt.	A-17	-
14	Equivocal	100.8	0	-	-			Trace	A-17	-
15	Nil appreciable	98.4	2 plus	-	-			Ft.Tr.	6-15	-

Abbreviations and Explanatory Notes (working from the left of the table to the right) :

General appearance : The method of making this assessment is explained on p. 76.

Max. temp. : The maximum temperature recorded during the acute stage of the illness (for further details, see p. 76).

Strep. haem. : Streptococcus haemolyticus.

(Although not directly relevant to the subject of the table, it was thought interesting to juxtapose the data regarding the occurrence of this organism with the previous column - regarding the maximum temperature).

0 : no colonies of the organism present on the blood agar plate.

1 plus to 5 plus : indicate that a particular number of colonies of the organism was present (for details, see p. 93).

? : indicates that the data were not available as the case was one of the 'incompletely investigated' group.

TABLE CONTINUED OVERLEAF

Table VII, continued.

Pulse chart :

S.S. : 'Shallow saucer' type of curve. The meaning of this and of the other terms used in this column is explained on pp. 73 and 78.

If the finding is placed in brackets, this indicates that there was considerable doubt as to it being of pathological significance; but in view of the other circumstances of the case, it was thought that it might have that significance.

Heart sounds :

Affected : This refers to that temporary diminution of the loudness of the first heart sound (as compared with the second) which is mentioned on pp. 73 and 77. In case no. 1, the only case in which this change was very marked, reduplication of the second sound was also present.

Blood pressure :

Suggestive : This signifies that serial blood pressure estimations showed a fall in pressure at the expected time (on the assumption that myocardial damage had taken place). In no case was the fall very striking.

(Inconclusive) : This signifies that there was a slight fall in pressure at the time referred to above, but that the fall was not considered to be sufficient to justify the formation of any conclusion as to its significance.

In cases in which serial pressure estimations were quite normal, the sign '-' is used in the table. When such estimations were not made, the space is left blank.

Other (Cardio-vascular system) :

(Death) : In this case death took place on the patient's sixth day in hospital (the tenth day of the illness) primarily from myocardial failure.

E.S. : Extrasystoles. There were occasional extrasystoles during the weeks specified.

Proteinuria :

Maximum : This refers to the greatest degree of proteinuria present during the illness.

TABLE CONTINUED OVERLEAF

Table VII, continued.

Proteinuria, continued.

++ : Heavy proteinuria; amount not estimated.

pts. : Amount in parts Esbach.

Ft.Tr. : Very faint trace.

From to : The figures quoted are the day of the illness when proteinuria first appeared (or 'A' if it was present on admission and persisted from then) and the day when it was last found to be present.

Paresis :

Multiple : The parts affected in this case are mentioned on p. 83.

K.J. : Absent knee jerks during convalescence.

Other comments on this subject are made on p. 80 ff.

Table VIII. Findings as to Streptococcus haemolyticus (H.S.) : 'Throat' cases (except those 'incompletely investigated') and the 'Normal' and 'Scarlet Fever' series.

Group of Cases	Total Cases	Cases with growth of H.S. specified													
		Nil		1 plus		2 plus		3 plus		4 plus		5 plus		2 plus or more	
'Diphtheria'	57	28	49.1%	11	19.3%	9	15.8%	6	10.5%	3	5.3%	0	0%	18	31.6%
'Other than diphtheria'															
'Non-virulent'	26	14	53.8%	2	7.7%	3	11.5%	4	15.4%	1	3.8%	2	7.7%	10	38.5%
'Miscellaneous'	4	3	75.0%	0	0%	1	25.0%	0	0%	0	0%	0	0%	1	25.0%
'Streptococcal'	98	1	1.0%	4	4.1%	20	20.4%	29	29.6%	33	33.7%	11	11.2%	93	94.9%
'Unknown Cause'	36	29	80.6%	7	19.4%	0	0%	0	0%	0	0%	0	0%	0	0%
Total	164	47	28.7%	13	7.9%	24	14.6%	33	20.1%	34	20.7%	13	7.9%	104	63.4%
'Normal'	50	33	66.0%	8	16.0%	8	16.0%	1	2.0%	0	0%	0	0%	9	18.0%
'Scarlet Fever'	50	3	6.0%	2	4.0%	23	46.0%	16	32.0%	5	10.0%	1	2.0%	45	90.0%

Note : For definition of the terms '1 plus' to '5 plus', see p. 93.

Table IX. Findings as to various organisms : the last 165 cases of the 'Throat' group, and the 'Normal' series.

Group of Cases	Total Cases	Cases with findings specified													
		Neisseria 2 plus or more		S. viridans/pneumococcus 2 plus or more		Staph. aureus				Haemophilus influenzae				Yeasts 2 plus or more	
						1 plus		2 plus or more		(fully) haemolytic				non- or partially haemolytic 2 plus or more	
										1 plus		2 plus or more			
'Diphtheria'	48	44	91.7%	45	93.7%	1	2.1%	0	0%	0	0%	0	0%	1	2.1%
'Other than diphtheria'															
'Non-virulent'	18	17	94.4%	17	94.4%	0	0%	0	0%	0	0%	0	0%	1	5.6%
'Miscellaneous'	2	2	100.0%	2	100.0%	0	0%	0	0%	0	0%	0	0%	0	0%
'Streptococcal'	75	64	85.3%	65	86.7%	7	9.3%	2	2.7%	1	1.3%	0	0%	3	4.0%
'Unknown Cause'	22	19	86.4%	21	95.5%	2	9.1%	2	9.1%	1	4.5%	1	4.5%	1	4.5%
Total	117	102	87.2%	105	89.7%	9	7.7%	4	3.4%	2	1.7%	1	0.9%	5	4.3%
'Normal'	50	45	90.0%	48	96.0%	3	6.0%	0	0%	0	0%	2	4.0%	1	2.0%
														0	0%