

A Contribution to
The Epidemiology of Diphtheria
Persistent Cases of Infectivity

and

A Mode of Treatment.

by

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(Being M.D. Thesis)

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Section.

Page.

Causation of Diphtheria -----	1
Control of Carrier Cases -----	6
Milk and Diphtheria -----	10
Domestic Animals -----	11
School Influence. -----	11
Persistent Cases -----	13
Virulence of Bacilli -----	15
Frequency of Persistent Cases -----	16
Causes of Persistence -----	17
Treatment of Persistent Cases -----	20

Diphtheria is at the present time almost universally looked upon as a disease which is infective only in the presence of the Klebs-Löffler bacillus, probably the most important determining factor in the spread of the disease being case to case infection.

Causation of Diphtheria.

There are certainly factors, other than actual personal ones, which play a part in the epidemiology of the disease, these are probably more of the nature of predisposing causes, the more important of these are:-

1. Meteorological conditions.
2. Insanitary surroundings.

Longstaff, in the Report of the Medical Officers to the Local Government Board for 1887 - says, that anything which tends to damage the mucous lining of the throat - such as ordinary Catarrhs, predisposes to attack by Diphtheria - given a sufficient cause of the disease.

Newsholme's researches show that preceded by dry seasons, a certain humidity of the atmosphere is favourable to the spread of Diphtheria, and this condition together with the insanitary conditions may afford an explanation of the greater susceptibility and cause of simple sore throats.

Both these predisposing causes were present in the Enfield epidemic of 1908-09, and also the presence of sore throats preceding and occurring alongside. In the spring and summer of 1908 it was fairly dry, and especially in the late summer and

autumn the rainfall was very small, then followed excessive rainfall, about which time the presence of "Septic Throats" made themselves evident, in which throats no Klebs-Löffler bacilli were to be found, and in such as recovered, no signs of paralysis, &c. were to be seen. (Vide Dr Wheaton's Report to the Local Government Board).

The examination by me of over a hundred of these cases of "Septic Throats" during the epidemic, revealed the existence in all of a Septic Follicular Tonsillitis, and on bacteriological examination both Staphylococci and Streptococci were demonstrable, but no Klebs-Löffler bacilli. The probable explanation I made and with which Dr Wheaton (Local Government Board) agreed, was that this condition of sore throat was indirectly the result of a combination of sanitary defects and a suitable series of meteorological conditions reducing the resisting power of the individual to the germs of Sepsis always present in the throat, and that this relaxed and diseased condition of the throat predisposed to the Diphtheria infection.

This association of Tonsillitis with Epidemic Diphtheria has been pointed out by Dr Thomas Orr (of Wakefield) in the Journal of the Royal Institute of Public Health; in his cases also he was unable to isolate the Klebs-Löffler bacillus.

The actual causes of Epidemic Diphtheria are capable of being divided for descriptive purposes into -

A. Case to case infection.

B. Milk Influence.

C. Domestic Animals.

D. School Influence.

A. Case to case Infection

1. Cases showing clinical signs of the disease.

2. Contact cases Immediate
 Remote

3. Recovered cases (including "missed cases").

1. The first class can easily be controlled, because of the nature of the disease being capable of diagnosis followed by isolation; all such cases however are not of such severity as to require medical attention (in the mind of the parent) and may be thought to and occasionally do, recover without medical treatment, and thus escape the Notification Act and the active measures which follow; such are described as "missed cases;" and can be understood to be a real source of danger. In the great majority of clinical cases the Klebs-Löffler bacillus can be cultivated from the affected parts, probably in the small minority of such as do not give a positive result bacteriologically, the reason is due to imperfections in technique. Sims Woodhead's figures in his report to the Metropolitan Asylums Board give 20% of cases proving negative while clinically classed as Diphtheria in the hospitals of the Board. Graham Smith from the record of certified cases (27,000) found 28% were negative on bacteriological examination. In the Edinburgh City Hospital cases (1905) the percentage was 17. In the Enfield epidemic 1908-09 in 500 cases there were 16 cases only which proved negative while showing signs clinically of Diphtheria, but if only one examination had been made it would have

4

been considerably higher, and if examinations had only been made from the throat, but in cases where on admission the first swab proved negative a further swab was taken and this generally gave a positive result. In all these cases the recognition of the bacilli was on morphological grounds using Neisser's method of staining. The discrepancy in Graham Smith's figures may be owing to the fact that the various people certifying have different views of the appearance of Clinical Diphtheria. In the report of Sims Woodhead the same fallacy obtains, namely, the experience of the observer in recognising clinical Diphtheria; and different observers in the various hospitals adopting different standards. The Edinburgh City Hospital figures are less liable to be wrong, because of one observer being retained throughout. But in the Enfield Hospital the clinical and bacteriological work is under the same observer, so that the same standard is adopted in each case, but on the other hand it may be reasonably averred that the results of bacteriological examination may be preconceived; this was obviously impossible because all the cultures taken from the cases were numbered, and it was only on going back to the ward that the name corresponding to the number could be ascertained. The discrepancy between the Enfield and the Edinburgh figures is explicable on the ground that only one cultivation was taken from the latter cases.

2. The next class of case (contact cases) is derivable from the last, and such are much more difficult to deal with, even when they are recognised. To control these cases requires just as much as actual clinical cases, a rigorous isolation. It is a moot

question, however, if this can be insisted upon under the powers conferred upon a local authority by the Infectious Diseases Acts, but probably a statement that bacterial as well as clinical cases are to be understood in reading the Act, would be accepted.

It is the practice among modern Sanitarians and Hygienists to examine bacteriologically all contacts, and the results certainly warrant active measures being adopted to deal with these cases. Graham Smith and Nuttall give the following figures as to liability to infection i.e. harbouring virulent Klebs-Löffler bacilli in their throats and noses.

Close contacts (relatives and attendants) 36.6%

Inmates of Hospital wards ----- 14%

Scholars of infected schools ----- 8.7%

Savage in the Colchester records finds for the years 1903-08 that the percentage of close contacts (inmates of same house and playmates) who harbour Klebs-Löffler bacilli is 8.6.

From collected statistics on the number of non-exposed persons who harbour virulent Diphtheria bacilli, in 2,132 cases there were only 4 who did have virulent bacilli in their throats, and 56 who had avirulent bacilli. (Graham Smith). In the same work we find statistics anent the virulence of bacilli from contacts - in 247 cases 182 were found fully virulent and only 35 were not so.

These figures all urge the necessity for some method of dealing with this problem by bacteriological examination of the throats and noses of all persons living or coming in close contact with any case of Diphtheria, this must not only be in such cases as show some

signs of inflammation about the throat, but also in many cases where there is no abnormality in the condition of the throat, yet bacilli fully virulent may be present.

3. Recovered Cases.

Cases of Diphtheria which have been isolated during the attack frequently retain virulent bacilli in the throat and nasal passages for very varying lengths of time, so that while it may be safe to pronounce one case free from infection after a certain period of time, in another case it may be exceedingly dangerous as the following figures show, from the date of disappearance of the membrane till the disappearance of the bacilli from the throat.

	<u>Mean duration</u>	<u>Shortest</u>	<u>Longest</u>
Cobbett	18 Days	3 Days	108 Days.
Graham Smith	28 "	- "	94 "
" "	- "	8 "	99 "
Writer's case (Lancet 1908)			9 months.

The above statistics point to the necessity for the accurate determination of the period of segregation by bacteriological examination, and to the danger of the fixed time method of discharging such cases; this point is especially important in cases which are treated at home, and do not come so much before the Public Health Officer, (being usually of the better class).

Control of carrier cases:-

Carrier cases are such cases as have the power of conveying the disease to others although themselves showing no signs of the

disease and may be divided into-

1. Contact cases.
2. Recovered cases.

1. Contact cases may or may not subsequently develop the disease, in either case, however, the potential danger to the community of a contact case harbouring the virulent bacilli of Diphtheria is the same, probably in the former case where the disease develops the danger is less because it is shorter lived and is sooner recognised. Probably the contact that does not develop the disease, perhaps because of receiving a prophylactic dose of the Antitoxic Serum, and the recovered case which still harbours the virulent germs are the most serious entities to deal with, especially so in the latter, because unlike Scarlatina there is no sign of infectiveness (discharging ears or nose). In a certain proportion of Recovered Cases it is found that the bacilli persist for very long periods after convalescence is established and such cases are frequently discharged from quarantine with fully virulent bacilli in their throats. Now these carriers ought to be carefully looked after and isolated until the bacilli disappear or lose their virulence. The practice generally adopted is for the contacts to be examined bacteriologically, and if Diphtheria bacilli are found a prophylactic dose of Antitoxic Serum is administered and no further notice is taken of them. This practice is certainly not scientific nor from the standpoint of the public health an economic routine measure, because 1. Diphtheria Antitoxic Serum has no effect on the bacilli, and simply prevents (sic) more or less the development of an attack in the individual. 2. It may be a positive danger to the cases

which do develop an attack within a certain period afterwards from the very dangerous symptoms associated with Serum supersensitisation, (Anaphylaxis) which may be seen from the appended history of two cases at Enfield.

Case 1. In June 1909 a boy 5 years was admitted suffering from a moderately severe attack of Diphtheria of the throat. Antitoxic Serum was administered, serum symptoms developed. After 23 days, on bacteriological evidence (3 cultures) of his freedom from infection he was discharged. In the middle of July he again became infected and was readmitted with distinct membranous exudation on one Tonsil, which on cultivation gave positive evidence of Klebs-Löffler bacilli. Local treatment was vigorously tried, Calcium Lactate ($7\frac{1}{2}$ grain doses) was given in case Antitoxin would be necessary. After 24 hours the exudation had spread so markedly (involving both Tonsils and Pharynx) that further delay in administering the Serum was deemed inadvisable, this injection was followed in 18 hours (exudation having disappeared) by a well marked and extensive Urticaria, Albuminuria, and severe collapse. After vigorous and continuous stimulating treatment recovery took place.

Case 2. In this case the interval between the attacks was longer. A female of 42 years was admitted suffering from a mild attack of Diphtheria of the throat. Antitoxin was administered, but with the exception of some slight articular pains no complication occurred and she was discharged after bacteriological evidence, (3 cultivations) of freedom from infection in 25 days. Five months later this woman became reinfected, this time with a much

more severe attack. On admission no Antitoxin was given, local treatment was vigorously applied, but the membrane spread so rapidly that in 24 hours Antitoxin had to be given - the membrane disintegrated and disappeared in 3 days, but in 5 days a very severe Arthralgia became evident, accompanied by distinct swelling over the joints, and distinct signs of cardiac failure, such as to require Strychnine and Digitalis being regularly administered - recovery took place.

The risks attendant on the administration of a second dose of Antitoxic Serum are of such moment as to necessitate mature consideration being given before it is administered in suspected or contact cases, because of the dangers arising when a reinfection does occur within a certain time after the first attack. It certainly appears an extremely dangerous practice when used wholesale as a prophylactic measure. Would it not be a much more reasonable and scientific plan to have all contacts who have Diphtheria bacilli in their throats carefully isolated and watched, and Antitoxic Serum administered only on the first sign of membrane appearing ? The result of some such method of treating contacts or suspected cases would be to dissipate that false sense of security engendered by the use of Antitoxin - the whole effect of which in these cases is that of "cloaking carriers". In Cambridge and Colchester this method of dealing with contacts has been successfully carried out, the Smallpox Hospitals being used for quarantine purposes, and all the contacts are under constant and efficient supervision, being only detained so long as bacilli are present in their throats;

10

any case showing signs of Clinical Diphtheria is at once given Antitoxic Serum and is removed to the Isolation Hospital.

B. Milk and Diphtheria.

The part played by milk in the epidemiology is not so great as in Scarlatina, but it is not uncommon, and probably the infection of the milk by an infected person handling it is the explanation in most cases. Several such cases are recorded, notably in the Guildford outbreak early in 1908 (Public Health Nov. 1908), and that reported by Dr Armstrong, of Sydney in Public Health (Jan. 1909). While this is probably the most frequent mode of infection of the milk, it is known that certain cases have occurred where the teats and udders of cows have been the seat of ulcerated conditions similar to that produced experimentally by Klein in these animals, (at the seat of inoculation) which condition was followed later by constitutional symptoms, but it is probably true at all these cases are infected by man in the first instance. When, however, the disease is spread by milk, the usual characters of a milk epidemic are apparent, viz. the incidence of the disease in population is in direct proportion to the quantity of milk consumed, and is sudden in its onset.

Diphtheria in the cow is always a severe and mostly fatal disease - the chief parts involved being the lungs (Klein). It is a disease which is really uncommon in cows, so that it is uncommon that an epidemic can be traced to cows, the notable exception being in the first Enfield epidemic (1888) investigated by Drs J.J.Ridge and Bruce Low, for the Local Government Board.

C. Domestic Animals.

Cats are known to suffer from a disease which in its clinical and bacteriological characters, conforms to the disease in the human subject. In certain recent outbreaks it has been found that the Klebs-Löffler bacillus could be cultivated from the domestic cat (Barras - Med. Off. Jan. 1910).

In the last Enfield epidemic, at the instigation of Dr Wheaton of the Local Government Board, I made many bacteriological examinations of the domestic cats from infected houses, but in no case was the Klebs-Löffler bacillus found.

Experimentally Klein has produced in the cat infection resembling in its characters the disease in man, and in its later stages (as in the cow) going on to Broncho-pneumonia and kidney disturbance.

It seems evident that cats are susceptible to the disease, and from the opportunity which the domestic pet enjoys in many households, of spreading the disease, it ought to be regarded with suspicion as a possible source of infection in epidemics of the disease.

D. School Influence.

In school life it is probable that the opportunities for case to case infection are at their maximum, and it is in school that the best results in controlling the disease are procurable by scientifically examining and excluding contact cases. Thomas (B.M.J. 1904) reporting on 29 school outbreaks of Diphtheria in London, found that 85% of the children who were spreading the disease were

between 5 to 8 years old. He next shows that the years of heaviest incidence of Diphtheria are 3 to 4 and 4 to 5 years; there is a slight drop from 5 to 6, considerable drop from 6 to 7, a further drop from 7 to 8, and then the incidence becomes fairly level. So that between the ages 5 to 8 children are passing from a high susceptibility to one of relative immunity, and therefore many of them may be liable to slight unrecognised attacks of Diphtheria. If a child under 5 years be attacked by Diphtheria it will go down with a severe attack and will not remain at school to spread the disease. There was no proof of children of this age being the source of the spread of Diphtheria in any school. Between the ages of 5 to 8 years, however, if a child with Diphtheria attends, a large proportion of that period is liable to an attack in a mild form, and the class becomes a source of danger, a few getting the disease and being excluded, others continuing to attend with slight clinical symptoms. There exist so many facilities for the transference of infective material from one scholar to another (by pencils, slates, &c.) that the great influence of schools on the spread of Diphtheria is not to be wondered at. In the Reports to the London County Council Sir Shirley Murphy has shown that when allowance is made for the incubation period, the incidence of Diphtheria at the ages of 3 to 13 years shows a distinct fall on the closure of the schools for the summer holidays.

Deycke has experimented with Klebs-Löffler bacilli by smearing on oil-painted wood, and was able to isolate virulent bacilli for 4 days. Other experiments by Orr (Royal Inst. of Pub. Hlth, Jan. 1910) with such things as pencils, slates, cloth, paper, and

13
Plasticine, show that Klebs-Löffler bacilli may remain a source of danger on the substances for several days.

Persistent Cases.

In many contact Diphtherias it has been seen that the Klebs-Löffler bacilli may remain for long periods in the throat; but in the throats and noses of "convalescent Diphtheria" patients, this protracted presence of the bacilli is much more evident. While most of the cases are free from the bacilli a week or two after convalescence is established, in a certain number of the cases the cultivations taken from the cases still prove to be positive on examination.

In the series of observations I have made in this connection, I have relied mainly on the morphological appearance of the bacillus from cultivations on Blood Serum or Löffler's medium, stained by Neisser's stain, the latter giving the characteristic polar staining. In connection with the bacteriological diagnosis of the disease, I may give a resumé of the practice at the Enfield Hospital. On admission, a case is put in a reception ward, a smear examination is made of the swab from the throat or other affected part; if the smear preparation shows no Klebs-Löffler bacilli a cultivation is made by smearing a sterile swab thoroughly over the affected surface and then transferring the swab to the culture medium, on the surface of which by gentle rubbing, the infective material is implanted. The Cultures are then transferred to the Incubator, where they are exposed to 37° C for 18 hours, then removed, stained by Neisser stain, and counterstained by Vesuvin.

14

Preparatory to the discharge of a convalescent case the procedure is, where no complications are present on the 18th day, to take a cultivation of materials removed on a sterile swab, from the throat and nose, to none of which surfaces any antiseptics have been applied on that day, and no food or liquid has been partaken of for $1\frac{1}{2}$ hours previously. If this first examination is positive no further swabs are taken for 3 days. If negative a second examination is made, and if the result of three examinations is favourable, the patient is discharged. An interval of 3 days having elapsed since the last positive swab, another series of observations are made, and if in all three, the bacilli cannot be found, the patient is discharged. In some cases the bacilli can be discovered in each examination, notwithstanding active local medication; in these cases at the end of six weeks our procedure is to have the virulence of the bacilli tested, and if these are found to be avirulent, the case is discharged, but if virulent the patient is detained for no case is discharged while harbouring virulent bacilli.

These rules I based on the report to the M.A.B. by Sims Woodhead (vide supra). He made out in that report that in the case of the M.A.B. hospitals in the year 1896, 13.8% of the cases admitted were discharged with Diphtheria present at the final examination. He is of the opinion that all convalescent patients should be isolated, in whose throats slightly virulent bacilli remain. The necessity for repeated consecutive examinations is important, as it tends to minimise the chance of error which might occur from various causes: viz. 1st, from the application of the

15

sterile swab to the affected surfaces at a time when the bacilli have been removed by some mechanical means, e.g. swallowing, or blowing the nose, &c. 2nd, the application may not have been thorough. 3rd, the inoculating of the culture tube may not have been satisfactory. 4th, examination, technique, and personal error. The following figures I calculated on 500 cases at Enfield 1908-09, where one negative swab had been obtained the second swab proved positive in 9%, and in cases where two negative examinations had been made the third proved positive in 7%, so that by repeated examination the chance of error is much reduced. Savage's (Pub. Health, Mar. 1909) equivalent figures were 24% and 5.3%. In a series of 100 cases, I found that where a swab from the throat was taken and found negative, that from the nose was positive in 7 cases, showing the importance of taking swabs from both nose and throat.

Virulence of Bacilli. In many cases where the bacilli are persistent, it is found that the bacilli have lost their virulence, and when inoculated on guinea-pigs, no result is produced, so that it is deemed safe to pronounce such cases free from infection. In connection with this point Dr Arkwright made experiments for me at the Lister Institute, to endeavour to render avirulent bacilli virulent by various means (a) by growing the bacillus within the peritoneum of guinea-pigs, (b) by inoculating and cultivating alternately, (c) by inoculating a mixture of Streptococci and Klebs-Löffler bacilli. These results have all been negative, except in so far as after a long period, a small amount of Antitoxin was to be found in the serum of a horse used in the experiments,

16

but it was very small in value. So that up to the present we are justified in pronouncing a case free from infection if bacilli are present, but are avirulent. There are no other recorded experiments on the attempt to make an avirulent organism regain its lost virulence, although up to a certain point in attenuation it has been found possible to take advantage of the symbiotic qualities of the Klebs-Löffler bacillus, and increase its virulence by growing with Streptococci (Muir & Ritchie). But in all persistent cases the bacilli do not become attenuated, nor do they lose their virulence, but can be shown to be fatal to guinea-pigs for long after the patient has shown any clinical sign of the disease. Roux & Yersin found by making cultures at various stages after the termination of the disease, that the bacilli gradually became attenuated, probably explaining the fact that while so many cases have been discharged from hospital with bacilli in their throats, there have been really few return cases of Diphtheria. Tobiesen investigated the results got from 24 cases discharged with bacilli still present. He could only discover one case where the evidence seemed to prove that a convalescent child had been the cause of Diphtheria in the mother.

Frequency of Persistent Cases. By a "Persistent Case" I mean a case which has completely convalesced from Diphtheria, and which has been bacteriologically examined preparatory to discharge from hospital (or freed from isolation) and is detained because of the fact that virulent bacilli are present in the nose, throat, or other parts of the body, beyond the average period. Taking these data, I found in 230 cases investigated at the Enfield Hospital

that 49 may be so described as persistent, making a percentage of 21.3. Other observers have investigated this same point in a slightly different manner.

Sims Woodhead in the Metropolitan Asylums Board report mentions in the years 1894-6 that 226 cases were detained for more than 100 days - the mean duration of his cases being 52 days - the longest period being 200 days.

Parke & Beebe (Med.Rec. N.Y. 1894) in examining 747 cases found that the bacilli were no longer present after 3 days from disappearance of the exudate in 315 cases; in 201 cases the bacilli had disappeared in 5 to 7 days; in 84 cases in 12 days; in 69 in 15 days, and in 5 in 5 weeks.

Walsh (N.Y. Med. Journ. 1898) in an examination of 800 convalescent cases found the bacilli absent as early as the 6th day, and present as late as the 8th week. Cobbett (Jour. Hyg. 1901) found the mean duration of his cases was 18 days, the shortest being 3 days, and the longest 108 days.

Various others found prolonged periods of resistance. Escherich found bacilli fully virulent after 5 weeks, Park after 7 weeks, Belfonti after 7 months, Westbrook after 135 days, Hewlett after 22 weeks, Golay after 362 days, and my own recorded case (Lancet 1908) 9 months.

Of the above mentioned 49 persistent cases in the Enfield Hospital, 40 were delayed over 45 days, 9 were delayed over 60 days, i.e. of the 230 cases (17.3%) and (3.8%) respectively. In addition to these there were in the Hospital 10 purely "carrier cases" with an average period of persistence of 59.6 days, one case retaining virulent bacilli as long as 117 days.

Causes of Persistence.

The reason for the persistence of the bacilli is not hard to find in some cases, such are those where

some mechanical means exist whereby the bacilli are offered a suitable nidus for growth and multiplication, and are more or less protected from whatever mechanical methods are used to hasten their removal; the commonest of such conditions are found in this list.

Deviation of the Nasal Septum.

Enlarged turbinate bones.

Polypi nasi.

Enlarged tonsils.

Adenoids in the Naso-pharynx.

These causes of persistence are simple, and the gross remedy is easy of application - surgical interference in Enlarged Tonsils, adenoid growths, &c. This treatment can be carried out without any special risk to the patient, if consideration is given to the interval since Antitoxin was administered, and to the amount given; if a sufficiently large dose of serum is given, and no complications of Diphtheria are present (Cardiac, &c.), then there is no danger from a recrudescence of the disease on the raw surfaces. In 4 such cases at Enfield this treatment was carried out successfully. In these cases it was found that the bacilli could be cultivated from the substance of the Tonsil, which on staining sections, showed the bacilli embedded in the depth of the tonsillar tissue, showing the futility of applying local remedies in such a case.

There are other cases where the bacilli are found to persist, and in this class no explanation can be offered, the throat and nasal passages are to all appearance normal; these cases are probably analogous to the "Typhoid Carriers;" this analogy is

74

further exemplified in some cases where the bacteriological examinations of the swabs from the nasal passages prove that the bacilli are only intermittently present. This similarity to the "typhoid carrier" cases I drew attention to in the Lancet of Nov. 1908, and in the Medical Annual for 1909 Dr Goodall quoting from this article, expresses his concurrence with my view that the Antrum of Highmore or other sinus opening into the nasal meatus acts as a nidus for the bacilli, where (of gall bladder in Typhoid carriers) the bacilli multiply and overflow periodically into the meatus, at which times, if a swab is taken, it is generally positive. This view has been further recognised, and at the Meeting of the British Med. Association at Belfast, Dr Andrew Wyllie of Golden Square Throat Hospital raised the question of operation and antiseptic treatment of the cavity of the Antrum in these cases.

Influence of Season on Persistence. My records mostly related to an epidemic time, but from a few cases I find that the general effect of summer is to reduce the duration of persistence. Walsh (N.Y. Med. Record, 1898) finds that the average was 20 days in summer and 24 in winter; this seems to agree with the figures of the Edinburgh City Hospital for 1905-6.

Season and Persistence

Edinburgh City Hospital 1905-06.

	Average duration days.
February - April -----	11.79
October -----	19.04
November -----	19.94

	Average duration days.
December -----	22.84
January -----	23.3
February -----	19.06
March -----	12.43

In the case of sex it is inconceivable that this can have any influence on the duration , and in no case was any special influence observed.

The age distribution of the investigated cases was:-

Under 5 years -----	30%
5 to 10 years -----	36%
10 to 15 years -----	20%
Over 15 years -----	14%

The calculated average duration of the cases at each age group is respectively 33.74; 41.24; 37; and 33.48 days, showing a tendency for longer duration in cases at the age group 5-10 years, when it is probable that the lymphoid tissues are increasing and thus enlarged Tonsils and Adenoid growths are more common at that age.

Treatment of Persistent Cases.

Since the fact was known that in the throats of persons who had once suffered from, or had been in contact with Diphtheria patients, Diphtheria bacilli may exist for a long time, attention

21
has been directed to the part which persons play in the epidemiology of the disease. E. Neisser first tried to kill the bacilli in the throats of Diphtheria carriers by means of disinfectants and an intensive serum treatment, but fruitlessly.

Effect of Diphtheria Antitoxic Serum.

It is of course understood that Antitoxic Serum has no bactericidal powers, but certain investigations have been made into the effect, on the duration of the persistence, of the quantity of Antitoxic Serum given, which is only another way of stating that the severity of the case has an influence on the persistence. In the Enfield cases the classification of severity adopted was 1st, Mild, 2nd, Moderately severe, 3rd, Severe, and the percentage of each type was 46, 33, and 21 respectively, the former cases having not less than 4,000 units, the second variety not less than 6,000, and the last group not less than 8,000 units, and the average duration of persistence in each group 18.7, 19, and 30.3 days respectively, so that the difference in these is simply stating that mild cases clear up quicker, and that the amount of Antitoxin administered is not the determining factor. Graham Smith in the Cambridge outbreak found the mean duration to be 36 days in treated patients, and 30 days in untreated contacts. Experiments were made at Enfield by inoculating sterile Antitoxin with Klebs-Löffler bacilli, and it was found possible to cultivate the bacilli from the inoculated Antitoxic Serum for 2 days, thus demonstrating the absence of any antimicrobial elements in the Antitoxin.

In considering the treatment of Persistent cases, it is advisable to classify them into

1st Those cases where there is a mechanical obstruction.

2nd Those cases where there is no evident cause.

Examples of the first class are found in Enlarged Tonsils and Adenoids, Deviation of Septum Nasi, &c. The next proceeding in this class of cases is to determine whether the cause of persistence is capable of removal by surgical means. Those cases which are amenable to surgical treatment are usually cases with Enlarged Tonsils and Adenoids in the Nasal-Pharynx, which cases in 500 admissions to the Enfield Hospital in 1908-09 constituted 30%. The treatment that serves best for these cases is the removal of the Tonsils and Adenoid growths, when the convalescence is established, care being taken with these cases on admission to give a sufficiently large dose of serum (protective as well as curative) with this object in view. I carried out this treatment in 4 such cases, which were persistent, with success. It is advisable that such cases should be observed on the occasion of admission, and sufficient Antitoxic Serum given, rather than the practice of giving more serum at the time of operation, because of risks involved in Serum Anaphylaxis.

In the second class of case, the bacilli having been found to be virulent to guinea-pigs, and where no mechanical explanation can be offered to account for the persistence, there are various measures which can be adopted for the eradication or removal of the virulent bacilli. Such measures may be described as -

1. Mechanical.
2. Bactericidal.

1. Mechanical means. The measures which are adopted for the removal of the bacilli may be described as the cleansing of the exposed surfaces by either of the following means:-

- (a) Gargling.
- (b) Spraying.
- (c) Douching.
- (d) Syringing.
- (e) Swabbing.

2. Bactericidal means consist in the application to the affected surfaces of some germicidal agent by any of these mechanical means. The common procedure consists in using a solution of an antiseptic of definite strength on the affected surfaces, in the hope that by a combination of mechanical and germicidal effects the bacilli will be removed or rendered harmless.

The results of the cases at Enfield treated with various antiseptics in the above way was not very satisfactory, as will be seen from the following table:-

	<u>Cases.</u>	<u>Average Persistence.</u> <u>Days</u>
Cyllin -----	27	35
Izal -----	20	34
Chinisol -----	100	39
Chlorine Water -----	23	37.4
Distilled Water -----	60	36

The results all show that the effect of a germicidal agent in the solution is not of great moment when we compare the result with that got by using distilled water. The solutions of the

antiseptic agents used were all such as were germicidal to the Klebs-Löffler bacillus "in vitro", but the probable reason of their defect was in the application, because no matter in what way the solution is applied, in order to have a bactericidal effect the germicide must have a certain duration of action. It seems impossible (1) to retain any solution continuously applied to the surfaces in question for the required length of time, or (2) that the solution can possibly reach every corner where the bacilli lodge (e.g. Crypts of Tonsils, &c.) in the required dilution, no matter what mode of application of the bactericide is adopted. It may be said that a stronger solution of a germicide may be employed, and the use of a strong solution of an antiseptic to the tonsillar surface may be feasible, to do so in the case of the nose is impossible because of the damage and resulting cicatrization of the tissues ensuing.

Mode of Application. - Gargling is the commonest way in which antiseptics are applied to the throat, but in cases where the nose is the seat of persistence of the bacilli, it is obviously useless. Even in the case of the throat its action on the Naso-pharynx is very limited, as is seen in the experiment with Methylene Blue Solutions which colour the tissues and show the extent of its application.

Spraying is a method which can be of no real service, because of the dilution which must ensue when the droplets of Antiseptic mingle with the mucus on the exposed surfaces, and the danger arising from the inhalation of any stronger solution prevents such

being tried.

Douching and Syringing are methods similar to each other, except that in the former the stream of fluid is constant, and in the latter it is intermittent. These methods are better than the previous, but are difficult in application, especially in young children, and there is a certain amount of danger arising in their use from the risk of some septic matters being expelled into the Eustachian tube and setting up an Otitis Media, &c. This risk is exemplified in the following figures from the records of Scarlet Fever cases at Enfield:-

Frequency of Otitis Media in Scarlet Fever.	
Cases with routine douching of Throat and Nose -----	30%
No local medication unless ordered -----	3%

Swabbing is probably the best of all the methods of local application, because it can be applied more directly and in stronger solution, but it must necessarily be only a surface application, and there are many nooks and crannies which cannot be reached in such a method (e.g. back of nose, tonsillar crypts, &c.). In connection with this method it may be applied with strong disinfectants for cauterising the tonsils, &c. but this method is dangerous as creating a raw surface for the possible recrudescence of membranous exudation.

Tablets impregnated with germicidal agents are a comparatively recent innovation for the local application of Antiseptics to the throat surfaces. My experiences are confined to those containing Formalin, and in these the amount of Formaldehyde procurable does not

26

seem to form a solution of sufficient strength to form a germicide. While using these substances I made a series of experiments by dissolving the tablets in 20 cc sterile distilled water, with the result that only in the case where 2 tablets were dissolved, after 72 hours no growth was obtained on Loeffler's Blood Serum.

No Tablets dissolved in 20 cc Sterile Water	K.L.B.		
	hrs 24	hrs 48	hrs 72
1	+	+	+
2	+	+	—
3	—	—	—

Now from the above table it is seen that the tablets must have a very long duration of action to be efficacious, and such circumstances are obviously impracticable in the application to the throat, and such tablets are necessarily of no value in nasal persistent cases.

A recent scientific product has been brought forward (Pyocyanase) the product of a broth culture of *Bacillus Pyocyaneus*, which has certain liquifying powers. These powers are of great use in the hastening the removal of the membrane in Clinical Diphtheria, and it has the power certainly of causing the complete disappearance of the Klebs-Loeffler bacilli in vitro, but whether it can be applied in the way recommended (spraying) so as to be of any value, is doubtful, for the reasons stated for the failure of the different antiseptics, certainly in a very limited trial at Enfield it did not have any very marked results.

27

Nasal cases of Persistence. In the treatment of such nasal cases as have been already described, it is obviously impossible to introduce Germicides into the various Sinuses (e.g. Antrum Highmore) which are probably the real seat of trouble. It has, however, been proposed (A. Wyllie, of London, at B.M.A. Meeting at Belfast) to adopt operative treatment for the Antrum, but this may only be one source, and there are other sinuses which may be equally infected; besides the difficulty in such cases of getting the antrum to heal requires mature consideration being given before this treatment is carried out.

Vaccine Treatment in Persistent Cases.

This treatment I had an opportunity of carrying out at the Enfield Hospital on 14 cases of persistent bacilli. In 10 of these there had been no clinical signs of the disease, they were purely "carrier" cases, the other four cases being persistent recovered cases. In all these cases the bacilli were virulent to guinea-pigs when the treatment was commenced, and the general trend of events during treatment was that the bacilli gradually became attenuated in virulence, and in most cases disappeared altogether, while in the others the bacilli became avirulent.

Petruschky first successfully employed a method of Active Immunisation for the treatment of "carrier" cases of Diphtheria. The method he employed was the following - the Diphtheria bacilli isolated and cultivated from the throat of the affected person on Löffler's serum, after being killed by chloroform vapour, were washed off with 10 cc of a sterile normal saline solution containing

.5% phenol, and from this turbid liquid a further dilution was made with the same normal saline. After testing on guinea-pigs, the patient was inoculated.

The treatment I employed at Enfield was practically on the same lines. The bacilli were cultivated and isolated from the particular case. After 24 hours growth they were washed off with sterile normal saline solution, sterilised by heat and standardised against red blood corpuscles, tested on guinea-pigs, and if they did not produce a swelling or any pathological symptoms the patient was subcutaneously injected with 300,000,000 bacilli, followed in 3 days by 600,000,000, then in 3 days if any bacilli remained, a further 1,200,000,000 bacilli was given. In 8 cases only 2 injections were necessary, when the bacilli on careful microscopical and cultural examination could not be isolated from the throat or nose. In 6 cases a third inoculation was required; in 4 of these the bacilli disappeared, and in the other 2 the bacilli became avirulent to guinea-pigs.

No	Duration of Perisistence	Doses	Result of Treatment.
1	97	2	Bacilli disappeared.
2	60	2	" "
3	51	2	" "
4	35	2	" "
5	47	2	" "
6	63	2	" "
7	52	2	" "
8	58	2	" "
9	117	3	" "
10	83	3	" "
11	77	3	" "
12	55	3	" "
13	68	3	avirulent
14	67	3	"

The injections produced in no case any disturbance of the general health, beyond a slight stiffness, the patients being able to go about the ward in about an hour after receiving the injection. No after effects of this specific treatment of any kind were observed.

Resumé of Vaccine Treatment.

1. Virulent bacilli are found persistent.
2. Swab, cultivate, and isolate Klebs-Löffler bacilli in each case.
3. Wash bacilli into normal saline.
4. Sterilise and standardise vaccine.
5. Test vaccine on guinea-pigs.
6. Inoculate patient with 300,000,000 bacilli.
7. In 3 days inoculate with 600,000,000.
8. In 3 days, if bacilli still present in patient, test virulence.
9. If found virulent give 12 hundred million bacilli.
10. Again in 3 days examine for bacilli.
11. If bacilli found, and virulent, continue treatment.

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