A STUDY OF

D I P H T H E R I A,

WITH SPECIAL REFERENCE TO

P R E V E N T I V E M E A S U R E S

Being a Thesis for the Degree of Doctor of Medicine in the University of Edinburgh. 1923

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I N T R O D U C T I O N '

Thanks in large measure to the activities of our Public Health Service, the last fifty years have been marked by a most gratifying fall both in the incidence of, and in the death rate from, infectious diseases.

This is speedily brought home to one by the reflection that in England and Wales the average annual death rate during the years 1871-1880 from the ten commonest serious infectious diseases---diphtheria, enteric fever influenza, measles, puerperal septic diseases, scarlet fever, small-pox, tuberculosis (all forms), typhus fever, whooping cough---together was 5.31 per 1000 population, whereas the corresponding figure for the year 1921 was 1.75. In other words the death rate is less than one-third of what it was fifty years ago, representing an annual saving of 134,871 lives---a most striking testimony to the efficacy of Preventive Medicine.

Unfortunately corresponding figures are not available to show us the decrease in the incidence, apart from fatality, of these diseases, but such a lowered death rate must connote a diminished incidence and therefore a great saving of sickness and invalidity and also of much physical impairment (through sequelae) which is largely unmeasured and unregistered.

But gratifying as these results are when one considers the group as a whole, on looking further into the matter,

investigating each disease, separately, one finds one very black offender on the list---Diphtheria. All diseases but this (and Influenza) now annually claim less victims per 1000 of population . (See Table 1.) But whereas the figure for this disease for the average 1871.1880 was 0.12, for the average 1911-1920 it was 0.141, and for the year 1921, lower than of late, 0.126. (See Chart 1).

And this, be it noted, is putting the case against Diphtheria mildly. The first decennium mentioned belongs to the pre-antitoxin days, the second to the days of antitoxin. We physicians claim that if there is one disease we can cure , it is diphtheria. Indeed, beyond that, and syphilis,malaria and dysentery, what diseases can we honestly claim to treat specifically? Their number is few. The case mortality of the disease now(based on average mortality of cases notified in London in 1890-94 and in 1917---see Table 2) is not a third of what it was in pre-antitoxin days, which goes to suggest that instead of our figures reading as above:

1871-1880.....0.12
1911-1920.....0.141

they ought to read:

1911-1920.....0.423.

The case against Diphtheria is even darker than it appeared.

Scarlet fever and Measles might be thought of all diseases the most comparable to Diphtheria, being also infections of fauces or naso-pharynx. Yet the figures for Measles are:

Av'ge
1871-1880....0.38 deaths per 1000 popl'tn.
1921....0.059 ,, ,,

and for Scarlet Fever:

Av'ge
1871-1880....0.72 per 1000 population
1921....0.034 ,, ,,

These show a contrast to Diphtheria which is nothing less than striking. (See Chart 1)

Proceeding now from a consideration of fatal cases of Diphtheria to the total number of cases reported, we find here too, unfortunately, an increase. The figures of last century are scarcely comparable, owing to the fact that only recently has bacteriological diagnosis become almost universal.

Table 3, however, goes to shew that during the last ten years there has been a more or less steady increase in the prevalence of Diphtheria, so that in 1920 there were as many as 40per cent more cases than in 1911.

Measles, of course, being not notifiable, is not comparable, but Table 3A shows that there is not a correspondingly great increase in the incidence of Scarlet Fever. The fact, however, that Scarlet Fever incidence follows a marked wave, the crests of wnich are reached every few years, makes somewhat misleading figures such

as those of Table 3, which only covers ten years. It can be stated definitely, though, that although the incidence of scarlet fever is increasing, it is not doing so at the same rate as is that of diphtheria.

Yet the campaign against the disease we are to consider, has been, and is being, waged quite as assiduously as that against scarlet fever and measles, and our success instead of being less, might rightly have been expected to have been greater, seeing that in the two latter the cause is still undiscovered, whilst our acquaintance with the causal organism of diphtheria is quite a long-standing one---a matter of thirty-nine years. And vigorous has been the fight against it.

But still Diphtheria(as an individual disease) ranks high as a cause of death, accounting for more than 1% of the annual death rate; not as bronchitis and pneumonia often are---death come kindly to the aged---but killing off, for the most part, children of from three to fifteen years who have successfully weathered the storm of early life, and of whom the State had a right to expect some fifty years of service. The fit are claimed as victims just as the unfit.

When one considers with these facts the frequency of paralysis and of permanent hypermetropia, the loss to the cause of education through school closure or exclusion, let alone the tremendous cost to the State of hospital

accommodation for this disease---when one considers these facts, I say, one finds great incentive for work on this disease which Sir George Newman rightly terms one of the most baffling from the point of view of the Public Health administrator.

A well-defined etiology, a comparatively easy bacteriological diagnosis, a specific anti-serum with generally recognised prophylactic and curative powers ---all these are ours; yet this disease breaks out and rages amongst the population more than ever; and in this thesis I propose to describe my work in connection with Diphtheria, hoping that some little light may be thrown on this very important subject.

H I S T O R I C A L

S K E T C H !

It will, however, be of interest and profit to proceed first to an historical consideration of this disease. Such a procedure is of value inasmuch as it aids one to view the task one has set oneself in more correct perspective.

Diphtheria appears to be one of the oldest diseases of the infectious group which have prevailed from time to time in epidemic form.

As this disease has been definitely defined only during the last century, it will be convenient if we set before us certain standards wherewith to measure accounts of various diseases which seem to bear resemblance to it.

For this purpose we may take it that the main points for which one would look out before deciding that a given description of a disease was that of diphtheria are:--

1. The presence of membrane in throat or trachea.
2. Difficulty in respiration owing to obstruction--- i.e. ''Croup,'' in many of the cases
3. Soreness of throat.
4. Febrile symptoms.
5. Evidence of infectivity.

The first writer to describe a disease which corresponds in a measure with these standards is an Indian physician named D'hanvantare[2] (circ. 550 B.C.) He includes in his

''System of Medicine'' a description very suggestive of Diphtheria. He speaks of a disease in which ''an increase of phlegm and blood causes a swelling in the throat, characterised by panting and pain, destroying the vital organs and incurable.'' He also says[3]: ''A large swelling in the throat hindering the passage of food and drink, and marked by violent feverish symptoms, obstructing the passage of the breath, arising from phlegm combined with blood, is called 'closing of the throat.' ''

Many hold that "Askara" frequently mentioned in the Talmud[4] as a fatal epidemic, was in fact diphtheria. We are told there that this disease ''sometimes breaks out in the mouth of a man and he dies from it. Sudden death ensues from suffocation. Strack[5] tells us that the meaning of the word "askara" is ''a stopping up,'' and so suggests death from choking.

If the two diseases are one and the same, it is evident that diphtheria existed in Egypt, Syria and Palestine even in ancient times (1,900 B.C.)

But the evidence is obviously very flimsy.

No reference seems to be made to the disease by the ancient Greek physicians. Neither Hippocrates, Celus nor Soranus ever make mention of a similar condition either as a sporadic or an epidemic malady. If some passages in the works of Hippocrates[6] relate to diphtheria, as certain writers have held, their brevity permits us

to doubt the fact. The most suggestive is that passage in ''De Dentitione'': ''Quibus cito in tonsillis ulcera serpentia considunt, felirebris ac tussi permamentibus, periculum est sursus esse generanda ulcera.'' But this falls lamentably short of our standards.

In the works of Aretaeus, a Cappadocian physician who lived in Rome during the latter half of the first century of this era, we find the most accurate early description of Diphtheria. He mentioned the frequency of the malady amongst children, and the prevalence in certain countries, Egypt and Syria particularly; indeed he speaks of the affection as having received the name of ''Egyptian ulcer.'' It was evidently no new disease.

It is remarkable that so shrewd an observer as he should describe no epidemics---a fact which leads us to infer that this disease must have occurred only sporadically and never attained the dimensions of an epidemic.

He gives us a faithful picture of the disease and one that agrees well with the standards one has named. He describes the varieties of Angina benign and malignant, he speaks of ulcers of the throat, soreness and inflammation of the part, and even the characteristic fetor. He describes the various appearances of membrane, notes the possibility of its extension to the respiratory tract, and the occurrence of death by suffocation:[7] ''Tussis spirandique difficultas enascitur, et modus vero mortis

quam miserrimus accidit. Pallida his seu livida facies, tristantur cum tonsillae comprimuntur. Cumque decumbunt, surgunt ut sedeant, decubitum non [illegible] ferentes; quod si sedent quiete carentes iterum decumbese coguntur; plesumque secti stantes obambulant, nam quiescere nequeunt. Inspiratio magna est, expiratio vere parva; raucitas adest vocisque defectio. Haec signa in pejus runut cum subito in tessam collapsis amina deficit.'' What a striking and animated picture he puts before us! On reading a description so graphic as that, one cannot fail to admire the powers of observation and of description possessed by the Ancients.

Interesting as the writings of Aretaeus are, space is not sufficient to allow one to quote from them further, nor to do other than sketch in briefest outline the history of diphtheria during the next seventeen hundred years.

The next description suggestive of this disease comes from the pen of Galen[8] (A.D. 130-201). He refers to the expectorationof a membranous tunic from the pharynx, but says little else. At the end of the third century, Coelius Aurelianus[9] describes the barking sound of the voice and its occasional complete extinction, the stridulous breathing and lividity of face. His work is of special interest as he makes the first reference to diphtheritic paralysis I have been able to find. At least he speaks of the defective articulation and of the

passage of fluids into the nose in swallowing, which are very suggestive of that condition.

During the year 380, Macrobius speaks of sacrifices which were instituted in honour of a heathen goddess ''ut populus Romanus morbo qui Angena dicitur, promisso voto, sit liberatus.'' This is suggestive only.

The next (and more characteristic) description of note is that of Aetius[10] of Amida in Mesopotamia, who lived in the Court of Justinian (circ. 550). He adds to the description of Aretaeus, delineating the disease as presenting white and ash-grey spots in the pharynx, slowly ending in ulceration and making reference to palatal paralysis as one of the sequelae. His treatment is interesting---astringent plant juices, honey, dung of a dog previously fed on bile or of boys who for two days before had been fed on bread and lapins. The physician of those days had evidently no need to study palatability when writing out his prescriptions!

Then follow the Dark Ages, and it is perhaps less from want of occasions of observation than from want of observers that we must pass from the sixth to the sixteenth century to find the disease again well described.

It was about the year 1581 that a vast pestilence marched over Spain and raged in that country, and later in Italy for over fifty years. In Spain it received the name of Garotillo, because those who were attacked by it

perished as if they had been strangled by a cord. !!Morbus suffocans'' was another name for this disease which undoubtedly was diphtheria. Many are the descriptions of contemporary writers and numerous are the clinical points they observed. Thus Villa Real[11] states that he has seen a thousand times a white substance in the throat and oesophagus of patients suffering from this disease; he adds that if you stretch it with your hands it appears elastic and has properties like those of wet leather---facts he gleaned from examination of the membrane in the dead as well as the living.

In those days permission for post-mortem examinations appears to have been difficult to obtain, owing to the conservatism of religious and other bodies. The records of Fontecha[12] and Herrera[13] are less valuable, as they apparently performed no post-mortems, at least no reference is made thereto. But their contributions are of value, inasmuch as they confirm the fact of the prevalence of Garrotillo in Spain between the years 1581 and 1611.

That the disease was recognised to be infectious, and to attack both rich and poor alike, is shown by Sgambati[14] (1620) who speaks of its often sweeping away whole families. Cortesius[15] (1625) also speaks of its infectivity, and describes a membrane in the throat, which could be easily torn away, as one of the symptoms. He gives it the name ''Gaulae morleus,'' and it seems clear from his writings that the disease spread later to Sicily and Italy. Bretonneau[16] tells us it carried off the son-in-law and, a

little later, the grandson of Cortesius, so that Cortesius would have due cause to speak of its infectivity.

It is worthy of mention that Severino[17], describing an epidemic of the disease which occurred in Chiaia, a market-town of Naples, in 1618, gives the first clear description of Diphtheritic paralysis.

Carnevale[18], describing the same epidemic in 1620. speaks of the different aspects which the disease presents in the pharynx, of its extension to trachea and œsophagus, and also goes into the questions of differential diagnosis, prognosis and treatment. He disagrees with those who term the disease ''Angina,!' maintaining that an element of suffocation is neither primary or universal in cases of the disease, but that the essential lesion is an ulcerous or inflammatory condition of the tonsil.

That the symptoms of this epidemic disease must have possessed some very striking characters is shown by the fact that Nola[19], describing the same epidemic as Carnevale, though working independently, records almost exactly the same facts as Carnevale.

In 1642 the disease seems to have died out. But after a period of quiescence of about seventy years the pestilence again flared up. From Italy and Spain it travelled to France (1730), and from France to Holland. Eventually it reached Great Britain, and was described minutely by many writers. In 1713, Dr. Patrick Bell[20], in a letter to a Dr. Mead, described a disease as the ''croops,'' which,

he says ''was epidemic and universal'' at Coupar Angus and which undoubtedly would be diphtheria. Fothergill[21] (1748) describes an outbreak of a severe throat affection with suffocation; but in most of his cases there was a rash---suggesting either scarlatina anginosa or secondary diphtheria. The same would also seem to be true of the Plymouth epidemic described by Huxham[22] (1757). Starr[23] (1750) describes an epidemic under the name of ''strangulatory disease'' which occurred in Cornwall. Its chief feature was the formation of membrane in the throat.

At the same time that the disease spread to Great Britain, it also spread to Switzerland, Germany and Sweden, and simultaneously it was carried to America, Washington himself contracting the disease at his country seat, Mount Vernon, near Alexandria.

The year 1765 is an important one in the history of diphtheria. It was then that Francis Home[24], an Edinboro pyhsician, published his treatise on this malady, a treatise which, though rather misleading, aroused the attention of the whole medical world and actively stimulated the study of the disease.

Home appears to have been rather a conceited fellow and scarcely familiar with the literature already extant on this subject. He claimed to have discovered a new disease. In his treatise, 'An inquiry into the nature,

cause and cure of Croop'' he describes twelve cases of this ''new disease'' known locally on the West Coast as ''chock'' or ''stuffing.'' Home pictures it most graphically and terms it ''suffocatio stridula,'' by reason of the shrill voice and difficult breathing. He says he has never seen nor heard of a case in a child of over twelve years. Damp weather, cold winter months, and proximity to the sea he found predisposing factors. He describes two forms---a simple catarrhal form (benign) and a malignant form shewing the occurrence of false membrane in the upper part of the trachea and spreading downwards. The membrane was easily detached, on account of there being ''pus'' behind it. He particularly mentions the rarity of the new disease, in Edinborough at least, and states that some may go through a whole lifetime and not see a single case, or at most only one or two---a striking contrast to the present time.

His treatment, we may note, consisted in venesection, leeches, blisters to the neck, attention to the bowels, and the inhalation of steam and alcohol vapour. Sudorifics or emetics he found of no special value. The membrane having once formed, he recommended that its removal be attempted, or if necessary, that tracheotomy be performed.

Home did good inasmuch as his widely circulated book stimulated study of this disease. But he also did harm. Before he published his book, it was coming to be under-

stood that the malignant angina and croup (laryngeal diphtheria) were merely two aspects of the same disease. But Home, with his dogmatic treatise, put observers off the ''scent.'' As Bretonneau[25] says: ''The authors of the Seventeenth Century had perfectly described the symptoms of malignant angina, and their attention had already been specially directed to the signs which prove that the disease extended from the pharynx to the air passages.'' (e.g. Carnevale,[18] Starr[23] and Ghise.[26] In the year 1740, the nature of the pseudo-membraneous exudation, which lines the air passages, was pointed out by Ghise[26] who also noted the paralytic phenomena and definitely linked the tracheal form with the pharyngeal under the name of "Angina streptosa perfida mortalis." In all countries physicians began to see that it was necessary to open dead bodies in order to ascertain the seat of diseases: it is even probable that after the new impulse given by Morgagni, they would not have failed to discover that malignant angina consists only in a gangrene of the mucous tissue, if, as Bretonneau continues, ''Francis Home, by publishing his treatise on Croop, had not suspended the progress of observation. It is difficult to conceive how a work, which contains only a small number of isolated and scattered facts, was capable of obliterating the traces of the ancient traditions and, for half a century, of preserving a great amount of influence over the opinions of practitioners! Such is, however,

the fact. Struck with the most ordinary mode of termination of malignant angina, Francis Home persuaded himself that he had just met with an affection that had hitherto escaped the attention of his predecessors; he thought that he ought to give it the popular name under which he had found it designated in a Scotch province, the novelty of his discovery was widely diffused, and the new denomination so fascinated all persons, that it prevented them from recognising a disease observed from the most remote antiquity, and which, in our own days, is accompanied by all the symptoms which it has uniformly exhibited.''

Although much of Bretonneau.s criticism may be just, nevertheless the Edinborough physician rendered medicine a most useful service, for he was the first to give a thoroughly good decsription of that form of diphtheria then known by the name of ''croop.''

Samuel Bard[27] helped to bring thought back into proper channels in his observations of the epidemic in New York (1771-1772). He published a brochure entitled ''An Enquiry into the Nature, Cause and Cure of the Angina Suffocativa or Sore Throat Distemper, as it is commonly called by the Inhabitants of this City and Colony.'' A perusal of this treatiseleaves one to infer that he believed angina and croop to be merely varieties of the same disease, and post-mortem, he traced the membrane from pharynx to trachea and bronchi in several cases. But he,

like many others, went too far and mixed up in his descriptions other throat affections, particularly scarlet fever and measles; for he speaks of inflamed watery eyes, livid bloated countenance, with a few red eruptions on the face.

Johnstone[28] also regarded angina and croup as being of the same nature. The majority of physicians, however, regarded angina and croup as two different diseases. Lepecq de la Cloture[29] (1778) in France, and Ramsey[30] (1786) in England described epidemics of that same disease Home had noted to occur sporadically. But these writers, too, make mention of the fact that during an epidemic of croup many cases of ''angina gangrenosa maligna'' occur.

It will be seen, then, that there was no definite classification of these various manifestations of what we now know to be the same disease; and this difficulty was further accentuated when John Millar described under the name ''Asthma Acutum,'' ''a disease clinically resembling croup in many ways save in the lack of cough, the rattling rather than the whistling respiration, and the absence of membrane'' (laryngismus stridulus.) Edinborough seems to figure prominently in the history of diphtheria.

John Cheyne in 1801 published an essay[31] in which he definitely describes diphtheria under the name of cyanche trachealis or croup. He gives a minute description and plates of the false membrane found in the trachea after death.

It was in 1802 that Dr. Cullen, then Professor of ''The Practice of Physic'' in our University, published his ''First Lines of the Practice of Physic.''[32] The book makes most interesting reading, and in it appears a description of cyanche trachealis (croup) in which we cannot fail to recognise the diphtheria of our own time. Now as for many years after its appearamce Cullen's work was the favourite text book on medicine in Britain. It's author may claim the credit of having rescued diphtheria from the region of discussion and monographs, and of having given it a fixed and recognised position in medical science.

The disease, however, was still a rarity in the British Isles, and probably only occurred sporadically. In France, however, epidemics of the ''croup'' seem to have frequently occurred, and having caused the death of a nephew of Napoleon I. in 1807, a prize was offered for the best essay on the subject. (The essays[33] on this subject sent in for the prize which was offered by the Société Royale de Médicine de Paris in 1785, acting upon the impetus given by Home's treatise, added little of clinical value.)

Essays were written by Roger Collard, Albers and Jussine, and though of value, dealt mostly with treatment, but, still inifluenced by Home's work doubtless, they missed the true starting point. Thus we find Jussine[34] writing ''Cyanche maligna might easily be confused with croup, one of whose symptoms, namely the false membrane it exhibits, if it did not at the same time possess other

distinguishing characteristics.'' The disease sometimes assumes croup-like characters, he asserts, as a result of ''the putrid influence of the epidemic''---a reason which would hardly satisfy a scientist to-day. He denies the infectious nature of this disease, and says that croup in his idea is due to ''a checking of the perspiration by the access of cold air.''

Lobstein[35.](1817) held that the false membrane was not the crucial factor in diphtheria, since the patient often dies despite the removal of the obstructing membrane and the consequent freeing of respiration. We can trace here the dawning of what we now know to be the truth---that the disease is essentially a toxemia. Autenrieth[36.], ten years before had expressed similar ideas, and his treatment is interesting. Besides the application of mercury, he first applied clysters of vinegar in order to drain the morbid material towards the stomach, and later cutaneous irritants to impel it towards the surface of the body and so diminish the ..concentration of irritability.'' He was modern in so far as he discountenanced local treatment. He also denied the advisability of tracheotomy, but his superstitions as to constellations prevented him from declaring the disease infectious.

It was left to Bretonneau[37.](1818.1826), however, to disentangle true diphtheria from the many throat affections so closely resembling that disease. His name must stand high above all others in importance in any historical sketch of

this disease, and the record of his extensive and painstaking work on this subject is given to us in his monumental ''Memoirs on Diphtheria. Until the year 1818, he admits to having only seen two cases of croup, but then occurred the circumstance which gave him his opportunity of investigating this subject. It happened thus; In the year 1818 the garrison ofLa Vendée was transferred to Tours, and many fell ill there of a disease characterised by ulcers in the mouth, inflammation of the gums, and the formation of grey-green deposits upon the mucous membrane of lips, cheeks and gums. The disease was first regarded as scorbutic gangrene of the mouth, but Bretonneau disproved this, showing that the patients showed no other symptoms of scurvy, and did not benefit by antiscorbutic treatment, (exhibition of orange juice, &c.), and also that it assumed all the features of malignant angina when it attacked the bowels and throat. He was a keen-sighted observer and attributed the fact that the disease primarily attacked the gums to the use of drinking-vessels in common. When the garrison was replaced after a time by another section of troops, the disease appeared among the latter in the form of severe angina maligna.

The disease spread from the garrison to Tours and the surrounding district, some people falling ill of severe angina maligna, and some of typical croup. Most of the deaths were among children. Epidemics occurred in the district for some eight years. Bretonneau conducted sixty post-mortems on people dead of the disease, so it

is evident he had plenty of opportunity of studying diphtheria both in the living and in the dead.

Let us pass to a consideration of the most important facts he established. He showed that the essence of the disease was the formation of false membrane; that it was not inflammation which had gone on to gangrene, but that it was a specific form of inflammation, from the outset; in other words it was not just different from other varieties of inflammation in degree but different in kind; he goes so far as to suggest a specific virus as the cause in each case. For ''whatever may be the structure of the tissue on which diphtheretic inflammation is developed, the disease preserves all its characters.''[38]---whether it be palate, tongue or skin. He is careful to point out that the membrane is not normal tissue altered, as in the case of apparent membrane in some severe cases of scarlet fever, measles and whooping cough, but it is ON the tissue, not of it, and can be detached from it. He also explained that this membrane was the source of the pestilential odour which had suggested a gangrenous condition. He thus differentiated the disease from others like it, to all of which the name of malignant angina was previously given if the throat symptoms were marked enough. ''I should not express my entire opinion if I did not add that I see in this membranous inflammation a specific phlegmasia, as different as from a catarrhal phlogosis as the malignant pustule is from Zona*, a disease more distinct from scarlatinal angina, than scarlatina itself is from small-pox; in fact a morbid condition

*Herpes Zoster

sui generis, which is no more the last degree of a catarrh than a squamous eruption is the last degree of erysipelas.

As it is impossible to apply to a special inflammation which is so marked, any one of the improper names which have been given to each of its varieties, let it be permitted me to designate this phlegmasia by the name of diphthérite, derived from (διφθερα) pellis,[39] i.e. a membrane.

It may be said that just as Sir Norman Walker and others are to-day trying to get rid of the word ''eczema'' and differentiate various specific skin affections which it now masks, so Bretonneau sought to rescue diphtheria and other throat affections accompanied by membrane formation from the vague term ''malignant angina.''

But more than that, he showed that the membrane might occur on gums, pharynx, oesophagus, larynx, trachea, bronchi, auditory tube or skin, and that wherever it did occur it always showed the same microscopic and macroscopic characters. His deduction was, therefore, that the cause in every case was the same disease-producing factor.

This deduction he found strongly supported by the fact that a person with one form of the disease could transmit another form to his neighbour---e,g, a person might have malignant angina, and then a person in the same house develop croup. He thus finally and for all time proved that malignant angina and croup were not two

definite clinical entities, as Home and others had taught, but were merely varying forms of the same disease. This may be said to have been his greatest contribution to medical science. Johnston, Starr, Double[40] and even Aretaeus had noted the same facts, but their observations were not sufficiently wide, nor did they realise the full significance of their findings, so that few people accepted their teaching, and even those who had done so were confined by Home's dogmatic treatise.

The cases Bretonneau cites in proof of his contention are interesting. He says:[41] ''The following were the circumstances which gave a new impulse to my inquiries. A pupil of pharmacy, attached to the hospital, was still suffering from the effects of malignant angina, when he went to pass a few days in the country. During this time one of the children of the vine-dresser of the house died of croup; after death the walls of the pharynx were found covered with exudations. This disease was seen to extend from the tonsils to the [illegible] velum palati in another child of five years old (the brother of the former child), who died likewise. The mother began three days afterwards to suffer from a slight sore throat and she died. During the last two days her attendants had been struck with the alterations in the tone of her voice. Her eldest daughter and a young woman who had nursed the patient were brought to the hospital, both already suffering from symptoms of malignant angina. In the trachea of the mother who died we found a slightly adherent membraniform tube, half-a-

line thick at its lower extremity which, consequently, must have extended itself downwards into the bronchi. It was evident that the exudation of the pharynx was of the same nature as the tube invaginated in the trachea. The two peasant girls were cured by applications of concentrated hydrochloric acid.''

Describing another series of cases, he says[42]: ''At the very time when this woman was most seriously affected'' (diphtheritic affection of external auditory meatus) ''his daughter, aged five, had behind her ears a slight excoriation covered with a membraneous coating; the symptoms of croup supervened suddenly: she died. The next day her younger brother appeared on point of perishing in a fit of croupal suffocation; but a few fumigations brought about the expulsion of a membraniform tube.''

By these and similar observations Bretonneau established his facts, even making pathology the handmaiden to clinical medicine, and this proved the key to his success.

Trousseau and Guessant observed epidemics of the disease at about the same time as Bretonneau. They confirmed and extended his fundamental observations.

Bretonneau taught that the disease was a purely local one, ''the mechanical obstruction offered to respiration by the development of the false membrane always appeared to have been the immediate cause of death.''[43] But

Trousseau conceived of diphtheria as being a general disease of which the specific changes on mucous membranes, &c., were but the local manifestations. Thus he shows that patients with cutaneous diphtheria often die from toxaemia, although these be no hindrance to respiration whatever.[44] Regarding the disease as a general condition, therefore, he suggested the name diphtheria instead of that of Bretonneau ''Diphthérite,'' and this name Bretonneau and the whole medical profession subsequently came to accept.[45] Guessant sought to point out that the presence of false membrane in croup was an essential character, and to differentiate that form of diphtheria from laryngitis stridulosa and Miller's asthma acutum, there being much confusion at that time about these diseases, which showed some similar characters.

It will be convenient here to make a digression in order to outline briefly the epidemiology of diphtheria during the Nineteenth Century. The Nineteenth Century saw the spread of this disease to many parts of the world. Now quiescent for a period, it would suddenly break out with added strength. As we have seen, the Twenties saw isolated epidemics in Europe, notably Spain and France. "There was an epidemic in Edinburough in 1826, but otherwise it was by no means a common affection in this country."[46] During the forties there was a comparatively mild visitation involving Europe and America. There was then a period of calm, but during the fifties it broke out with great violence and involved practically the entire world. Commencing in Paris in 1853, it spread in all directions,

almost decimating the child population of some districts--- particularly S.W. Russia. Iceland encountered the disease in 1856 for the first time, and in two decades or so hardly a country remained untouched. 1866 saw the commencement of an epidemic in Pekin which carried off thousands of the population. Eleven years later the disease reached Japan for the first time, and it has been endemic there ever since.

In studying the epidemiology of this disease one cannot fail to be impressed by the way in which it disappears from a district and then, after a comparatively short interval, it suddenly reappears. This phenomenon has only been marked during the last sixty or seventy years, and furthermore during this time the intervals have become shorter and shorter. This period has been marked, too, by ever increasing facilities for intercommunication and transit generally. One cannot but feel that it is highly probable that these two facts are connected. Regarding the epidemiology of this disease in this country, diphtheria appears to have been so rare as to have passed from the minds of English physicians after the brief notoriety conferred upon it by the writings of Bretonneau, until 1855 when there occurred an epidemic at Boulogne which was specially fatal to the resident English. In 1856 there was imported to Folkestone the first case of the greatest recorded epidemic in this country. In 1858 the disease assumed alarming proportions in the country, raging as a widespread and fatal epidemic for some four years.

"There has been no epidemic of similar magnitude since,

although, as we have seen, it still claims a few thousand victims annually and from time to time expands into a limited epidemic.[47]

Continuing now the story of the investigation of this disease, we find in 1844 Virchow, the German Pathologist, opposing the contention that croup and diphtheria were manifestations of the same disease on pathological grounds. He regarded inflammation on mucous surfaces of three distinct varieties (1) Catarrhal, (2) Croupous, (3) Diphtheritic, and so great was his personal power he won many scientists to his cause. Bretonneau, however, deplored the false teaching of Virchow, and strongly reasserted his convictionsthat all forms of the disease were contagious and of the one source. His arguments are well set out in his Fifth Memoir.[48] He instances the three deaths from different forms of the disease in the Napoleon family,[49] the case of Professor Herpin[50] who contracted diphtheria of the nose by being coughed upon by a child whose throat he was cauterising for diphtheria---he later developed typical faucial diphtheria with subsequent paralysis,---and the case of a man who trod with naked feet upom the expectoration of a diphtheria patient and later developed the specific lesion on his foot.[51]

One sentence of his Fifth Memoir is quite prophetic. He seems to foresee the discovery of the Klebs-Löffler bacillus. ''But the speciality of contagious disease,'' he says, ''belongs to the great medical truths revealed by clinical observations; I therefore repeat that a special

germ, peculiar to each contagion, gives origin to every contagious disease."[52.] "Epidemic visitations are engendered and disseminated only by their reproductive germs."

But still many clung to Virchow's teaching, and it was only with the advent of bacteriology that the question was finally settled and Bretonneau's teaching vindicated.

The next forty years were characterised by enormous activity, partly by the clinician, but more especially by laboratory workers.

Thus about 1865 a theory arose to the effect that croup was caused by the inspiration of irritant vapours. Albers, Lusine and others attempted to produce the disease by this means but without avail. Bretonneau,[53.] however, by injecting cantharides and olive oil into the trachea of goats and dogs was able to produce membrane and a disease with some symptoms like those of croup. Others obtained similar results. They would doubtless produce, of course, a membranous laryngitis. But Bretonneau was too keen an observer to be led away by even his own experiments. Despite the similarity between cantharides croup in dogs and diphtheria in man, he clearly recognised their specific differences and unhesitatingly urged them. He observes, for instance, that in cantharidic croup, if the membrane is expelled or removed, it never forms again, that a "tolerance" is produced so that not even a further injection will induce the formation of membrane again,---and also that the mode of death is different.[54.]

Numerous animal experiments were conducted at this time, but they were of little avail, and darkness continued to hang heavily over the etiology of diphtheria, until the light came in the shape ofBacteriology and gradually made things increasingly plain.

In giving a brief resume of the casual organism of this malady one must first say that the germ theory o f disease obtained ascendency about 1840. This theory was suggested by the observation that various fungi were often found upon the dead bodies of fish, silkworm, &c., and the erroneous beliefs that such fungi were the cause of death.

The first to suggest a definite causal organism for this disease was an Edinburgh physician named Laycock[55.] who, in 1859, published his theory that diphtheria was caused by the yeast fungus Oidium Albicans (which we now recognise as the cause of Parasitic Stomatitis. His theory was supported by some and denied by others, who held that leptothrix buccalis was the cause. Laycock's deductions were wrong, but he was on right lines, and his work stimulated others to experiment with the aim of discovering an organismal cause. Hallin, Oertel and Hasiloff all worked on the subject during that and the following decade.

In 1880, Letzerech[56.] cultivated diphtheritic material upon solid medium for the first time, an isinglass medium being used. Klebs a year later made cultures from material obtained from the tonsillar deposit of a child just dead of the disease. They were thus the first to cultivate

diphtheritic material on solid media. But the first account of the bacillus now known to be the cause of diphtheria was given by Klebs in 1883. He describes a short slender rod, (staining with methylene blue,) which he found in the superficial layers of the false membrane. The rods contained spores at their ends.[57] It will be noted, however, that Klebs never obtained pure cultures of the organism. It was first obtained in pure culture by Löffler, who published his observations in 1884,[58] and to him we owe the first accounts of its character in cultures and some of its pathogenic effects in animals. The organism is for these reasons known as the Klebs-Löffler Bacillus. By experimental inoculation with the pure cultures obtained, Löffler was able to produce false membrane on damaged mucous surfaces. Inoculation of guinea-pigs gave striking and characteristic results, but, owing to the small numbers of organisms found at the lesion, and their absence from the blood and tissues, he concluded that the disease was due to a poison elaborated locally and absorbed from there into the circulation. But he hesitated to conclude definitely that this organism was the cause of the disease, for he did not find it in all the cases of diphtheria examined; he was not able to produce paralytic phenomena in animals by its injection at that time, and further he obtained the same organism from the throat of a healthy child. These phenomena are with us still, but perhaps better understood. In 1890 however he produced paralysis in several guinea pigs after inoculation with the organism.

"The organism became the subject of much inquiry, but its relationship to the disease may be said to have been definitely established by the brilliant researches of Roux and Yersin[59] which showed that the most important features of the disease could be produced by means of the separated toxins of the organisms. Their experiments were published 1880-90."[60] If any doubt still existed it was finally dispelled a few years later when it was found that, if a guinea-pig be injected with several lethal doses of toxin plus a sufficient amount of antitoxin, neither disease nor death would follow, in contradistinction to the effect of injecting a similar amount of toxin without antitoxin.

The last decade of the Nineteenth century was marked by remarkable activity in Britain, on the Continent, and in America. Neisser[61] in 1897 described the special staining process which now bears his name. Especially was research carried out regarding the visibility and length of life of the organism and, in 1894, at a Congress at Budapest, Löffler affirmed that "Convalescents from diphtheria should not be permitted to resume social intercourse until complete disappearance of the bacilli have been demonstrated by bacteriological examination", and on the same occasion urged the necessity for disinfection."

This statement, of course, was the foundation on which National public health measures for the control of this disease began to be built.

During this decade also much attention was given to the

questions of immunity and susceptibility of animals. There was much evidence and from many sources, going to show that a diphtheria-like disease amongst birds, particularly fowls, was identical with diphtheria in man. This was eventually disproved, but for a long time considerable doubt existed on the subject. It has however become increasingly certain that diphtheria is spread almost entirely, if not entirely, by human agency.

Simultaneously Löffler and Behring investigated the effects of chemical agents upon the life of the bacilli. If Bretonneau's name holds first place in the history of the pathology and diagnosis of diphtheria, that of Behring[61] ranks equallt prominently in the history of the therapeutics of this malady. Inspired doubtless by the results of his research he collaborated with Kitasato in connection with tetanus anti-serum, he conducted experiments which led him to discover the antitoxin power of the blood of highly immunised guinea-pigs---that immunity having been attained by means of an artificially produced non-fatal attack of diphtheria. He published his results in the year 1891 at the International Congress of Hygiene and Demography. Frankel, Wernicke, Roux and others confirmed his discovery and as a result the treatment of the disease was revolutionised. In 1893 the preparation of the serum on a large scale was instituted, and the following year saw the end of the pre-antitoxin days, by then the serum having become known to most. Since then the serum has been used more and more

with a corresponding lowering of the case mortality. There are, however, still a few misguided individuals who are criminal enough to withhold this form of treatment; they assert that the diminished case mortality is due not to use of antitoxin but to diminished virulence. This however was disproved by the comparison of the mortality among cases treated without antitoxin and that among cases treated with antitoxin during the same epidemic.

Many observers, including Tirard[62] (1897) soon came to advise the administration of antitoxin before the result of the bacteriological examination came to hand, owing to the great importance of early treatment in this disease. During the thirty years which has elapsed since the institution of antitoxin treatment, many etiological factors have been brought to light and many phenomena associated with its clinical employment have been noted and discussed, and theories as to their raison d'etre have been expressed.

At the same time, which has been one of phenomenal activity, the bacteriologist has added to our store of knowledge upon the subject. Larger experience and more detailed knowledge have shown certain dangers, greater or less, which may be met in the routine administration of serum - such as joint pains, serum rashes, and other symptoms of anaphylaxis and alleged nephritis; but these incidents are of such relative infrequency, and so rarely grave, that they cannot be looked upon as contra-indicative to its exhibition provided proper precautions are taken.

No historical outline of this disease would be complete without some reference to the Schick test, discovered in the United States and brought into prominence during the last four years. It is essentially a test for recognising susceptibility to Diphtheria by means of the injection of a toxin-antitoxin mixture, with the aim of giving prophylactic injections of antitoxin to those susceptible people in a home or institution where a case of diphtheria is present.

It seems likely to prove a most important factor in the control of this disease, but as it will be necessary to deal with this question later no further mention of it need be made here.

SOME POINTS CONCERNING EARLY SYMPTOMS

AND DIAGNOSIS.

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1. INTRODUCTORY.

PREAMBLE.

THE IMPORTANCE OF EARLY DIAGNOSIS.

EARLY HISTORY.

2. SIGNS AND SYMPTOMS REFERABLE TO THE LOCAL LESION.

A. THE FAUCIAL FORM OF DIPHTHERIA.

1. EARLY SYMPTOMS.

2. EARLY SIGNS.

3. DIAGNOSIS FROM APPEARANCE OF THROAT.

4. THE ODOUR.

5. GLANDULAR ENLARGEMENT.

6. ABSENCE OF PAIN FREQUENT.

B. LARYNGEAL DIPHTHERIA. (CROUP).

1. SYMPTOMS AND SIGNS.

2. DIAGNOSIS.

C. NASAL DIPHTHERIA.

D. OTHER FORMS OF DIPHTHERIA.

3. SYMPTOMS AND SIGNS REFERABLE TO SYSTEMIC DISTURBANCE.

1. THE TEMPERATURE.

2. THE PULSE.

3. THE GENERAL ASPECT.

4. ~~ACBUOEINURIA~~ ALBUMINURIA.

5. THE PATELLAR REFLEX.

4. CERTAIN LABORATORY METHODS, OTHER THAN BACTERIOLOGICAL, DISCUSSED.

1. THE BLOOD.

2. THE CEREBRO-SPINAL FLUID.

3. CUTANEOUS AND INTRADERMAL TESTS.

5. CONCLUSION.

1. INTRODUCTORY.

PREAMBLE. One cannot control diphtheria until one can diagnose it, and an essential of control, as far as its ravages in an individual patient are concerned, is an early diagnosis. One, therefore, proposes to discuss, now, the early symptoms and signs of this disease, one's methods of diagnosis, and then (~~where~~ more particularly) the question of bacteriological diagnosis..

It is beyond the scope - or, indeed, the purpose - of this work to attempt to give a systematic or complete account of the symptoms, varieties, sequelæ &c, of diphtheria. It will be more valuable, fitting and useful to discuss, in this section of one's thesis, those points which one's work has led one to consider of special importance or interest.

No attempt, therefore, will be made to consider the symptoms and signs of the later stages of the disease, but, as far as is consistent with clarity, one will confine oneself to the early stages of the disease.

A case of diphtheria which has gone on for 3 or 4 days, generally presents little difficulty in diagnosis.

THE IMPORTANCE OF EARLY DIAGNOSIS. But to wait till the so-called typical washleather membrane has formed, in the typical place, and of the typical size, before exhibiting specific treatment is perhaps best compared to delaying abdominal section, in a case of appendicitis; till there is generalised peritonitis, or in a case of gastric perforation till there is considerable distension. And unfortunately the results are well-nigh equally serious; this is brought out graphically in Chart 2. (Appendix).

It is drawn from a set of statistics given by Ker[63], which relate to 8,591 consecutive cases of the disease admitted to Edinburgh City Hospital.

As antitoxic serum is practically always injected as soon as a diagnosis of diphtheria has been made, it will be clear from the Chart that a delay in diagnosis of one day makes a fatal result twice as likely, of two days three times as likely, of three days seven times as likely and so on.

Statistics are often said to be cold, dead, things, but these figures looked at from the aspect of early treatment are full of meaning and of life. A personal reference may be forgiven if one says that one's keen interest in this matter springs from the fact that the death of a friend and fellow student in the Edinburgh City Hospital always seemed due to a practitioner labelling the condition "Tonsillitis", and for many days treating it with levity-instead of antitoxin. Having seen, then, the great importance of early diagnosis, what are the considerations which would lead one (apart from bacteriological examination) to diagnose this malady in the early stage.

EARLY HISTORY. The history is often of value, provided one makes it one's servant and not one's master; it may be misleading either because, on the one hand, the symptoms are so mild, or on the other, because they are so severe.

After an incubation period of from one to even seven or ten days (but more usually of two or three) one would expect fever as the first symptom, along with malaise, some headache, anorexia, indefinite pains

(in back and limbs commonly), lassitude, rapid pulse, and not uncommonly vomiting or even diarrhoea. But the disease, though febrile, does not often begin in the acute way characteristic of small-pox, scarlatina and others. These symptoms, then, are rarely severe, and beginning common to many other diseases are often disregarded and underrated and thus valuable time may be lost.

Amongst infants and very young children, however, the onset of the disease is often sudden and severe; rigors, convulsions or even urgent laryngeal symptoms, one finds, in some cases, the first sign of the onset of this malady.

2. SYMPTOMS AND SIGNS REFERABLE TO THE LOCAL LESION.

A. THE FAUCIAL FORM OF DIPHTHERIA.

1. EARLY SYMPTOMS. It is only after these indeterminate symptoms that attention may be directed to the throat. There is present a certain slight sensation of discomfort without at first, often, any actual pain during swallowing. The throat may feel hot and dry and the neck be somewhat swollen and tender. These symptoms referable to the throat, are more marked in adults and less marked in children-especially young children. They may, indeed, be entirely absent; and one has come to feel that one cannot overemphasise the importance of a routine examination of the throat in all cases of febrile, and even non-febrile, disorders of children. However the majority of our patients suffering from this disease are children of from 1 - 4 years - too young to draw the attention to the throat, and indeed quite often the throat is not sore. All the more, therefore, does it behove one to examine carefully the fauces.

A large proportion of deaths from this disease are preventable deaths; they are not due to want of competence or skill on the part of the practitioner, but to carelessness. The membrane is often there and has been for many days before marked glandular swelling or urgent laryngeal symptoms shouts to the practitioner of his neglected duty and causes him to examine the throat - but then it is often too late.

The late Dr. J. W. Simpson in the class of Diseases of Children used to teach "If ever in doubt about the diagnosis of a child's ailment:- Examine the throat, examine the heart, examine the urine" - an aphorism the extreme value of which,one came to realise later, when Resident at the Edinburgh Sick Children's Hospital.

2. EARLY SIGNS. We are endeavouring to diagnose this condition at the earliest possible moment - before the typical membrane has appeared - we examine the throat and what do we find? The tonsils, pillars of fauces, uvula and back of pharynx are red, swollen and turgid. The uvula one finds often considerably swollen, the effusion of serum into the submucous tissue giving it a jelly-like transparency and aspect. There is however nothing here to distinguish the condition definitely, from an ordinary catarrhal sore throat, indeed the more red and swollen the fauces appear, and the more diffuse the redness, the less likely is the condition to be one of pure diphtheria, and the more likely is it to be, e.g. scarlet fever. If the palate is pale and the redness only marked, or more marked, on one side of the fauces onewould be suspicious of a diphtheritic condition.

And if in addition to these things there were enlarged glands behind the angle of the jaw, some nasal discharge (maybe epistaxis) and this malady prevalent in the district one would resort to specific therapy at once. If the patient had already had scarlet fever or the papillae of the tongue were neither enlarged nor redder than usual one would feel still more confident in diagnosing this malady.

F. H. Thomson,[64] summing up the possible appearances of the throat in an early case, states "Diphtheria may evince itself in a varying degree of reddening of the tonsil, or tonsils, and fauces, without any deposit, either pultaceous or membranous; as a definite membranous or pultaceous deposit with an amount of inflammation and oedema corresponding more or less to the amount of deposit; as an ulcer or ulcers caused by mixed infection with membrane or pultaceous deposit; or as a most pronounced inflammation and oedema of the fauces, with or without a membranous or pultaceous deposit. That may be taken as a very general description of what may be met with in the first day or two of the disease".

The most usual teaching is that the membrane does not appear until from 24 - 48 hours after the commencement of the illness, but one has come to agree with Ker[65] that even at this early stage, when symptoms first appear, a careful examination of the throat will frequently, if not generally, reveal some patching with membrane on tonsils, palatine arch or uvula - a case with a patched uvula almost always proves to be diphtheria.

One has noted that this membrane in the very early stages is easily wiped off; failure to recognise this fact has

frequently led to errors of diagnosis. A little later it has to be torn off, and, even then, commonly leaves a raw bleeding surface. But though, early, it is fairly easily wiped off, it quickly re-forms again, thus differentiating it from membranes produced in most other diseases and constituting a very important point in diagnosis. The edges of the membrane are generally everted. One has seen a beginner suspect diphtheria through finding one half of the fauces of a child covered with thick mucus from the trachea. This is so common in the throats of young children that it is, perhaps, worth mentioning. It has commonly a green tinge, no membrane that size would be easily wiped off and, of course, has other very familiar and obvious characters.

The commonest site for the primary lesion is one or other tonsil, then the pillars of the fauces, uvula, and, rarely the posterior pharyngeal wall.

3. DIAGNOSIS FROM APPEARANCE OF THROAT. Regarding the deductions from the throat examination, Ker's[66] dictum is useful. "It really amounts to this, that, if we can exclude scarlatina and thrush in these young patients (under 7 years), any visible patching or specking of the throat must be regarded as suspicious, and in any case should be treated as diphtheria".

Some points in the examination of the throat in relation to scarlet fever have already been considered, it remains to state the appearances in thrush. The site of the membrane is useful, tongue, palate, buccal mucous membrane and lips are common sites for the membrane of thrush but rare for that of diphtheria. The membrane of thrush may be found on the fauces, however.

The membrane of diphtheria is greyish or pearly white, while that of thrush is milk white in colour, in both cases the membrane is surrounded by a red line but this is less marked in thrush. But the chief point of distinction is the fact that the membrane of thrush swabs off easily, leaving behind it a red patch of mucous membrane but no ulceration nor bleeding points. It has to be noted that the membrane of thrush may re-form, thus simulating diphtheria. The symptoms and general condition of the child are, of course, different in the two cases, and microscopic examination would show the characteristic morphological features of Oidium Albicans if the patient be suffering from thrush.

The most common mistake to make on looking at the fauces is to diagnose a case of diphtheria as follicular tonsillitis, for, especially at this early stage, just a few small whitish plugs may be seen on the reddened tonsil, the Klebs-Löffler bacilli having been lodged in the crypts. It is almost impossible to distinguish one from the other by the local examination although the plugs in follicular tonsillitis are more yellow than white, both tonsils are affected more commonly than in diphtheria, and the exudate wipes off more easily.

Drinkwater[67], however, claims he can differentiate diphtheria from this and other diseases (except Vincent's Angina) by an examination of the throat above. He states that in every case sent to the East-Denbighshire Fever Hospital during the three years 1917-20, and diagnosed by him as diphtheria, on clinical grounds, the bacteriological examination confirmed the diagnosis, Klebs-Löffler or B. Hoffmanni being present.

For convenience he divides the fauces into three areas, on each side of the mid-line; the tonsillar area, the uvular area, and the palatal area. The naked-eye character on which he pins so much faith is this, that in diphtheria there might be five or six patches but never more than one patch in any one area. He states that he has never met an exception to this rule, so that if, in a given case, two or more distinct deposits are seen in one tonsillar area the disease is not diphtheria, and a bacteriological examination except for confirmation, unnecessary. Writing later, in the Lancet,[68] he states that when two or more patches are present on one tonsillar area the disease is generally follicular tonsillitis or influenza. He adds "If in a given case of membranous deposit on the fauces, the patch is raised above the level of the mucous membrane, has sharply defined edges and is single in each affected area, there can be no doubt that the disease is either diphtheria or Vincent's Angina. The colour may be glistening white, bluish, yellow, or spotted with black or red; it rarely has the wet wash-leather appearance described in text books". His descriptions, of course, apply only to the early stages of the disease. Although Drinkwater's description is a useful guide, his contentions lend themselves to criticism under several heads. Thus he speaks of the finding of Hoffmann's bacillus, only, as confirming the diagnosis. This means that many of his cases which presented the feature he considers pathognomonic of diphtheria were probably not cases of infection with the Klebs-Loeffler bacillus at all, for we are going back a good many years if we

assume that B. Hoffmanni is a cause of the disease.

Furthermore, although the appearance of one patch in any one area mentioned may mean diphtheria, the appearance of two or more does not exclude the disease. There is ample evidence, especially in adults, to show that what is clinically, follicular tonsillitis, bacteriologically is diphtheria and ought to be treated as such. Thus Palmer[69] found that in 4 cases out of 6 of definite follicular tonsillitis, the Klebs-Loeffler bacillus was present.

Also Gordon[70] points out that in scarlet fever faucial appearances are frequently found, overriding all Drinkwater's postulates.

From the small beginnings described - a mere speck maybe - the diphtheritic membrane generally increases and increases till it is of the familiar size, nature, and appearance. Such a stage it is not the purpose of this thesis to consider, but it has to be remembered that the membrane in the fauces may never develop beyond the stage of a minute unlikely looking patch, but if any laryngeal symptoms are present, it must always be regarded as diphtheria; "similarly rhinorrhea, provided scarlatina can be excluded, taken in conjunction with doubtful patching of the fauces, should always arouse suspicion"[71] the greater part of the membrane in these cases developing out of sight - in the larynx and naso-pharynx respectively.

4. <u>THE ODOUR</u> from a diphtheritic throat, Prof. Gulland[72] used to teach us, was characteristic. Although the breath of patients has been noticed to be often foul one cannot lay claim to having reached the point when one can call it characteristic.

Bretonneau[73] and his contemporaries, and even Aretæus, speak in strong terms of the same condition. Guersant[73] likens it to the smell of carious teeth. It was at one time regarded as an outstanding feature of the malady; any apparent discrepancy between their records and ours, however, regarding this point, one feels is probably explained by the fact that antitoxin prevents the natural development of the disease; and that those of us who are seeing cases in hospital, at least, are dealing with throats to which local antiseptics and deodorants have, in many cases, been already applied.

5. GLANDULAR ENLARGEMENT is a useful early sign. Coincidently with the inflammation of the throat, the submaxillary and anterior cervical group of glands, together with those at the angle of the mandible, become enlarged and tender. A similar condition is likely to occur in septic sore-throat but in this latter disease the submaxillary and cervical glands often remain unaffected and never are so enlarged as in a severe case of diphtheria. The glandular enlargement, one has found of little use in distinguishing this disease from scarlet fever.

Blackburn is a town in North-East Lancashire with a population of 133,000. We have had comparatively little diphtheria of late. But one has been able to inquire into several points concerning the last 55 cases (up to Jan.1923) of all forms of the disease, admitted to the Blackburn fever hospital.

Regarding glandular enlargement one found this to be present in 69·23% of the cases on admission; it is

therefore a very common but not a constant sign of the disease.

Sometimes the glandular enlargement is so marked as to distort the picture and lead to a serious error in diagnosis. F. H. Thomson[74] speaks of "the peculiarly susceptible individual who develops rapidly increasing faucial swelling, rapid swelling of neck glands, with accompanying cellulitis. Usually there will be formation of membrane well within 24 hours and the diagnosis will be easy, but a considerable number will show no membrane at the end of 24 hours and it may even be postponed for 36 hours, though that is uncommon.

The glands at the angle of the jaw will be much enlarged, the cervical glands to a lesser degree, and the neck will be puffed out by cellular infiltration. This class of case will usually die if left untreated for 36 hours, may even die if adequately treated in 24 hours, and very rarely dies if treated within 24 hours"

It is just this type of case that one finds sometimes diagnosed as mumps, and it is here that failure to examine the throat has constituted criminal negligence.

6. ABSENCE OF PAIN, though rather a negative fact, is worthy of note, because in the first place it is comparatively common, in the second place it misleads many who tend to think that so serious a malady would have a corresponding amount of grave discomfort in the throat to arrest their attention, and in the third place it is one factor which is often of material aid in distinguishing between the symptoms of cases of diphtheria and those of other similar diseases, follicular tonsillitis, scarlet fever, quinsy,

Early in the disease there is generally a certain sensation of discomfort in the throat, but often this does not amount to actual pain in the affected part, or even to pain on swallowing. It is also noteworthy that though the patient may complain somewhat of stiffness during movements of the neck, there is usually no discomfort on opening the mouth, even in severe diphtheria. Contrast this with quinsy, where the swelling and pain make it so difficult to open the mouth that it is difficult to get a view of the throat at all. Furthermore quinsy is not common in young children, there is frequently a history of a previous attack, and, when a view of the throat is obtained, the tonsil is seen to be more enlarged than is generally the case in diphtheria, and a double sided quinsy is usually less common than a double sided diphtheria.

Pus from the peritonsillar abscess may simulate membrane, but, if the patient will allow it, this is easily wiped off in a case of quinsy.

B. LARYNGEAL DIPHTHERIA (CROUP).

As the very first symptom of this disease may be referable to that organ a note must be added concerning this condition.

1. SYMPTOMS AND SIGNS. The symptoms of laryngeal diphtheria are almost entirely due to obstruction of the air passages, toxaemia being slight or absent. This is said to be explained by the fact that lymph channels are few in the mucous membrane of the larynx. One's attention is called to the condition by the ordinary symptoms of acute laryngitis - slight hoarseness, loss of voice, and a harsh, shrill, dry, rough and peculiar

"brassy" cough. Later there is inspiratory stridor, and later still, of course all the signs of impeded inspiration, indrawing of epigastrium, intercostal spaces and supraclavicular areas. One endeavours to diagnose the condition and treat it before these unfavourable signs appear. On examining the chest in even the early stage "both inspiratory and expiratory sounds are found to be prolonged, and the normal respiratory murmur is lost in the laryngeal stridor which occurs in inspiration" [75].

Doubtless a laryngoscopic examination, if one were capable of making it in such young patients, would show the presence of membrane on the larynx. By this method Gover[76] found membrane to be visible in 112 out of 200 cases of "croup".

Occasionally some membrane is coughed up, or "shreds of membrane may become visible on shaking up any sputum present, with water"[77]. The presence of membrane is practically pathognomonic,

In only 10% of cases, however, is laryngeal diphtheria primary, so that generally the examination of the throat will give valuable information - patches of membrane etc. The cervical glands are not enlarged in primary forms of the disease.

Laryngeal diphtheria is very rare in adults. Rolleston[78] (1916) relates four cases which occurred amongst the 821 cases of diphtheria, in patients over 21 years of age, admitted to the Grove Fever Hospital in 16 years. He states that it is very insidious and until the small bronchi are invaded gives rise to no symptoms calculated to cause alarm.

Doubtless this is explained by the large size of the larynx in adults. Aphonia may be the first sign. Once dyspnœa has set in, both antitoxin treatment and tracheotomy are of no avail.

It will be evident that in laryngeal diphtheria the phenomena described later as due to the systemic disturbance will tend to be in abeyance whilst symptoms due to the local lesion will be marked.

2. DIAGNOSIS. Membranous croup is sometimes difficult to diagnose from false croup (Laryngitis Stridula). Points helping one to distinguish the latter ailment however are: "its sudden commencement, its less severe character, and the more markedly spasmodic nature of the symptoms; also by the appearance of the fauces. In doubtful cases the history of previous attacks of a similar nature in the patient, or even in other children of the family is reassuring" (John Thomson[79]). The stridor in this condition invariably comes on at night. If diphtheria were present in the house or epidemic in the district it would suggest the former malady.

Measles beginning in the larynx gives rise to a laryngitis which is often difficult to distinguish from commencing laryngeal diphtheria. (Ker[80]).

Laryngismus stridulus ought not to be confused with this malady. It occurs almost exclusively in children under 2 years who always show symptoms of rickets, often facial irritability, and sometimes tetany, with carpo-pedal contractions, or convulsions.

The value of bacteriological examination in the diagnosis of laryngeal diphtheria will be evident.

C. NASAL DIPHTHERIA. The chief thing to remember about nasal diphtheria is not to forget it.

One will not soon forget a child admitted to the Blackburn Royal Infirmary whilst one was House-Surgeon there. The boy was admitted (though, as it happens, not to my ward) with a fractured femur. One day, several weeks later, his nose began to bleed. Symptomatic treatment was given with fair success. A few days later he suddenly collapsed and died. The case proved to be one of nasal diphtheria.

The signs and symptoms due to the local lesion are more or less common to the two forms of the disease viz:- the one in which the systemic disturbance is but mild.

E. W. Goodall[81] gives as the chief local sign "a discharge from the nose, at first thin and watery, later muco-purulent. Not infrequently it is blood stained".

Allbutt & Rolleston[82] state "it may happen that there shall be no discharge, and 'stuffiness' be the only sign of nasal disease. Very seldom do membranes come away so as to be discovered in the discharge; they can sometimes be seen by inspection of the nasal fossæ, more commonly they are limited to the hinder parts of those cavities".

The brown ichorous discharge, which frequently is also offensive and puriform, is often so irritating to the nostrils and upper lip as to cause redness, sores, or excoriations of the alae nasæ or on the lip and occasionally only dry crusts are to be seen. These have a significance in the prevention of diphtheria

which will need to be mentioned later.

The glands at the angle of the jaw tend to be swollen and tender.

Lachrymation may be present. Describing the possible extension of diphtheria from fauces to nose, Tirard[83] states: "The extension of the disease to the nasal passages may be inferred not only by sanious discharge from the nose, and by fetid odour, but also by lachrymation, which is sometimes as severe as in persons suffering from obliteration of the nasal duct. This lachrymation is the direct consequence of obstruction of the nasal duct by inflammatory thickening of its lining membrane. In these cases it is not unusual to find that the conjunctiva shares the inflammatory changes, and is occasionally coated with false membrane".

Regarding the symptoms and signs referable to the systemic disturbance, in this form of disease, they may be very severe or very mild.

In the severe cases it will almost always be found that the fauces are also affected. Such are generally examples of malignant diphtheria, and the spread to the nose makes the prognosis even more grave.

Nasal catarrh however is often present in the ordinary forms of faucial diphtheria, and has been seen to be a useful sign in early diagnosis, as it is never present in tonsillitis.

That form of the disease in which the systemic disturbance is mild is of great importance from the stand point of Preventive Medicine. The child is thought to have just a common cold and is not much attended to. He goes to school and perhaps remains a carrier for

quite a while - spreading the disease amongst his associates.

Indeed Santos[84] has found diphtheria bacilli in the nose of young children more often than in the throat, a primary diphtheria of the nares being comparatively common in infants exposed to infection. Rolleston[85] found it present in 1·5% of 3000 cases admitted to the Grove Fever Hospital. But probably few cases reach Hospital, as there are more cases of this disease missed than diagnosed, and it will be evident that bacteriological methods afford the only certain method of diagnosis.

He states that Fibrinous Rhinitis, apart from diphtheritic infection, is very rare.

Santos calls attention to nasal diphtheria to emphasise the importance of isolation, and the necessity for school doctors and others to examine the nose as well as the throat of children.

D. OTHER FORMS OF DIPHTHERIA.

Diphtheria does occur in situations other than those mentioned, but as these other sites are affected but rarely and have little practical importance, it will be sufficient just to mention them.

They are :- 1. Auditory tube, middle ear and mastoid antrum,
2. Trachea, Bronchi and Alveoli of lungs.
3. Oesophagus and Stomach.
4. Skin, Conjunctiva and Wounds.
5. Vulva, Vagina and Penis.

It will be clear that in the first three groups the disease generally reaches the sites named by direct spread. In the last two groups infection is generally

conveyed by the hands.

The local lesions are those of membranous inflammation, and systemic disturbance very slight.

Regarding the relative frequency of the various forms of the disease, the Blackburn cases referred to fell as follows :-

Faucial.	78·19%
Laryngeal.	16·36%
Nasal.	5·45%
	100·00%

Their total number, however, is too small to generalise upon, regarding this matter.

3. SYMPTOMS AND SIGNS REFERABLE TO SYSTEMIC DISTURBANCE.

1. THE TEMPERATURE is a factor which is of considerable importance in diagnoses.

In the severest cases the temperature is often quite low, even subnormal - a point which is apt to mislead the unwary.

The most notable feature about it is that even a typical case has not a temperature proportionate to the degree of illness.

The average temperature of the Blackburn series of cases on admission was 99·9·F, but it needs to be added that the average duration of illness before admission was 3½ days, so that that does not represent the temperature at the commencement of the disease. Chart 3 however shows their average temperature on admission according to the day of the disease on which they happened to be brought in. It will be seen that

the average temperature of these cases on the 1st. and 2nd day of the disease was only 100°F.

42·5% of cases on the evening of the day of admission had a subnormal temperature, only 5·5% of the cases were above 101°F. the highest being 102·2°F.

It is quite exceptional, therefore, for the temperature to rise above 102°F, and in fact this comparatively low range of temperature is one of the most helpful early diagnostic means of distinguishing between diphtheria and the more simple forms of affections of the tonsils - e.g. septic sore throat, quinsy, tonsillitis in children, and scarlet fever (as already illustrated).

2. THE PULSE is a very useful aid to the early diagnosis of this condition, and a point worthy of the greatest emphasis. Its outstanding characteristic is its disproportionate rapidity as compared with the temperature, during the first two or three days of the disease. The pulse in diphtheria is generally far more frequent than it is in other cases of sore throat, such as tonsillitis, ulcerated throat and Vincent's Angina, and even, also, than in scarlet fever, although here too the pulse shows a disproportionate rapidity as compared with the temperature.

This point is illustrated by the Blackburn cases where one finds that although the average temperature on the evening of admission was 99·9°F, the average pulse rate was 111. In these cases admitted on the 1st, 2nd, or 3rd day of the disease the average figure was 112.

A further feature of the pulse in this disease is its unusually low tension, as shown by its softness.

This would appear to be due to the influence of the diphtheria toxin, on the suprarenal glands, either destroying much of the adrenalin forming tissue, or combining with the adrenalin to form a physiologically inert substance, and so resulting in diminution of vascular tone. Gulland favours the latter view; but recent work by Harding[86] has shown the presence of marked macroscopic and microscopic changes in the suprarenal glands of rabbits and guinea pigs injected with cultures of the diphtheria bacillus - congestion, oedema, fatty degeneration, marked shrinking of medulla etc. suggesting a destruction of the gland tissue as the cause. Whatever the pathological explanation may be, the clinical fact remains, that even an early case of diphtheria shows a marked lowering of blood pressure, and this taken in conjuncion with the unduly rapid beating of the heart, makes the careful examination of the pulse a factor of considerable value in the early diagnosis of this malady.

3. THE GENERAL ASPECT of the patient, even at the earliest stage, gives much help to the keen observer, and, though a factor the value of which is often overlooked, is one to be reckoned with in making an early diagnosis. Nowadays we speedily run for the swab and to the laboratory; and there are those who fear that that somewhat broken reed "Test-tube Medicine" is drawing many from the simpler, but sound and sane, method of the older clinicians - an intelligent use of eyes, fingers, ears and nose. Nineteenth-century observers had wellnigh no other methods of investigation, and their observations are well worthy of note. No apology is needed, therefore, for quoting the sixty year old writings of Wm. H. Jenner[87]. "The general aspect of the patient in some cases, adds weight to the local evidence. The skin has a dirty opaque appearance, and in many a pallid pasty aspect, very peculiar, though by no means diagnostic. If the patient has had scarlet fever, or if the papillae of the tongue be neither enlarged nor redder than natural, the probability is still higher that the case is one of diphtheria. When the inflammation has spread to the larynx, all doubt ceases in regard to the diagnosis".

And again,[88] "soon however, the pulse is rapid and feeble, the sense of weakness and of illness extreme; the skin is not very hot, but there is a peculiar feverish pungency in its heat as appreciated by the touch. The complexion has that dirty pallid and opaque aspect". One has found that this alteration in colour of the skin is most frequently to be noted in very young children. It is a very early sign and commonly the skin is seen to exhibit an amount of pallor and waxiness which is almost suggestive of severe hæmorrhage, indeed the explanation

probably is that the child has "bled into its veins", chiefly those of the splanchnic pool.

Such then, or similar, information the first glance at a moderately severe case will give to us; a second glance will probably reveal to us the fact that our patient is languid. He wears an apathetic expression and the face is pale. It is a characteristic of even the earliest stage of this disease, that the patient is tired and listless, he just lies there in his bed and can't be bothered with anything. To use a common expression "he's got no 'kick' in him".

Kerr[89] phrases it well, "It is rare for these children not to be under perfect discipline within two days. Contrast them with children suffering from scarlatina anginosa, who in the hands of the selfsame nurses may struggle and fight every time the throat is treated for three or four weeks, and, never resigned to hospital discipline, are constantly attempting to sit up".

It is of interest to inquire the cause of these phenomena. One's own view is that they are explained by the changes found in the suprarenal glands, to which reference has already been made.

During a fit of anger, by ways we cannot even dimly perceive, the emotion results in a stimulation of the Sympathetic nervous system. As a direct result of this, the suprarenal glands, which bear very close relationship to that system, pour out large amounts of adrenalin which, entering the blood stream, adds tone to every muscle, contracts the peripheral vessels, increases the blood pressure, makes more forcible the heart's contractions and sets the individual on the

alert, ready for any emergency - which for man in his natural state was a fight.

In even an early case of diphtheria, however, the very reverse is true. The child is listless and languid, the blood pressure is markedly lowered, the muscles are relaxed and show diminished tone. One would maintain that the state of the pulse and the general aspect of the patient both owe their origin to the damage wrought on the suprarenals by the diphtheria toxin, thus preventing the normal formation of adrenalin; and of such damage there is ample evidence, both macroscopic and microscopic, as we have previously noted.

4. ALBUMINURIA may be mentioned, not that it is a useful sign in the early diagnosis of the disease, but because it is commonly thought so to be. It is of the same value in diagnosing diphtheria, as cachexia in diagnosing cancer. Yet one sees it copied from one text-book to another as a frequent early sign of the disease. Taylor[90], Tirard[91], and Wheeler and Jack[92], all suggest its being commonly present at the commencement of the disease - and of being of value in diagnosis.

It is of value, if one finds it present in a case admitted on the 4th day or thereabouts, but as it is not common before that day its absence is of no significance. Its earliest appearance of which I have found record is a case of Burdon-Sandersons[93], in which it appeared eighteen hours after the development of the first symptom.

Furthermore it has to be remembered that if the patient's temperature is above say 104°, the albuminuria is likely to be just febrile in origin and not

at all indicative, necessarily, of diphtheritic infection - e.g. tonsillitis, in such cases, often gives it,

Taylor[94] states the urine is albuminous in a large proportion of cases variously estimated at 25 to 60%. Ker[95] states that in averagely severe diphtheria the proportion of patients with this symptom is about 30 to 40%, but when the epidemic is benign may be very much less; also that when it appears it is chiefly to be found between the fourth and tenth day, and never outlasts convalescence.

Goodall[96] says it may be found in as many as three-quarters of the cases, is most commonly to be detected about the fourth day of the disease, but may occur as early as the first.

Northrup[97], quoting figures of the M.A.B. for 1900, states that it occurred in 31·7% of the 8238 cases examined.

Observers[98] in pre-antitoxin days (1860) found albuminuria occurred in from 55 - 70% of cases - a statement which should clear the use of antitoxin of all blame as the cause of this condition. One has investigated this question in 50 out of the 55 Blackburn cases cited - Albumin was present on admission in 34% of the cases, (but it has to be remembered that the average duration of illness before admission was 3½ days), so that these figures do not go to show that albuminuria is an early sign.

One concludes, therefore, that albumin is present in a very variable number of cases of diphtheria, but that, as it practically never is found early in the disease, it is a sign which is of very little value in

diagnosis.

5. THE PATELLAR REFLEX. Tirard[99] is interesting when he says "One symptom which affords a certain amount of help in diagnosis of any form of diphtheria is the early abolition of the knee-jerk. The value of this symptom for diagnostic purposes is very great, and it is so easily recognised, and it differentiates so thoroughly from ordinary tonsillitis, that it should not be neglected". I found that my "Chief", too, at the Royal Infirmary, Dr. Edwin Matthew, placed considerable reliance on this sign. One must admit, however, to not having found the knee-jerks abolished in the early days of this disease. Moreover one is unable to find any reason why these reflexes should be absent at such a stage. Such a phenomenon would be essentially a form of paralysis, and therefore more likely to become evident late on in the disease than at an early stage.

Furthermore one is unable to find any support of Tirard's statements from a study of the literature. Hector Mc.Kenzie[100], in a large number of non-fatal cases found the knee-jerks to disappear from the fourth to the tenth week; but in many of the fatal cases the knee-jerks disappeared more early, the percentage being greatest at the sixth day, although it is still high on the seventh and eighth day. It seems likely, then, that in a very few of the fatal cases the reflex would be absent in the first two or three days of the disease.

One concludes, therefore, that the condition of the knee-jerks, gives no information of value in the early

diagnosis of diphtheria.

4. CERTAIN LABORATORY METHODS OF DIAGNOSIS OTHER THAN BACTERIOLOGICAL, DISCUSSED.

There are certain laboratory methods of diagnosis which are of value in other disease, and which, a priori, it might be thought would be of use in the diagnosis of diphtheria. These it will be well to dismiss before proceeding further.

1. THE BLOOD.. "A well-marked leucocytosis, the degree varying as a rule directly with the severity of the disease, is present. It is chiefly polymorphonuclear in type". (Mallory[101]).

The leucocytosis has, however, no features uncommon to many other diseases, and furthermore it is not well marked in the early stages of diphtheria. It is, therefore, a feature of no value for our present purpose.

The Arneth Count shows a marked movement to the left, which, according to Taylor[102], in grave cases is very marked, and thus constitutes a valuable method for determining the prognosis.

A fairly marked movement to the left is,however, present in scarlet fever and similar other diseases, so that this method has little value from the point of view of diagnosis.

The changes in the red blood corpuscles are also unimportant. There is a diminution in the percentage of haemoglobin.

2. THE CEREBRO-SPINAL FLUID. Considering the predilection of the diphtheria toxin for the nervous system, it might be thought that changes in the cerebro-spinal

fluid might be found in this malady, even to the point of being an aid to diagnosis.

The evidence concerning changes in this fluid is conflicting. Regan[103] (1918) maintains that in practically all the cases showing obvious nerve involvement, (i.e. to the extent of paralysis), the cerebro-spinal fluid is normal.

Lavergne[104] (1921), on the other hand, finds an excess of glucose and albumin associated with a normal lymphocytosis.

In any case, however, paralysis only occurs in some 10% of cases and is a late sign, so that whilst such a painful method of investigation may give interesting results, one would dismiss it as of no clinical value.

3. CUTANEOUS AND INTRADERMAL TESTS. One has been unable to find any reference in the literature to work on the effects of the cutaneous inoculation of dead diphtheria bacilli - similar in technique to the Von Pirquet test. But even if any useful results were to come from a test devised on those lines, it is very unlikely to be of any value in diagnosis for reasons analogous with those given below.

Regarding the intradermal toxin or Schick test, it might be argued that in view of the fact that some 60% of the population give a negative reaction (i.e. are immune to the disease), and considering the fact that we are able to tell whether a person is liable to take the disease within a short time of carrying out the test, - in view of these facts, it might be argued, the test might be useful to diagnose a doubtful case,

e.g. of tonsillitis. Acting on this line of reasoning, a positive reaction would show the patient to belong to the 40% of people liable to take diphtheria, and therefore make that diagnosis more probable.

A negative reaction, on the other hand, would point to the patient's being one of the 60% of people immune to the disease, and thus exclude a diagnosis of diphtheria.

But a test on such lines, if only carried out by the methods our present knowledge makes possible, would give no help, indeed be merely more confusing. One would point out that the fundamental fallacy lies in the fact that by the time the person has had the disease only a few hours, the body will have produced some antitoxin in response to the formation of toxin. And therefore even although the person would previously have given a positive reaction, the reaction will now be negative owing to the presence of antitoxin of his own manufacture.

One's conclusion on this point is found to be supported by the results of work done by Johnson[105]. He performed the test on patients who were actually suffering from diphtheria at the time, and found the reaction to be negative in these cases (with a very few exceptions) Gladys Ward however has come to the opposite conclusion. She regards a negative reaction in tonsillitis or nasal discharge as indicating that the patient is not suffering from the disease. One's reasoning and a consideration of Johnson's investigation, however, make one at variance with this view. One is of the opinion, therefore, that a negative test

in these circumstances, does not mean the patient is not liable to diphtheria, indeed it is just as likely to mean he is actually then suffering from it. But, in light of these facts, let us now turn to the consideration of the significance of a positive reaction.

On theoretical grounds, and from the reasoning just given, it appeals to one as likely that a positive reaction might prove a use-ful factor in diagnosis. We have seen that Johnson found cases of diphtheria practically always give a negative reaction; if therefore the Schick test is performed on a doubtful case, e.g. of tonsillitis, and a positive result, it would follow that the case is not one of diphtheria.

One can conceive therefore of this test being useful, e.g. in some cases with marked symptoms the swab examination gives unreliable results, and an organism apparently B. Diphtheriae may really be just avirulent.

It may be replied, inter alia, however, that it is unwise to use a test which sometimes causes considerable systemic disturbance, on a patient already seriously ill, and that although one can generally predict the result of the test with moderate accuracy at the end of 24 hours, 3 days are required before a final opinion can be expressed. Methods of diagnosis are well-nigh valueless unless they give a result early.

5. CONCLUSION.

It will have become clear that the early symptoms and signs of the different forms of this disease will, in the majority of cases, lead one to an accurate diagnosis with fair certainty.

But it will also have been noted that ~~a~~ typical cases are so common, and that other diseases occasionally resemble diphtheria so closely, that the most expert diagnosticians are apt to make mistakes. The wider one's experience in this disease, indeed, and the more one comes to feel that there is a sense in which it would be true to say "anything may be diphtheria" - anything from "a common cold" to a condition of grave toxaemia with a marked erythematous rash.

There is, however, one invaluable aid to the identifying of this malady we have not yet considered - bacteriological diagnosis.

To this we shall now turn.

BACTERIOLOGICAL DIAGNOSIS IN PATIENTS AND OTHERS.

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1. DETECTION OF THE, OTHERWISE, UNKNOWN CASE.
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5. PRACTICAL CONCLUSIONS.

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1. INTRODUCTORY.

The question of bacteriological diagnosis, in this disease, is inseparably bound up with the questions of the recognition and treatment of the disease, and more especially with its prevention.

No attempt, therefore, will be made to separate these considerations in what follows.

Preventive measures in this disease, more than in any other, mainly depend on the facts of bacteriology.

It will be necessary, then, to attempt to give a somewhat comprehensive account of the evidence relevant to this subject, for it is largely on this evidence that one's views on prevention are founded. Later therefore, in the discussion of preventive measures, these facts may be taken for granted.

In what follows it will be one's endeavour to give an account of the opinions and conclusions to which one has been led by one's work, along with a review of the recent work of others and one's criticism of it (where one feels in a position to criticise).

As such an end is perhaps brought about best in the form of discussion, one has largely adopted this method.

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2. METHOD.

1. PRECAUTIONS IN OBTAINING MATERIAL FOR BACTERIOLOGICAL DIAGNOSIS.

We are generally dealing with the throat. No antiseptic should have been applied for, at least, an hour previously. Since milk often contains diphtheria-like bacilli, it is advisable that the patient be not allowed milk for an hour or so before the swab is taken.

It is one's practice to use the ordinary swab and test-tube, sterilised at 150°C. for 3 hours. But in an emergency, a skewer with some non-medicated gauze on the end, and thrust into the cork of a medicine bottle (wide enough to prevent its sides touching the swab) has served.

A good light, a spatula, a firm sensible nurse, and a determination to carry the procedure through as properly as possible, however refractory the child, are all most desirable. From performances one has seen, one is of the opinion that many of the "negative swabs" from clinical cases of diphtheria are due to faulty technique. A rough dab is made at the throat through the half-closed mouth of a struggling child, it is not known whether the swab has struck a likely site for the organism or not. Or maybe the swab is withdrawn carelessly, and touches cheeks, tongue or teeth; thus grossly contaminated identification of the organism is rendered much less probable. Little wonder some positives are returned negative!.

In cases of the disease one endeavours to rub, with the swab, near the edge of the membrane, and not

over the centre of the patch, as the organisms are said to be more numerous and accessible in the former situation, a method commended by Osler and Macrae[106].

In many cases it will be necessary to swab the nose, or even conjunctivae, ears, wounds or vagina etc., Graham-Smith[107] recommends that, in the case of contacts "the swab should be taken from any unhealthy areas that may be seen, and also from the surfaces of both tonsils, special care being taken to inoculate the swab with any exudate seen coming from any of the crypts, or capable of being made to appear therefrom by pressing the tonsil inwards, with the fingers, below the angle of the jaw".

A practical point of some importance is that when it is impossible to sow the swab on culture media for several hours, e.g. transmission through the post, it is advisable to moisten the swab with broth or sterile water before applying it to the throat.

2. SOME POINTS CONCERNING MORPHOLOGICAL AND CULTURAL CHARACTERS - THEIR VALUE. THE "TIME" ELEMENT IN DIAGNOSIS.

A swab having been taken from a case of diphtheria, time is the most important factor, and so a direct smear should be made.

A permanent preparation is not necessary and one has found, in practice, that the clearest results are obtained by putting a drop of dilute, (1 in 5), Löffler's Methylene Blue on the dried smear, and examining the specimen in the stain.

Regarding the morphological characteristics of the organism, various writers appear to have different, and

often conflicting, standards as to what features constitute and what do not constitute the diphtheria bacillus.

And yet the question is of the greatest practical importance, for harmless, but diphtheria-like, organisms are so common. Most of these are easily distinguished by a careful observer, and furthermore one is of the opinion that many so-called "avirulent diphtheria bacilli" would be found to be merely diphtheroid organisms, if proper standards were used - even without a consideration of their macroscopic, and chemical, cultural characters.

As Dr. G. S. Graham-Smith is probably the greatest living authority on the bacteriology of this disease, one's own standards are based on teaching received from him whilst a member of his Class of Public Health Bacteriology at Cambridge University.

The characters, therefore, to which one pays special attention are :-

1. The organism may be long or short.
2. Nearly all are dilated at one or both ends - "clubbing".
3. The sides of the organism are not uniform - a character not common in diphtheroids.
4. Staining shows the organism to be segmented in varying degrees, and where the segmentation is complete the band is placed obliquely - never transversely as in the diphtheroid forms.
5. If some 2% Acetic Acid is run under the coverslip of the preparation described above, by placing one drop of the reagent at one side of the coverslip and a piece of blotting paper at the other side, the stain will be seen to leave the protoplasm which

previously gave rise to the segmented appearance, but to remain in the polar bodies (~~by Neisser's method~~).

6. 60% of the true diphtheria bacilli show the presence (by Neisser's method) of polar bodies. Many have regarded their presence as proof positive that the organism was the Klebs-Löffler bacillus. Many diphtheriod organisms, however, possess the same character.

7. The "Chinese letter" grouping of the organisms, found by Dr. Graham-Smith to be due to "post-fission snapping", is an aid to diagnosis. But it is not invariably present, and many other organisms of the same group show the same phenomenon.

8. Whilst organisms that are segmented are likely to be b.diphtheriae, those which stain evenly, or with just an unstained narrow band running transversely at the centre, are likely to be b.Hofmanni (present in 30 - 100% of the throats of the children of most elementary schools).

Another point we were taught to regard as characteristic of b.Hofmanni, was the fact that many of them appear as "ghosts", e.g. just the margin is stained, thus O .

Such, then, are the morphological features one has come to regard as of most importance in deciding whether a certain organism is, or is not, the diphtheria bacillus.

If, therefore, one were to find organisms with such characters in e.g. a direct smear from a suspicious throat, one would exhibit antitoxin at once.

Dr. Graham-Smith used to teach us that it is not

wise to make a smear direct, because other organisms and debris complicate the examination and often give great difficulty in detecting the organism.

But one would say that he spoke as a bacteriologist and not as a clinician, for though a direct smear is apt often to give a negative result in a positive throat, the employment of this means will generally clinch the diagnosis within 10 minutes. Thus Ker[108] states that of 75% of his cases in which a positive culture was obtained the bacilli were also detected in the direct smear. Also this point one investigated in the Blackburn cases, and found the figure there to be 85%.

This evidence is striking testimony to the value of the preliminary bacteriological examination.

An investigation conducted by Mason[109] on this point, however, did not give equally good results. 99 cases were examined, of the 54 cases that proved positive on culture, only 68% gave positive smears. And of the 45 cases which proved negative on culture, 6·6% showed organisms which, in smears, were taken to be diphtheria bacilli; and 17·7% showed doubtful organisms.

But even these facts, whilst revealing possible fallacies, do confirm one in the belief that much valuable information may be obtained from smear preparations. Indeed there is one disease which can be best diagnosed from an examination of the direct smear - Vincent's Angina - as the organisms associated with that condition cannot be cultivated aërobically.

In the detection of carriers, time is not an important factor, and so for such purposes one does not prepare a direct smear.

As just indicated, cases of the disease frequently give a negative result from a direct smear; it is, therefore, one's custom to have cultures prepared in addition. The result of this further examination is obtained in some 12 - 18 hours, in hospital; but in the case of a country practitioner, even if the result is sent by telegraph, the reply will not be obtained for 36 - 40 hours, too late to be of value from the standpoint of therapeutics,as has already been demonstrated. The great value of direct smear, therefore, is evident.

Many cases of true diphtheria, however, show a negative smear, and some apparently positive or doubtful positive smears will prove negative on examination of the culture. This is of special importance from the standpoint of preventive medicine. A slope culture therefore should always be made. Dr. Graham-Smith used to teach us that where, as often, there is likely to be a copious growth, it is best to rub the swab thoroughly over one side of the slope and pass it lightly over the other. The result is that at least on one part of the slope more or less separate colonies can usually be found. This hint one has found of value.

Alkaline Glucose-serum is generally recognised as the best medium to use and great care is needed in the preparation of the medium. As Osler and Macrae[110.] say, "many positives have been returned as negatives owing to the medium being too alkaline, not alkaline enough,

or too moist". A consideration of these, and many other factors with which one is brought into contact, makes one lean more and more on clinical findings for one's diagnosis, and less on laboratory methods; it makes one smile, too, as one reflects of the great faith one had as a medical student (doubtless typical) in that wonderful and distant thing, - the bacteriological laboratory. One is not long in practice before one feels even these few remaining pillars in medicine to which one had clung as being definite and infallible, - falling.

The forms of the b.diphtheriae are so numerous, the organisms with similar features so many, the effect on its growth of even slight changes in the media so striking - and after all the bacteriologist is quite mortal; and if he is in a private laboratory supported by the fees of general practitioners he has to think of his living. The general practitioner commonly thinks a doubtful report means ignorance.

Is the swab"positive"or is it"negative"? All who have been in this work know that with ordinary methods the result is often doubtful. Should we put "Yes", - or "No"?! And the bacteriologist is often very human - especially in his "off" moments. And the doctor won't pay for a guinea-pig. Even if he did the result of the investigation would come too late to be of therapeutic value. The patient would likely be dead.

There is one new and speedy aid to diagnosis, however, which promises to be of value. It comes from America. The chief objection to waiting for a culture is the time involved. Frost, Charlton and Little[111], However, say, "We are convinced we can make a diagnosis

with as much certainty by our method as by the regulation method and in one third of the time". - i.e. in 5 hours. Their conclusions seem beyond criticism as they have examined unknown cultures and cultures from normal and suspected throats, in a large number of cases, both by the orthodox and their new method. In every case the results were the same. They give full details of their method in the Journal indicated in the Bibliography. Essentially it consists in putting on to the smear a drop of warm agar-milk-serum medium, which solidifies, and then is incubated - thus forming what they term a "little plate culture". After five hours incubation slides are prepared and examined in the ordinary way. One would think discrete colonies would be more difficult to obtain and the familiar macroscopic appearance of the stroke-culture lost. The method, however, sounds promising but, not having given it a trial one cannot at present express a personal opinion. Having obtained a slope-culture the next thing to do is to make smears from the circular, raised, dome-shaped, slightly opaque, greyish colonies, with a perfectly distinct margin; they are then stained in the ordinary way, or they may be stained by a method suggested by Delépine and described by Angus Mc.Donald.[112.] He states that this method enables him to distinguish b.diphtheriae from b.xerosis and some similar organisms (Eagleton & Baxter[113.] having just published an article to the effect that these germs were morphologically indistinguishable from the Klebs-Löffler Bacillus).

Macdonald claims the method taught him by Delépine

differentiates the greater number of virulent from avirulent forms. It consists in staining a 16-hour-old culture, on Löffler's medium with half-strength Ziehl Neelsen's stain, briefly, and then washing immediately.

To sum up then: Always bearing in mind the fact that in occasional cases of diphtheria no b.diphtheriae are present on the first or even the second swab taken, we have therefore these facts:-

If, on the smear, organisms with the morphology described are found, we have presumptive bacteriological evidence that the case is one of diphtheria, and should be treated as such. The reverse does not hold true.

If, on culture, we have the macroscopic and microscopic appearances detailed, we have bacteriological evidence that the case is probably one of diphtheria. If no such appearances present themselves, save for the possible exception above-mentioned, the case is not one of diphtheria.

The most crucial cultural test, however, consists in growing the suspected organism, (having first obtained it in pure culture), on glucose-broth; and then observing the reaction of the medium. Such a procedure takes 3 - 4 days. The Klebs-Löffler bacillus produces acid from glucose. It is this feature which Graham-Smith [114] stresses so much, for neither Hofmann's bacillus nor the pseudo-diphtheria bacilli, which, are merely forms of Hofmann's bacillus, have this cultural character. If an organism does not produce acid from glucose it is not the diphtheria bacillus. B. xerosis and b.Septus also produce acid from glucose but can be differentiated from the diphtheria bacillus by the fact that they have different effects on

saccharose and dextrose.

3. THE DIAGNOSIS OF THE VIRULENT FROM THE AVIRULENT B.DIPHTHERIAE.

Only thus, i.e. by noting its morphology and its effect on various media, can one prove a given organism to be the diphtheria bacillus. But, even so, one cannot be sure the bacterium is dangerous either to the community or to the individual, for it may be virulent or avirulent. Some rather heroic research workers,[145.] in Baltimore, had their throats sprayed with organisms "Morphologically, tinctorially, and culturally" identical with the Klebs-Löffler bacillus. No ill effects resulted either in them or in those in contact with them. Braver still, they had their throats sprayed with Klebs-Löffler bacilli, first proved virulent by injection into a guinea-pig. Half of them fell ill of diphtheria! Their investigation is of such import, however, that it will need to be considered later, in connection with one's work on the prevention of the disease.

For the present let it suffice as proof that it is impossible, short of animal experiment, to positively affirm that any given organism is the virulent Klebs-Löffler bacillus. Even this is more complicated than it first appears, for Graham-Smith insists that the organism must first be made used to growing on broth, the broth must be glucose-free, as glucose hinders toxin formation, (many observers' work is useless through neglect of this precaution), and finally, two guinea-pigs are needed for the experiment, because organisms other than the Klebs-Löffler bacillus may cause the death of the

animal. Into one animal 0·2c.c. of a 48-hours old glucose-free broth culture, from the suspected throat, is injected, and into the other a similar quantity, but also antitoxin simultaneously. If the first dies, (generally in about 36 hours), and the other lives, the organism is positively the virulent diphtheria bacillus. If both die the organism is some other germ pathogenic to guinea pigs.

Although most of us now regard animal inoculation as the only real test for virulence, there are those who think they can distinguish the avirulent organism form the virulent by morphology. Most of the literature on this subject, however, tends to the opinion that the pathogenicity of diphtheria-like organisms has little connection with the morphological characters.- Graham-Smith is of the opinion that "some, at least, of the so-called non-virulent diphtheria bacilli belong to a separate saprophytic species, though at present they cannot be distinguished morphologically, or by culture, from true virulent diphtheria bacilli".

More recently Gelien, Moss, and Guthrie[115], in a series of observations on 160 carrier strains, concluded that virulent and non-virulent diphtheria bacilli were exactly alike, and could only be distinguished by animal inoculation. Also Havens[116], from observations on a series of 154 strains, decided that the somewhat common belief that solid staining bacilli and certain granular and barred forms are avirulent, is erroneous. He states that "morphology is no more a criterion of virulence in the diphtheria bacillus, than it is in the

pneumococcus".

One has at least this comfort however, (although we have not been sure of even this till lately), that the avirulent diphtheria bacillus, and the virulent, breed ~~true~~, that the one cannot become the other, or the other the one. We know that they are almost certainly quite distinct organisms, which unfortunately we can only differentiate, as yet, by animal experiment.

There seems no reason why some medium should not be found eventually, whereby to differentiate them; but even most recent work, (Jordon, Smith, and Kingsbury[117]), on this subject has been of no avail.

When such a medium is found it will result in considerable saving both of time and money. Recently, however, Eagleton & Baxter[118] have introduced a method of intracutaneous injection of the guinea pig. They claim that by their method many virulence experiments can be performed on the same animal, for this method doesn't cause death. This has bearing on an important practical point, viz:- the expense of a complete investigation.

Similar methods have been devised by Zingher and Soletsky[119], and also by O'Brien[120] and his colleagues.

One has given a sketch of the elaborate methods one has, reluctantly, come to conclude are necessary for an accurate bacteriological diagnosis, not that one considers, clinically, such methods to be always essential, but because reference to them will be necessary in regard to the conclusions to which one has come concerning preventive measures, particularly in relation to the question of carriers and their isolation.

4. THE EXTENT OF INVESTIGATION NECESSARY FOR BACTERIOLOGICAL DIAGNOSIS UNDER DIFFERENT CIRCUMSTANCES.

It will now be evident that before one can arrive at an absolute bacteriological diagnosis it is necessary to carry through a long, tedious, and expensive undertaking.

Commonly, however, only a few steps of the full process, above described, are necessary in practice.

One will now endeavour to indicate the extent of the investigation, necessary under certain conditions, as this varies with varying circumstances. The more common circumstances will be given in the order in which they generally arise.

But little need be said as to the reasons for adopting such standards as these will become evident, later, in a consideration of arguments for and against the use of bacteriological diagnosis.

1. In examination of cases clinically resembling diphtheria, time is the important factor.

A direct smear, if positive, gives valuable information.

A culture also should be prepared, a diagnosis may thus be given with fair accuracy within 12 - 18 hours.

Further examination is not usually necessary, for, as one has shown, avirulent diphtheria bacilli, and even pseudodiphtheria bacilli, are not common in throats which clinically resemble diphtheria.

However, in the case of certain institutions, e.g. private schools, a positive diagnosis of a primary case

should not be given, short of a positive result on inoculating glucose-broth with a pure culture. The patient can generally be isolated for the three or four days necessary for this test to be carried out. (Therapy, however, should not await the bacteriological diagnosis). The importance of considerable care in such a case lies in the fact that a positive diagnosis, if incorrect, leads to a great amount of unnecessary trouble and considerable expense.

2. In the examination of contacts, a swab should be taken of both the pharyngeal and nasal mucosæ. Macroscopic and microscopic examination of cultures on Löffler's medium should be made and, if any organisms with the morphology of B. diphtheriae are discovered, no opinion should be given until the action of pure cultures on glucose media has been determined.

If organisms conforming to the characters of B. diphtheriae, on these tests, are present, and the individual is a contact of a definite case of the disease, they may be considered of the virulent variety and any necessary administrative action taken.

Here, again, much inconvenience and pecuniary loss might well result from giving a hasty opinion which subsequently was proved erroneous. This is a point of great practical value and one, the importance of which, it is impossible to over-emphasise.

3. An examination of convalescent cases of diphtheria and of infected contacts has always to be made, for the purpose of deciding whether the diphtheria bacilli have disappeared, or not.

In the later stages this is often difficult owing to the fact that no organisms ~~are~~ may be on the surface of the tonsil, but nevertheless are nestling in the crypts and ready to come out, and do mischief, e.g. if the person catches "cold". In these cases, therefore, the first swab may be "negative" although the individual is still harbouring the organism. Three successive negative results should be obtained before announcing the individual no longer a source of danger to the community.

Both the pharyngeal and nasal mucosae should be swabbed, and each examination be made not less than 3 hours after the discontinuance of local antiseptic applications.

The same cultural methods should be employed as for the first examination of contacts.

If, however, in spite of treatment the person continues to be a carrier for more than say 10 weeks, more or less according to the persons occupation, one is of the opinion that as a routine a virulence experiment should be made. Many of these cases, as one will show later, are merely harbouring avirulent organisms, are of no danger to the community, and their detention or restriction but an unnecessary nuisance.

4. In the examination of discharges from the ears, female genital organs, skin lesions, ulcers, abscesses etc, and also of milk and various other materials, special care has to be taken before giving a positive diagnosis, because in these situations, in contrast to sore throats, organism almost identical, (in morphological

and cultural characters, with the diphtheria bacillus are so common.

One feels it would be unwise to accept any standard short of animal inoculation.

5. For the purpose of discovering carriers, it is sometimes necessary to examine large numbers of people although they are not known to be possible contacts of a preceding case of the disease.

Here again, no standard short of animal inoculation can be accepted.

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It will already be evident that there are objections to the employment of bacteriological diagnosis in this disease. These objections, along with arguments in favour of them and against them, will now be discussed.

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3. ARGUMENTS AGAINST THE USE OF BACTERIOLOGICAL DIAGNOSIS PROPOUNDED, DISCUSSED, AND CRITICISED.

A. ARGUMENTS BASED, ESSENTIALLY, ON THE DIFFICULTY OF RECOGNISING THE CAUSAL ORGANISM.

1. APPARENT ABSENCE OF B.DIPHTHERIAE IN PERSONS SUFFERING FROM THE DISEASE.

Against the use of bacteriological diagnosis in this disease, it may be argued that the chances of a case of diphtheria giving a positive throat-swab on the first examination, by ordinary bacteriological methods, are only 71 for, and are 29 against. These figures are based on the results of 30,000 bacteriological examinations (smear and culture), and represent the average findings of many independent observers, Novy[121.] Woodhead[122.], Josias and Tollemer[123.], and others. Their findings are reliable, statistically speaking, since they all approximate to the same figure.

It is only fair to say, however, that these figures refer to notified cases and that, doubtless, many of them were not cases of true diphtheria, but notified and sent into hospital for safety, just in case they happened to be the serious disease. One feels, therefore, the basis for argument against the use of bacteriological diagnosis, on the ground that as many as 29% of the cases of actual diphtheria show a negative swab, is in part, at least, fallacious.

The chances that a swab which gives a positive culture would have given a positive smear are, according to Ker's figures, 3 to 1, and according to Blackburn

statistics almost 6 to 1. It seems regrettable, therefore, that a method which the practitioner can so easily apply and which is so likely to give help, is so little used by him. Especially is this so in view of the importance of early treatment.

2. THE QUESTION OF THE B.PSEUDODIPHTHERIAE AND B.HOFMANNI.

It may be argued that bacteriological examination in this disease is rendered valueless, or of little worth, owing to these facts, considered together, viz:-

1. That the pseudo-diphtheria bacillus is so similar to the diphtheria bacillus that even a bacteriologist may mistake the one for the other, and so diagnose the disease when it is not present.
2. That this is still more likely is shown by the fact that the b.Hofmanni and b.pseudodiphtheriae (merely a variety of the former) are present in 32·9% of the population - according to an analysis of the work of a number of investigators[124] on 15,360 unselected individuals.
3. That this persentage is still higher if we confine ourselves to morbid throats, with which, after all, we are dealing. Cobbett[125] gives this figure as 50%.

To these arguments one would reply:-

That although one grants it is sometimes impossible to help mistaking b.Pseudodiphtheriae for b.diphtheriae, in direct smear preparations, on culture this organism

almost always becomes the typical Hofmann's bacillus which is easily differentiated from the diphtheria bacillus by its morphological characters and by its lack of polar bodies when stained by Neisser's method. Furthermore even the typical segmented forms, occasionally found, can be readily recognised by a practised observer.

The argument that the difficulty is accentuated, owing to b.diphtheriae -like organisms being still more common in sore-throats, is scarcely tenable. Cobbett's figures, one finds, are only based on an examination of 18 cases - too small a number to allow one to generalise with confidence. Indeed later work by Graham-Smith[126], in an extensive outbreak of diphtheria at Cambridge, showed the proportion of persons, infected with Hofmann's bacillus, to be nearly the same among convalescents recovering from diphtheria, contacts infected with diphtheria bacilli, non-infected contacts and non-contacts.

But still there are some who not only insist on the apparent identity of b.Hofmanni and b.Diphtheriae morphologically, but maintain that b.Hofmanni is the cause of disease in man, and that these two organisms are but two forms of the same bacterium.

In view of the great importance of such statements, if established, on the subject of the prevention of diphtheria, which one is to consider later, it will be well, here, to summarise the position concerning these questions. Graham-Smith[127] writes "It has frequently been asserted that diphtheria bacilli, during convalescence,

gradually change their morphological type and become converted into Hofmann's bacilli; but many of the investigations on this subject are, for various reasons, of doubtful value. In fact there is much evidence to show that such a change does not take place. Changes of morphological type do not seem to occur by transference from one individual to another.

According to some observers prolonged cultivation is apt to change the morphological type, according to others it is not. In regard to changes of morphological type by passages through animals the statements are conflicting.

On the whole these experiments and observations also point to the conclusion that diphtheria and Hofmann's bacilli are not related to another.

It has been asserted on various occasions that Hofmann's bacilli may be pathogenic to man, but no bacteriological proof has been produced, and, except by one or two observers, Hofmann's bacilli devised from all sources have been found to be non-virulent to guinea pigs in fairly large doses. Attempts to give virulence to this organism, or to change its morphological type, have mostly been unsuccessful. Further the evidence derived from the bacteriological control of outbreaks of diphtheria, and the fact of the very general distribution of this organism, are against the etiological significance of Hofmann's bacillus in this disease.

Finally, most modern investigators appear to regard the diphtheria bacillus and Hofmann's bacillus as belonging to "different species".

One may therefore conclude that b.Hofmanni has no significance either in the diagnosis or etiology of diphtheria, or other disease.

3. THE QUESTION OF THE AVIRULENT B.DIPHTHERIAE

A further argument which may be brought against the use of bacteriological diagnosis, in this disease, is that even although in a case of e.g. sore throat the diphtheria bacillus is discovered, with all its peculiar morphological and cultural characters, there is no proof short of animal inoculation, (generally impracticable), that the case is one of diphtheria.-. The organism may be avirulent.

And still further, it may be argued that the avirulent organism is more common in the morbid than in the healthy throat. How very serious a matter this may become in practice is shown by the work of Moss, Guthrie and Marshall[128] who investigated the throats of 81 inmates of an orphan Asylum of Baltimore. They found 30 diphtheria bacillus carriers amongst the 81 inmates examined; and, what is of great importance, from the point of view of our present consideration, they found "pathological conditions" of the throat common amongst the children generally, and, be it noted, slight fever was also common amongst those carriers with pathological throats. And yet of 44 cultures from the 30 carriers, all were avirulent, as shown by animal inoculation.

The discovery of a positive culture in a child with an evidently pathological throat, (although no membrane was present), might readily suggest the diagnosis of diphtheria, and indeed many diagnoses are made on no greater evidence than this.

Only the investigators knew of the presence of these conditions; and so the inmates were left undisturbed. No cases of diphtheria developed in the carriers nor in their associates, and the Superintendent of the Orphanage stated that there had been no case of the disease in the institution for 30 years.

But suppose a case of the disease had occurred in the school these children happened to attend, the Public Health authorities would prosecute inquiries, the children in the school would be examined in the ordinary way - some would be found to yield positive cultures, a further examination would have shown the presence of slight sore-throat, and just a little temperature - Diphtheria! It would only have needed a well-meaning enthusiast to have created a pseudo-epidemic in no time.

Further work showing the frequency with which the avirulent organism is found in the throat is that of Sholley[129]. He examined 1000 children attending for treatment at New York hospitals, for ailments other than affections of throat or nose. He found that 1·8% of them harboured virulent and 3·8% non-virulent diphtheria bacilli.

Guthrie, Gehen, and Moss[130] examined 1217 school children in Baltimore. Although 3·61% were found to harbour the b.diphtheriae, of this percentage only 18·18% were virulent.

In other words the avirulent form was 3 times more common than the virulent, in the first series, and 5 times more common in the second.

And therefore, considering these two series, the

argument would run: If you rely upon ordinary bacteriological methods of diagnosis, the chances are 4 to 1 that you will be misled, diagnosing a patient who gives a positive swab as diphtheria, whilst, all the while, only the avirulent organism is present. Plausible, however, as this whole line of argument may seem, it does not represent the whole truth.

That avirulent diphtheria bacilli were present in 30 out of 81 inmates of the Orphan Asylum, and that sore throats were common there, is no proof that avirulent diphtheria bacilli are more common in sore throats than in healthy throats. Further inquiry shows that sore throats were common, at the time, in the school these children attended, and yet that avirulent diphtheria bacilli were present in only 2·9% of the scholars. The greater incidence of the avirulent diphtheria bacilli amongst the orphans is likely due to these children living in close contact - one infecting another.

Furthermore one's clinical medicine would be far divorced from one's bacteriology, if the result of bacteriological examination so blurred one's vision as to diagnose cases such as those cited as diphtheria - in the absence of any one defined case. The writers admit that membrane was not once present.

In view of these facts a little sore throat, even with a slight temperature, ~~are~~ is not going to lead an average observer astray, although a positive swab, (owing to avirulent bacilli), were more common amongst individuals with some morbid condition of the throat than amongst healthy individuals.

Indeed, on the contrary, although in the normal throat the avirulent bacilli are more common than the virulent, there is some evidence to show that they are less common in throats which are sufficiently morbid to lead one to seriously consider the diagnosis of diphtheria.

Thus Graham-Smith[131] examined several schools during an outbreak of diphtheria at Cambridge. Of the 29 scholars who actually took the disease, all showed the presence of the virulent diphtheria bacillus, whilst none showed the presence of the avirulent bacillus - and this in spite of the fact that avirulent bacilli were present (0·9%) in the throats of healthy contacts.

It would seem therefore as if the virulent diphtheria bacilli lead to the disappearance of the avirulent type, when the patient takes the disease. This therefore goes far to increasing one's confidence in the reliability of the morphological and cultural tests in cases of the disease, and leads one to the conclusion that animal inoculation is not as essential, even to the bacteriological diagnosis of diphtheria, as might first appear.

B. ARGUMENTS NOT BASED, ESSENTIALLY, ON THE DIFFICULTY OF RECOGNISING THE CAUSAL ORGANISM.

We will pass now to several arguments, against the case of bacteriological diagnosis, of a different nature.

1. THE QUESTION OF THE EQUAL VALUE OF ANTITOXIC SERUM IN NON-DIPHTHERITIC THROAT AFFECTATIONS.

It has been held by a recent writer[132], in the Lancet, that diphtheria antitoxin is as specific a a cure of non-diphtheritic tonsillitis as of diphtheria.

It may, therefore, be argued that it is waste time, to make a bacteriological diagnosis, and merely making a needless differentiation, seeing the treatment is the same for either condition. Indeed it might be held, further, that a bacteriological examination which proves negative is leading those of us who are unenlightened to withhold from our tonsillitis patients a valuable therapeutic agent!

The writer, who, by the way, is anonymous, maintains he has had such constant and striking results with this line of treatment of non-diphtheritic tonsillitis that he states it is his custom to guarantee to make his patient comparatively well again within 12 hours.

One has not had such uniformly good results in cases of tonsillitis which were treated by antitoxin, and later came to hand the negative report of the swab. Some cases may be benefitted, but one would suggest that these are of the 29% of diphtheria cases which show a "negative swab" at the first examination, and referred to above.

Whilst not wishing to doubt the accuracy of the above writer's statements regarding his own experience, one cannot help feeling it strange that such an apparently valuable remedy for tonsillitis has not found its way into any of the standard works on this subject which one has consulted.

Any beneficial effect present is hardly likely to be due to the antitoxin; ordinary horse-serum, which he states he has not tried, is likely to give equally good results, if any.

Moreover, if one were to omit bacteriological diagnosis, on the score mentioned, many mild cases of diphtheria would go undiagnosed, and so would occur all the dangers incident to such an incorrect diagnosis - danger to the patient through improper treatment, and to the community through the possibility of the patient's becoming, later, an unknown "carrier" of the disease.

The last objection one would urge against such a line of treatment is that if every patient with tonsillitis is to receive antitoxic serum, if the patient does later take diphtheria, there is going to be considerable risk of anaphylaxis. The occurrence of this unfortunate phenomenon would become much more common, and many cases of diphtheria would occur in which one would hesitate to use antitoxic serum owing to their having received it already in the treatment of a previous attack of tonsillitis.

Apart from the question of the efficacy of antitoxic serum in tonsillitis, this last argument urged is quite an important one in favour of the use of bacteriological diagnosis in this disease. It might be argued that serum is often given just in case a certain sore throat should turn out to be diphtheria, and that, as frequently such a case proves not to be one of this disease, diphtheria does occur in the same patient, later, there will be a danger in employing specific treatment. If, however, bacteriological diagnosis were first made, an unnecessary exhibition of the specific serum might be saved. There are however flaws in such reasoning which one has already considered.

2. QUESTION OF THE TENDENCY TO NEGLECT OBSERVATION.

A further argument against the employment of bacteriological diagnosis in this disease is that the use of such a method leads the practitioner to place too much reliance on the test and to a certain amount of "atrophy of dis~~ease~~use", of his powers of observation. There are many now in practice who have been taught that there are many cases which appear, clinically, to be diphtheria, yet are not cases of that disease, and vice versa. Not only have they been taught this but it has been impressed upon them. Even a recent medical text-book states that: "An examination of the membranous exudate is the only reliable method of diagnosis". Whilst there is a sense in which this is true, it is dangerous doctrine.

Man always hankers after something infallible. "Rules of thumb" have a great attraction for most of us. And in Medicine there are no "rules of thumb". Bernard Shaw is nearer the truth than usual when he says "There is only one Golden Rule, it is that there are no Golden Rules". It's very true in Medicine.

Yet through the desire for something definite, and inspired by teaching such as that mentioned, there are many who sacrifice clinical observation through a touching faith in that distant bacteriological laboratory.

And there are many laboratory workers who think that even out of the mouths of test-tubes and Petri dishes, they can make a perfect diagnosis. When Falstaff[133] asked his page, "Sirrah, you giant, what says the doctor to my water?", the boy replied, " He said, sir, the water

itself was a good healthy water; but for the party who owned it, he might have more diseases than he knew of". There are many such doctors in these days. Entrenched in the laboratory, they are quite prepared, without seeing the patient, to diagnose the existance of many diseases, e.g. diphtheria, when maybe the medical attendant never even suspected it.

One has given an account of the early faucial appearances in this disease, and the clinical findings on which one relies for an early diagnosis. One hopes, further, that one has made clear the grounds for one's belief in the possibility of making a fairly accurate early diagnosis, on clinical grounds.

But the price of ability to do this is constant and careful observation. It is just this ability, however, which fails to develop when the practitioner, impressed with ideas mentioned above, takes a hurried glance at the throat and says "Oh, I'll take a swab" - an attitude pregnant with danger to the patient's health, - and to his life.

It is just this attitude, too, which F. H. Thomson[134], is bemoaning when he writes "It is rare for patients to have had antitoxin before admission to hospital, and still rarer for an adequate dose to have been given. The practitioner suspects diphtheria, sends a swab to the bacteriologist - and waits". And writing again, in the same journal, to the effect that cases come into hospital far later than is desirable for adequate treatment, he[135] suggests that although the reason may be, in part, that the parents don't call in the doctor early enough, it is due in large measure to

the practitioner awaiting the result of the bacteriological examination before commencing specific treatment, or sending the child to hospital.

Experience at Blackburn only bears out what Thomson has said. Of the cases one has investigated, omitting 8 cases which were very mild or carriers and which gave a history of being affected for more than 5 days, on an average they had been ill 3½ days before admission. It seems hard to always blame the practitioner, but in twenty cases into which the duration of medical attendance was specially enquired, one found, on an average, that the doctor had been in attendance 2½ days before sending the child to hospital. And in only 10% of cases had antitoxin been given at home.

3. THE QUESTION OF TIME.

One of the greatest objections to reliance on bacteriological diagnosis in this disease, however, is the time factor. The importance of this has already been mentioned, so that little more need be said here. It is, however, of such significance as to merit comment under a separate heading.

It may be argued that an absolute bacteriological diagnosis is not possible in less than 48 hours, (12 hours for culture, and 36 hours for animal inoculation), even if a laboratory exist on the spot, and that if specific treatment is to await such a diagnosis, the chances of successful therapy are much diminished. This is graphically demonstrated in Chart 2. Ker[136] in his book "Infectious Diseases" makes a statement the importance of which it is quite impossible to exaggerate: "I have never", he says, "seen a fatal result in a case

which developed in hospital, and in which injection was practised on the first day of the disease". The significance of such a statement is striking. It would be well burned on the mind of every practitioner.

Against such an argument as the above, however, there are several facts to be weighed. Thus it has already been shown that in three fourths of the cases in which the cultural examination proves to be "positive", an examination of the direct smear would have given the same results. This is only a matter of five or ten minutes.

Furthermore, if the methods of the American workers quoted (regarding the use of "little plate cultures" in diagnosis) prove to be as reliable as they promise to be, bacteriological diagnosis to the extent generally proceeded with, (i.e. examination of cultures), is possible in five hours#. This would not cause a very serious delay in the exhibition of specific treatment, whilst at the same time it would give very valuable, and, in some cases, indispensable, help in diagnosis.

And then, also against this objection now being discussed, there are several factors which, it is hoped, have been made clear during one's criticism of arguments raised in other sections of this thesis - and to enter into which here, would be needless repetition.

ARGUMENTS IN FAVOUR OF THE USE OF BACTERIOLOGICAL DIAGNOSIS IN THIS DISEASE.

Under this heading but little need be said, as one has endeavoured, at least, to make clear one's views on most aspects of this subject in one's criticism of the

arguments against the employment of bacteriological diagnosis.

One would, however, mention several main points, and one or two minor considerations to which one has not yet referred.

A. ARGUMENTS CONCERNED WITH THE WELFARE OF THE PATIENT.

DIFFICULTIES IN CLINICAL DIAGNOSIS.

Although at one extreme we have people like Drinkwater, who affirm that they can diagnose the disease from clinical examination alone, most of us have to admit that, in spite of a consideration of the many valuable clinical signs and symptoms one has shown to be present even in the early stages of this disease, not infrequently we are left in doubt as to the diagnosis. Bacteriological examination will settle this matter well-nigh finally.

1. THE QUESTION OF THE MILD CASE.

Particularly is this difficulty present in mild cases of the disease, which in some epidemics are numerous, and cause similar harm to the community as the "missed case" of Scarlet Fever - an important fact to which we shall need to return later.

There are some throat affections in which no membrane is present, the child perhaps has a sore throat and feels rather "out of sorts". Bacteriological diagnosis reveals the presence of b.diphtheriae, and whilst some would treat the condition lightly, arguing that the presence of the organism, (if it really is the b. diphtheriae), is a mere accident, and not the pathogenic agent, one feels such people

are "skating on thin ice". One would not like to be responsible for witholding antitoxic serum from such a case. One admits the possibility of the b.diphtheriae being merely superimposed on such a morbid condition of the throat, but the condition may become aggravated at any time - and if it does who is to say when the diphtheria bacillus has come into action and at what stage the other organism, e.g. the streptococcus has ceased to dominate the scene?.

One has seen, too, cases of paralysis, in the Sick Children's Hospital, in which the only history was a mild degree of sore throat a few weeks before and where there was no more evidence in favour of diphtheria than of polio-myelitis as the disease responsible for the paralysis. Such condition would probably never have developed if bacteriological methods of diagnosis had been employed and antitoxic serum administered.

2. THE QUESTION OF FORMS OF THE DISEASE OTHER THAN FAUCIAL.

A further argument in favour of the use of bacteriological methods in the diagnosis of diphtheria lies in the fact that it is frequently very difficult, and indeed often impossible, to identify certain non-faucial forms of the disease, apart from the employment of such methods.

Thus the difficulty of an early diagnosis in laryngeal diphtheria has already been considered. Until marked symptoms of obstruction appear the clinical findings are commonly insufficient to distinguish this disease from any other form of laryngitis (e.g. that of measles). Even when symptoms due to obstructed inspiration

are present, one has shown that there are several other diseases with which it might well be confused. And although a careful examination of the throat will commonly reveal the presence of membrane, and so lead to a correct diagnosis, this is often absent.

Bacteriological examination, however, will frequently make the diagnosis clear, and so be, quite likely, the means of saving the patient's life, and of preventing the spread of the disease to others.

The same things may be said, mutatis mutandi, of bacteriological diagnosis in nasal and other forms of diphtheria. Bacteriological diagnosis is of special importance, in these forms, from the standpoint of preventive medicine.

3. THE QUESTION OF SEVERE FORMS OF THE DISEASE WITHOUT MEMBRANE.

Another factor, testifying to the practical value of bacteriological diagnosis in this disease, arises out of the fact that a severe form of the disease may occur in certain peculiarly susceptible people without membrane formation for 24 - 36 hours. The local and general symptoms are marked, there may be a rash present, suggesting scarlatina. The patient is obviously very ill indeed, if the case is diphtheria it is likely to proceed to a fatal issue, unless specific therapy is early exhibited. The clinical findings are generally insufficient to warrant an accurate diagnosis, which generally lies between diphtheria and scarlet fever.

The examination of a smear preparation may, at once, clench the diagnosis, and so indicate the correct line of treatment and prevent spread of the malady.

4. THE QUESTION OF OTHER MEMBRANOUS THROAT AFFECTATIONS, NOTABLY VINCENT'S ANGINA.

And them, too, it might be argued that bacteriological methods of diagnosis are indispensable, owing to the fact that membrane is sometimes found in the throat, during other diseases, which it would be impossible to smear was not diphtheritic apart from bacteriological examination. Thus, amongst other diseases in which an apparent membrane may be present in the throat, there are :- Vincent's Angina, Thrush, Scarlet Fever, Herpes, Tonsillitis, Quinsy, Syphilis, Small-pox and Typhoid fever.

The clinical appearances are, however, generally distinctive and it is against just this argument that Drinkwater, and many whom he represents, are up in arms when they declare they can accurately diagnose the disease by a consideration of the location of the pieces of membrane.

True as this may be in most of the diseases mentioned, one feels one must make a very definite exception to Vincent's Angina, and admit that one can lay no claim to ability to diagnose that condition apart from bacteriology.

It is just here, however, that bacteriological methods are invaluable. The recognition of the fusiform bacilli and spirilla, (constantly associated with this disease), in the direct smear, makes the diagnosis clear in a few minutes. We see, therefore, that Bacteriology is in these mild and in these typical forms of the disease, what Ker calls "the final court of appeal".

B. ARGUMENTS AFFECTING THE WELFARE OF THE COMMUNITY.

1. DETECTION OF THE, OTHERWISE, UNKNOWN CASE, WHICH MAY BECOME A CARRIER.

When a person has had diphtheria, the causal organism remains in the individual's throat for a short or long time. It may remain in the throat of the person a very long time. Such a person is called a "carrier" and is a danger to the community, inasmuch as he is liable to convey the disease to anyone with whom he comes in association. If a person is known to have had diphtheria, the State is aware of his location and can take measures to prevent his conveying the disease to others, so long as he is harbouring the germ.

The mild case, however, which through lack of bacteriological examination goes undiagnosed, and the other varieties of diphtheritic infection, (such as nasal), which, for various reasons just enumerated, are not recognised as being diphtheritic - these cases, on recovery mix freely with the rest of the community. Some of them, however, are "carriers" and convey the disease to others.

Such cases would have been discovered if bacteriological methods of diagnosis had been employed, and due precautions could then have been taken. But without the aid of Bacteriology it is commonly impossible to accurately diagnose the condition.

For reasons which will be given later, one is of the belief that one of the chief factors responsible for the continued heavy incidence of diphtheria is the "mild", "missed", and "unrecognised" case of this disease.

It is necessary to mention this matter here, though, because it forms one of the most powerful arguments in favour of the routine employment of bacteriological diagnosis.

2. DETECTION OF UNKNOWN CARRIERS.

It is in the detection of the otherwise unknown carriers, however, either amongst contacts or others, that bacteriological diagnosis is invaluable. It is, therefore fitting to make note of this matter under this head. One's views however on a factor of such paramount importance in the control of diphtheria will be more properly considered in a further section of this thesis.

PRACTICAL CONCLUSIONS.

It will be evident, from the review and criticism of arguments one has just given, that much can be said on both sides, regarding the value of bacteriological methods in this disease. Indeed it is like every other branch of medical science, the more one studies it, the more involved and complicated it becomes; and the more one feels that almost every statement one makes needs to be hedged around with safeguards, with provisos, and with conditions.

There are certain conclusions to which for practical purposes, however, one must come. And there is sufficient evidence to make one feel emphatic regarding most of them.

TREATMENT. The whole essence of treatment is immediate administration of antitoxic serum.

This is so vital a matter that the mistake of

giving serum, to a case which proves later to be non-diphtheritic, is as nothing compared with the failure to at once exhibit specific therapy in a case which does prove to be diphtheria.

In so far as the employment of bacteriological methods of diagnosis delays early treatment of the disease, it is a bad thing.

In any case, clinical methods of diagnosis of an early case are as likely to lead to as correct a result as bacteriological methods, e.g. many cases of the disease give, at first, a negative swab. "The first duty of the practitioner is to treat a doubtful case, after which he is at liberty to diagnose it". (Ker[137]). In ill people, if a throat is so suspicious as to merit the taking of a swab, it is suspicious enough to call for the administration of antitoxin.

From the clinical aspect, bacteriology in this disease is a good servant but a bad master.

It must always be regarded as merely an aid to diagnosis and not THE one factor.

The great danger is to fall from clinical observation and sane judgement, into the ~~rest~~ rut of a mechanical routine.

So great is this danger that there are those who even say that were it not that the finding of the diphtheria bacillus later gave to us antitoxin, it is a pity the causal organism was ever discovered.

In mild and typical forms of the disease, however, bacteriological diagnosis is of special value.

PREVENTION. But bacteriological diagnosis has its greatest sphere of usefulness in the prevention of the

disease. Here, indeed, it is indispensable.

Its importance lies in the fact that only by this means are we able to detect mild cases and carriers, and determine how long they are of danger to the community. But a fuller discussion of this subject will be made when one considers the question of prophylaxis.

ETIOLOGY,

MODES OF INFECTION

and

PREVENTIVE MEASURES.

I. INTRODUCTORY.

II. THE SOIL. i.e. THE HUMAN ORGANISM.

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2. SEX.

3. HEREDITY.

B. FACTORS WHICH CAN BE MODIFIED.

1. BY NON-BACTERIOLOGICAL AND NON-SEROLOGICAL MEANS

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(a). Vaccines.

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(c). The Schick-test and Toxin-antitoxin inoculation

C. THE SCHICK TEST AND ITS SIGNIFICANCE.

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2. RELATION TO ADMINISTRATION OF ANTITOXIC. SERUM IN CONTACTS.

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D. TOXIN-ANTITOXIN INOCULATION.

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1. MAN THE GREAT RESERVOIR OF THE GERM. HIS OWN ENEMY.
2. A CONSIDERATION OF THE POSSIBLE INFECTIVE SOURCES.
   (a). Faeces, (b) Urine, (c) Perspiration and Milk.
   (b). Throat, Nose and Ears, THE source.

D. THE RELATIVE IMPORTANCE OF VARIOUS TYPES OF CASES AND CARRIERS IN THE SPREAD OF THIS DISEASE.

1. FREQUENCY AND SIGNIFICANCE OF VARIOUS TYPES OF CASES AND CARRIERS.
   (a) Ordinary cases.
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B. ISOLATION OF PATIENTS.

C. DISINFECTION ETC.,

D. THE DETECTION OF CARRIERS.

E. ISOLATION OF CARRIERS.

SCHOOL CLOSURE.

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1. BY LOCAL APPLICATIONS.

2. BY GENERAL MEASURES.

3. TONSILLECTOMY ETC.,

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1. INTRODUCTORY.

The numerous facts and theories which fall to be considered, under this section of this thesis, can be classified in many various ways.

The most orthodox classification would seem to be :-
1. Notification. 2. Isolation. 3. Disinfection.
4. Detection and treatment of carriers.

It will, however, perhaps bring out the authors' views in the most clear and systematic manner if one considers this subject under the headings:

1. The Soil i.e. the Human Organism.
2. The Seed i.e. the Diphtheria Bacillus.

The process of infection does bear striking resemblance to the development of seed in soil. Certain conditions of the soil and certain conditions of the seed are necessary for growth of the plant. Transferring then our thought from Botany to the subject of diphtheria, it will be clear that if we can so alter the soil, or so destroy, attenuate or otherwise control the virus, and thus prevent the seed flourishing, we shall be in a fair way of preventing this disease, which is still so great a scourge to the community.

No system of classification, of the various preventive measures against this disease, is perfect or complete, and many facts and arguments set out for convenience under some sub-divisions of this subject, need to be borne in mind in considering other aspects of the subject though they be not expressly set out thereunder. Moreover as it was necessary to consider several points which bear on prophylaxis under "Bacteriological Diagnosis",

the conclusions there established will be taken for granted, in what follows, without further discussion.

Numerous monographs have been written on the subject of the prevention of this disease. Probably it is the vastness of the subject which causes most of them to be confined to just one aspect of it. Such a procedure tends to warp judgement and it will be one's endeavour in this thesis to present a survey of the various factors affecting this question, considering, in some detail, those measures of control one has come to regard as most important, whilst only touching on factors in prevention which are without practical bearing.

2. THE SOIL. i.e. THE HUMAN ORGANISM.

A. FACTORS WHICH CANNOT BE MODIFIED.

Proceeding then, now, to a consideration of the soil i.e. the human organism, we find several factors which are weighty but which cannot be modified directly.

1. AGE. One of these is the age of the patient. (See Chart 7) That 75%[138] of cases are between 1 and 14 years of age is a fact that must have great significance which we shall need to consider later. But we cannot alter the age of our patients.

2. SEX. No more can we alter their sex, although in this country girls are more often affected than boys, the proportion in the Blackburn series of cases being 54 to 46.

3. HEREDITY. is another very important factor. Lenner[139] lays great stress upon family constitution as being "one of the most important elements favouring

the development of the disease and determining its progress".

Morell Mc.Kenzie[140] gives a striking instance of family susceptibility which came under his notice. "Four families occupied a house near Woodford, in Essex. In all of them there were several children. Two of the families were related, the mothers being sisters. All the children who were related to each other had diphtheria severely, whilst the children of the other two families escaped entirely. During the progress of the disease no attempt at isolation was made, the healthy children frequently entering the rooms of the patients".

Although one has classed heredity as a factor which cannot be modified, there is evidence suggesting it may not always come under that head:-

Dzierzgowski[141] carried out a series of experiments on the inheritance of acquired diphtheria immunity, using hens for his investigation. The immunity was produced by first injecting antitoxin only, and later combined toxin and antitoxin. During the time when serum was being used, the eggs laid contained no antitoxin, but in those laid after toxin and antitoxin had been injected, antitoxin could be demonstrated in the yolk. The blood of the chicks hatched from some of these eggs contained antitoxin.

This is suggestive and may come to assume practical importance. Since the introduction of the Schick Reaction we have been producing immunity to Diphtheria by means of injections of toxin-antitoxin mixture.

Sufficient time has not yet elapsed to allow us to generalise and say whether or not the production of immunity in the parent will produce a lasting immunity in the offspring - in contrast to the present very transitory immunity. In the work of Dzierzgowski, however, we have some promise of what may possibly prove to be of importance in our fight against this disease.

B. FACTORS WHICH CAN BE MODIFIED.

1. BY NON-BACTERIOLOGICAL AND NON-SEROLOGICAL MEANS.

Passing now to factors regarding the soil which we can be more hopeful of modifying, it will be convenient first of all to consider those factors capable of being altered by non-bacteriological and non-serological means.

(a). And first amongst these comes General Health. It is a well known fact that disease generally has its heaviest incidence amongst those who are "below par". This commonly incurs in the poor. But general health has very slight, if any, influence on the distribution of diphtheria.

In 1861 Jenner[142.] wrote that in most of his cases "hygienic conditions were good; there was nothing patently bad in regard of drainage, ventilation, overcrowding, water-supply, food, or work", also most of his patients "were in the middle rank of life, and resided in good-sized houses, and in fairly open situations".

And what was true of Jenner's time is true of to-day. One has seen the fit and the unfit attacked by this disease, and in about the same relative proportions. Hygienic measures have resulted in the health

of our people being at a much higher level than it was, say, 50 years ago, the incidence of infectious disease, generally, has accordingly diminished. But not so diphtheria. If modification of the soil is to prevent the organism of that malady from producing disease it must be on different lines from attending to "General health".

(b),Health of Naso-Pharynx. There is, however, some evidence to show that conditions affecting the vitality of the tissues Locally, i.e. the mucous membrane of the throat, predispose to the disease. Thus when a case of diphtheria is introduced into a scarlet-fever ward, the scarlet-fever patients commonly take the disease - more commonly than classes of patients without faucial infection. Similarly cases of measles are very apt to take diphtheria. The explanation would seem to lie in the fact that such patients have a considerably lowered local resistance. Furthermore "insufficient air-space and defective ventilation of school dormitories and classrooms tend to produce inflammatory conditions of the throat (follicular and ulcerative tonsillitis), which in some instances, as the outbreak progresses, may be indirectly responsible for attacks of true diphtheria, probably due to the accidental introduction of the b.diphtheriae, which at once assumes virulence under the prevailing morbid throat conditions". (Parkes & Kenwood 1917)[143].

A damp atmosphere increases one's liability to colds and sore throats, since it, too, devitalises the mucosa of nose and of throat. It is not surprising, therefore, to find that Thursfield[144] observed that

diphtheria hung about certain damp houses, and that his observation was confirmed by others.

In light of recent knowledge, it would seem that the explanation of these phenomena probably is that the b.diphtheriae were probably hidden away in the tonsil, (and so harmless), all the time,but the devitalisation of the tissues locally, either through deficient ventilation or excessive humidity gave the seed its chance to flourish, and so diphtheria resulted.

Preventive measures, likely to yield a certain amount of benefit, and desirable to counteract these factors will be too obvious to call for description.

(c).A third factor which we have very definite means of controlling is the proximity of the soil to the seed. Amongst the better classes especially, the patient is often nursed at home. In such circumstances it is generally an easy matter to arrange for the susceptibles to be transferred to e.g. their grandmother's till all danger of infection is over.

(d). There is another factor which makes the soil liable to infection, and one which is often overlooked. It is the psychic factor. Why is it, taking everything into account, that doctor's don't often take diphtheria?. When a group of students first attend their course of instruction on "Infectious Fevers" there are always some who are rather tremulous, and convinced they will become victims of one of that group of diseases.

One remembers Dr. Ker set all at rest, however, by saying that a fairly sure road to immunity, for us, was to have no fear, and that of even nurses who come in intimate contact with patients, a surprisingly small

number contract infection, and those that do are mostly those who are afraid.

Certain precautions are necessary, of course, but a doctor can do a lot by quietening the mind of the household, and, by so doing, not only save its inmates from worry but even give a certain measure of protection against disease through this psychic influence.

2. BACTERIOLOGICAL AND SEROLOGICAL MEANS OF MODIFYING THE SOIL.

There are certain methods of protecting individuals from infection more specific than the general measures above discussed. These methods are bacteriological and serological in their nature.

(a).Vaccines. One has been able to find practically no published records in the literature of this country regarding the value of vaccines as a means of producing immunity, although one has been given to understand that some unpublished work was done by Benson. (Edin. M.D. Thesis). American workers[145] have been led to suggest that the administration of vaccines along with toxin-antitoxin may aid in the production of immunity.

The question of prophylaxis by vaccines, however, must be held to be sub judice.

(b).The protective value of antitoxin, one dose of 500 - 1000 units intramuscularly, to diphtheria contacts is well recognised. Here we have a powerful agent wherewith to modify the soil, and there are those who use it as a routine. Unless one is cautious however and realises that the need for bacteriological examination is not less but greater, one is apt by this

method to produce carriers who are unrecognised and so not watched. It leads also to a false sense of security, for although the immunity thus immediately produced generally lasts some four or five weeks, it is not generally recognised that persons who have received prophylactic injections have often developed the disease weeks after infection without re-infection. Thus Peters[146] (1907) found that 7 out of 21 infected contacts, who received prophylactic doses of antitoxin (500 units) developed diphtheria within 3 weeks.

But a large number of even infected healthy contacts never show symptoms of the disease, and the attempt to inject all infected contacts causes much labour, arouses much opposition (witness the outcry even against Vaccination) and involves the sanitary authority in considerable expense.

In any case the Schick test has shown us that of, even children, only 37% are susceptible to the disease. (This figure is based on the work of Gladys Ward)[147].

Furthermore there is the very serious danger of anaphylaxis if the disease does develop more than 10 days after the administration of a prophylactic dose of serum, for this would necessitate the exhibition of a further dose.

In cases away out in the country, or where the parents cannot be relied upon to immediately call in their doctor on the development of the first suspicious symptom, in a contact one would give prophylactic injections.

But, if the infected contacts are under supervision, one feels such a method unnecessary, as on the occurrence of the first suspicious symptom (which may be merely a

"running nose" or a slight sore throat) one can administer appropriate protective treatment.

(c).The most potent method of modifying the soil, however, would appear to be by Toxin-antitoxin inoculation, employed in conjunction with the Schick test. There are,indeed,those who would say that this procedure will eventually be to diphtheria what vaccination now is to small-pox.

Having had no personal experience of this method one will have to confine oneself to recording and correlating the work of others.

The method consists essentially in finding out the diphtheria-susceptibles, by means of the Schick test, and in immunising them, by means of the inoculation of a standardised toxin-antitoxin mixture. The technique is fully described in a recent report by the Ministry of Health[148].

It is held that, by the means indicated, a diphtheria-proof population can be secured.

C. THE SCHICK TEST AND ITS SIGNIFICANCE

1. PERCENTAGE POSITIVE AT AGE GROUPS.

Considering the Schick test first, (quite apart from the use of toxin antitoxin inoculation), it has given us valuable information regarding the susceptibility of people to the disease. The results arrived at by many and widely scattered observers are in general agreement.

The originator of the test, Schick[149], found positive reactions (indicating susceptibility to the disease) in not more than 7% of the newborn, the numbers mounting, however, to 43% during the second 6 months of life,

and to 60% between the ages of 1 and 5 years, thereafter falling again to 50% between 5 and 15 years.

Zingher[150], working at New York, Copeman[151] in Bristol, (but after a diphtheria epidemic), Dickinson[152] at Monsall Fever Hospital Manchester, and Leete[153] and Gladys Ward[154] at the Edinburgh City Hospital (mostly scarlet fever patients), all obtained results which are fairly comparable, in view of the varying circumstances. The main figures from these researches are set out in Table 4.

It will be clear from a study of these statistics that about 50% of individuals between the ages of 6 months and 5 years are susceptible to the disease, 33% between 5 and 15 years and 20% over 15 years.

Susceptibility, therefore, gradually decreases after the age of 3 years and hence Park & Zingher[156] conclude that a negative reaction in a child that has reached that age, indicates that it has an immunity which is probably permanent. But changes in the Schick reaction from negative to positive during the first 3 years of life, owing to the loss of congenital immunity, were found by Blum[157] to be sufficiently numerous to justify re-testing, at least in large institutions, during this period.

2. The value of the Schick test will be apparent. Till lately, it has not been realised that only about 1/3 of the population can possibly take diphtheria. Therefore to employ the preventive measures against this disease (some of them somewhat elaborate and expensive) for all the population, is doing three times as much work and causing three times as much trouble as

is necessary - so these facts would suggest. Consider for instance, the administration of a prophylactic dose of antitoxin to diphtheria contacts - still widely practised by many, and often indicated.

If we knew how the various individuals reacted to this test we should only need to give antitoxin to about 1/3 of them, thus minimising the risk of anaphylaxis and also saving pain and expense.

3. The test finds practical application, too, in the case of nurses and others specially exposed to risk of diphtheria infection. The frequency with which nurses contract this disease is well known, indeed Thorne Thorne[159.] maintains that the excessive diphtheria mortality amongst females is due, at all periods of life, to greater exposure of females to infection in nursing.

Gladys Ward[157.] suggests, therefore, that no nurse giving a positive reaction should be employed in a diphtheria ward.

A similar principle would apply to home, residential school or institution.

4. Another valuable role of the Schick test is in the treatment of carriers. As will be seen later, it is desirable that carriers should be isolated. But, in view of the fact that 2/3 of the community are immune to the disease, it will be quite safe to allow carriers to mix up with such members of the population, previously determined by this test - There is an outbreak of diphtheria in a school. Several carriers are discovered. Under the old regime they will be excluded from school maybe for months - but under the new they may return,

the susceptibles being taught in another class and kept separate after school hours.

Zuckerman[160] points out its value in residential institutions of all kinds. "In a large institution, diphtheria is constantly making its appearance in the course of the winter, and in most asylums the problem of providing isolation, with the expense involved, is a difficult and ever-recurring one. This winter, using the Schick as a guide and criterion, we have placed diphtheria carriers among children who give a negative skin test, and in no instance has infection resulted" (These remarks apply to an institution containing about 500 children).

Similarly[161] in the Scarlet fever pavilion of the Willard Parker Hospital, New York, 1,200 patients were tested and of these 556, or 46·3%, gave a negative reaction. Although the negatively reacting patients were in contact with cases of diphtheria, developing amongst the Schick positives, none developed clinical diphtheria.

The same facts are borne out by Leete's[162] observations. Amongst the 500 cases of scarlet fever he examined, 11 cases of diphtheria developed. One of these had given a doubtfully positive Schick, the other 10 were definitely positive. No negative Schicks developed the disease.

In a ward of 3 beds, one case developed diphtheria; his two neighbours (aged 2-3 years), having given negative Schicks, were not immunised. Neither developed the disease.

These observations are sufficiently convincing to

make one feel quite safe in allowing carriers to mix with negative "Schicks", and so able to largely remove, what have previously been, irksome restrictions.

5. A likely further use of the Schick test one has suggested in the section of this thesis devoted to Early Symptoms and Diagnosis. The principle outlined there may have a value in deciding whether a patient is a carrier or is really suffering from diphtheria. A patient may have a nasal discharge or a sore throat and give a positive swab. If, however, we know he is a negative Schick we shall be able to decide that the patient is only a carrier and not really suffering from diphtheria. But personally, if the affection were severe, one would risk being unscientific and give antitoxic serum.

As in most other tests, so in the Schick Reaction, careful technique is essential. Thus Leete's first series of observations were found of little worth for 2/3 of the positives were found to be giving a negative reaction. This was found to be due to the fact that the toxin used, though bought from a large drug firm, had been too weak.

6. But the greatest field of usefulness of the Schick reaction promises to be in determining susceptibles with a view to the production of IMMUNITY by means of toxin-antitoxin inoculation, several points concerning which we will now consider.

D. TOXIN-ANTITOXIN INOCULATION.

1. An illustration of this, the latest preventive measure against this disease, is given by Eagleton[163.] in a paper read to the Royal Society of Medicine recently:

of 329 children, (aged 3 to 16 years), at a residential school at Mitcham, 102 i.e. 31% gave a positive Schick reaction. These were inoculated with toxin-antitoxin mixture.

Eleven weeks later the test was repeated on 99 of the 102 inoculated children - 3 having left the institution in the meantime. Only two still gave a positive reaction, 98%, therefore had been made immune.

2. When Eagleton published his paper sufficient time had not elapsed for him to be able to say whether his work had rendered the institution free of diphtheria for any considerable period, but Blum[164] made observations in a home for infants, (529 inmates), where diphtheria had been endemic as late as 1915. Immunisation was carried out on the 37% susceptible children and the institution was diphtheria-free up to the time of his writing (1920), i.e. for five years.

Then, too, Parke and Williams[165] say of their work on this subject: "The best results were obtained with the full immunisation, consisting of 3 injections of 1c.c. each, given at weekly intervals. The duration of the active immunity was studied in a group of children, followed up for over 3½ years; these cases indicating that the active immunity persisted for at least that length of time".

The Schick test was only discovered in 1913. Toxin-antitoxin inoculation has been employed for a still shorter time. Therefore one cannot yet say how long artificial immunity will last but the above findings point to its being of considerable duration -

at least five years.

This method of preventive treatment has been in general use in New York for several years now. The fact that in 1921 there were 1,852 less cases than usual, and 155 less deaths[166], is valuable testimony to the efficacy of this hygienic measure.

All these facts, therefore, go to show that we are here dealing with a preventive measure of the greatest importance.

3.Toxin-antitoxin immunisation, however, does not solve all our difficulties. Mention will be made of what appear to the author to be its main drawbacks and limitations.

(a).It takes 5 - 6 months to develop maximum artificial immunity by toxin-antitoxin inoculation, therefore immunisation of the members of a house or institution where a child has developed diphtheria will need to be done by means of antitoxin- if at all.

(b).Toxin-antitoxin inoculation does not always result in immunity, 5% of cases remain susceptible[167]. There is thus a danger of false security being produced if the individuals are not re-tested (by means of the Schick test), about six months after inoculation.

(c) Although evidence has been given which suggest that the immunity produced by the above means is long lasting, there has not been sufficient time for us to be sure of this point. There are facts which are against it. When a person suffers from a thorough-going attack of diphtheria i.e. receives a very adequate dose of both toxin and antitoxin, he is not always thereby rendered immune

to the disease for life. Moreover Johnson found that many cases which had had diphtheria (3 or more years before), frequently gave a positive Schick reaction.

Leete[169.] was led to the conclusion that good toxin in competent hands gives a 1% - 2% error. He found that one of the hospital staff who had given a negative reaction, took the disease all the same.

A consideration of these facts should lead us to act with caution till time has allowed more evidence to accumulate.

(d) Furthermore there is the danger of the production of an increased number of carriers. Toxin-antitoxin does not seem to prevent the lodgement of the diphtheria bacillus. Infection with the organism would commonly produce the disease, (in the ordinary or in the mild form) amongst the members of an ordinary population, and so the authorities would be on their guard and prevent the confluence of any resulting carriers with the rest of the community. But, in the case of a partially immunised population, many individuals will become infected, harbour the bacilli, and, not becoming frank cases of the disease, be undetected carriers. Hence ill-results are likely to follow owing to their sowing the virus amongst non-immunised members of the community. Therefore if inoculation is ever adopted as a routine for a section of the population (e.g. in institutions), more attention and not less will need to be given to the detection of carriers.

That this is a consideration of practical importance is borne out by the fact that although none of the 556

negatively reacting individuals referred to on page 112 took diphtheria (when exposed to infection), 111, i.e. "20% became carriers of diphtheria bacilli - in many instances of virulent type".

(e) It must be remembered, too, that Toxin-antitoxin inoculation is not always without untoward results. Under the age of five years, as a rule, there is neither local nor constitutional reaction but older children and adults may exhibit reaction. "General symptoms of malaise, with a temperature of 100° to 102°F., were noted in 10 to 20% of the cases; in a few the temperature rose to 104°F. The symptoms generally last from 24 to 48 hours, and then rapidly subside. In certain cases superficial abscesses developed". (Park & Williams[169]).

All recovered, however, and although the literature shows that some writers have laid some very serious results at the door of inoculation, no fatalities are on record.

But the influence of all this upon public opinion needs to be borne in mind before launching out on any wholesale scheme of toxin-antitoxin inoculation, as some would suggest. Already, indeed, there has been a certain amount of opposition raised in Parliament to the work at the institution at Mitcham, talk of "experimenting upon the children of the poor" - and so forth.

One only needs to remember how this enlightened twentieth century opposes that great boon to humanity - vaccination .....

4. RANGE OF USEFULNESS

It will be clear, therefore that this preventive

measure has its drawbacks and limitations, and that it is not as wise to employ it universally as might first appear.

What is the range of its usefulness?.

There would appear to be two main indications for the employment of this measure:

(a) In the case of nurses and others specially exposed to risk of diphtheria infection.

All who give a positive Schick should be immunised. The measure promises to be invaluable in these circumstances.

(b) During an outbreak of diphtheria in institutions or residential schools. Here the application of the Schick test will enable one to select the susceptible children, who may be only 20 - 30% of the total, and immunise them with toxin-antitoxin. It will thus be possible rapidly to control an outbreak. The individual thus acquires an immunity likely to last for years, and such an institution would, in a short time, contain a population immune to the disease, and therefore would run little risk, if infection should again be introduced.

Formerly each child, including the 75% non-susceptible, received antidiphtheritic-serum, which gave but a short period of immunity (3 - 4 weeks) and a risk of anaphylaxis.

But in America, Toxin-antitoxin inoculation is used most extensively, and Zingher goes so far as to maintain that all infants under 12 months, and if possible all under 18 months, should be immunised irrespective of their Schick Reaction, and that all

youths and adults who give a positive Schick should be immunised.

5. WISDOM OF PRESENT ATTITUDE OF MINISTRY OF HEALTH?

The Ministry of Health, would appear desirous of following America and of using this measure over a much wider range than that suggested above. One views with some alarm the suggestions contained in their Report. Copeman[172] writes "In view of the high morbidity and mortality from diphtheria of children under five years old, active immunisation of as many children as possible between the ages of 6 months and 2 years especially, would seem to be desirable".

And again, speaking of this method Buchanan[173] says "The object of its adoption is not the separation from the population of infective cases and carriers; it is assumed that risk of infection from such cases must always be considerable and to a large extent beyond control, and it is consequently considered preferable to adopt a method which secures a substantial immunity of the general population concerned, or at least of a large part of it".

Quite apart from the storm of public opinion the wholesale employment of this preventive-measure would raise, and quite apart from several other considerations above-mentioned, one feels that the results of following the lines laid down by these Medical Officers of the Ministry would be most unfortunate.

Their policy would appear to be - Immunise the population. Never mind about carriers.

This appears to the author a case of putting the cart before the horse.

To immunise the whole population is not practical politics.

To immunise a part, and allow carriers to go about undetected and uncontrolled, will be to make the last state of our people worse than the first.

No system of prevention devised in light of our present knowledge, can be complete unless it includes measures for the detection and treatment of carriers.

3. THE SEED, i.e. THE DIPHTHERIA BACILLUS.

Passing from a survey of those preventive measures which have as their raison d'etre the modification of the soil, we will now consider those factors which have as their aim the destruction of the seed - the stamping out of existence the diphtheria bacillus.

A. LIFE OF THE ORGANISM IN THE WORLD

It will be convenient to deal first with the life of the organism in the world (as distinct from its life in the animal body). Cholera and Typhoid fever have practically disappeared from this country largely as a result of a campaign waged against the causal organisms, as they exist outside the animal body. Is there possible anything comparable in the case of diphtheria?.

The evidence goes to show that outside the body, with the warmth, moisture and darkness of its nooks and crannies, the organism is fairly short lived.

1. IN AIR. Diphtheria bacilli have not been found in even the air of a diphtheria ward, although Wright & Emerson[174], and Cobbett[175] carried out investigations, independently.

IN WATER: Montefusco[176] found the organism remained

alive in ordinary water for 20 days. Gehrke[177] found that bacilli suspended in pure water exposed to the sunlight died in 2 - 8 hours. But no recorded outbreaks show the features of a water-borne infection.

IN SOIL: Reyes[178] found that organisms in dry sand remained alive for 5 days, but in moist sand remained alive for 34 days. In dry mud they remained alive for 74 days, but in moist mud 120 days.

Soil more than 2 yards below the surface is sterile.

IN DRAINS AND SEWER GAS. "The belief is extremely widely held, particularly in Great Britain, that sewer gas is the predisposing cause of diphtheria and scarcely a case occurs, but it is attributed to "drains" by the friends, and frequently, by the medical men. But diphtheria bacilli have never been found in drains, or sewer gas, or in refuse heaps, and there is no bacteriological evidence to show that the emanations from the latter can originate true diphtheria; nor is there evidence that bad drains and insanitary environment can ever convert non-virulent into virulent bacilli:" (Graham-Smith[179]). Moreover Montefusco[180] found that diphtheria bacilli introduced into strongly polluted water (such as a drain would contain), only remained alive 6 days.

And then, too, we have the fact that during the last fifty years great improvement has been made in regard to sanitation generally. But the incidence rate and death rate of diphtheria have not fallen. An attack, as it were, has been made on the organism as it exists outside the animal body, but having been so

fruitless it has gone to show that the bacillus never flourished in the world at all.

Whilst dealing with the relation, if any, of sanitary defect to the etiology of this malady it may be as well to recall that Sweeting[181] investigated this point in connection with the M.A.B hospitals, and found that post-scarlatinal diphtheria had prevailed in like degree in hospitals with ventilated and those with unventilated soil pipes: in hospitals with automatic flushing apparatus, and in hospitals without such appliances: in hospitals with elaborate systems of ventilation and disconnection, and in hospitals where these were of the most meagre and incomplete kind.

2. EFFECT OF SUNLIGHT. It is important, too, to consider the effect of sunlight upon the Klebs-Löffler bacillus, since this is a most ubiquitous and potent germicide.

Diffuse daylight hinders the growth of diphtheria bacilli, whilst direct sunlight has a much more powerful bactericidal influence. Gehrke[182], for example, found that agar cultures were killed in 6 hours, when placed in direct sunlight and Ledoux[183] found that bacilli dried in thin layers were still more rapidly killed by direct sunlight.

It will be clear from the foregoing that when once the diphtheria bacillus leaves the human organism, unless intimate contact allows it soon to find another host, its death-knell is rung, - that the bacillus does not lead a saprophytic existence outside the animal body but gradually ~~fades away and~~ dies. The organism is practically unknown in earth or water or air, it

depends on man,(generally a carrier), for its continued existence. Here, as we are gradually coming to see to be the case in most infectious diseases, man is his own chief enemy.

We can, therefore, hope little from an attack on the life of the organism which causes this disease, as it exists in the world, (apart from its presence on certain articles which have been in intimate contact with patients or carriers, a matter to be considered later).

3. NEWSHOLME'S THEORY DISCUSSED AND CRITICISED.

This, however, is not universally admitted, and considerable attention has centred round the work of Sir Arthur Newsholme which suggests that the cause of the disease lies in the soil but can only become active when the soil becomes dry. He says[184] "I formulated the following working hypothesis of the causation of diphtheria. The specific micro-organism of this disease has a double cycle of existence. One phase is passed in the soil, another in the human organism. One is saprophytic, the other parasitic, though it is not contended there is any regular alternation between these phases" He then gives figures which purport to show that the years of greatest prevalence of the disease are the years when the rainfall is low. Chart 4. represents the Rainfall and Diphtheria death rate in London between 1859 and 1904 and is drawn from statistics given by him. It graphically illustrates his contention. It will be seen that the peaks of the diphtheria death-rate graph are roughly synchronous with the depressions on the rainfall graph.

But there are several facts which prevent one from accepting Newsholme's theory. In the first place a study of the figures giving the maximum death rate from diphtheria in each metropolitan borough over a period of years, shows that while one part of the metropolis is suffering severely from diphtheria, others are relatively exempt, these in their turn being invaded later. All these boroughs have approximately the same rainfall and stand on a similar soil and subsoil. If Newsholme's theory were true, they ought all to suffer severely from the disease about the same time. Furthermore, the disease is most prevalent in October, November and December, as is brought out in Chart 5, which shows the monthly incidence of the Blackburn cases investigated. These months are not the driest months of the year. Similarly one has found that the disease is least prevalent in this district when the rainfall is least, (April, May and June).

1921 was an exceptionally dry year. But the diphtheria death rate reached a lower level than it has ever shown for 20 years.

But not only is recent statistical evidence against Newsholme's theory, bacteriological evidence is against it. References are occasionally to be found relating to the origin of diphtheria from polluted soil, but very little evidence is to be found in support of this view, although Sharp[185] stated that he found organisms morphologically like diphtheria bacilli and having similar colonies in two soils (obtained, by the way, from a locality in which diphtheria existed). But no furthur tests to prove their identity appear to have been made.

Moreover, evidence has already been given which shows that it has been found experimentally that the organism survives longer in a damp soil than a dry soil. And Thursfield[186.] has published records illustrating the way in which diphtheria hangs about certain damp houses.

But even if in spite of all these facts, Newsholme's theory should prove to be correct - what practical preventive measure would result? We cannot alter the rainfall. Are we to build our houses on damp clayey soils, or on low lying ground? Any possible advantage it might prove to have ~~qua~~ in relation to diphtheria would be very much outweighed by its disadvantages viewed from the standpoint of hygiene generally.

We are, therefore, compelled to turn away from hopes of preventing this disease by stamping out the causal organism in water, air, or earth. One can expect more hopeful results to follow an attack on the life of the organism as it exists in the animal body. We will first consider animals other than man.

B. LIFE OF THE ORGANISM IN THE ANIMAL BODY, OTHER THAN THAT OF MAN.

1. CATS have been thought to harbour the causal organism of the disease and to transmit it to human beings. Simmons[187.] reports a case of an elderly woman who developed diphtheria, after fondling a cat which had been ill for a week. Virulent and morphologically similar organisms were found in both woman and cat.

Numerous instances are quoted, in the literature, of cats, apparently, communicating the disease to children. But very few of these cases have been bacteriologically examined and in none has the presence of

diphtheria bacilli been satisfactorily proved.

More recently Savage[188] examined the nose and throat of eight healthy cats and twelve kittens and found that none of the kittens had any organisms resembling diphtheria bacilli, while in five of the eight cats organisms more or less closely resembling Klebs-Löffler bacilli were found, but with one possible exception were definitely not diphtheria bacilli. Examination of five cats associated with human cases of the disease showed no anatomical lesions resembling diphtheria, and no definite diphtheria bacilli. Experiments on young kittens were exceptionally uniform and concordant, it being found impossible to infect them by throat swabbing, though very massive doses were invariably used.

Savage concludes that the common view that cats can suffer from diphtheria is entirely unfounded and is based on an insufficient examination and differentiation of the bacilli, due to failure to realise that a large proportion of normal cats contain in their throats organisms which closely resemble true diphtheria bacilli.

One may therefore exclude cats as a reservoir of the virus of this disease and as being anything other than a negligible means of spread. It still finds a place however in systematic teaching and serves to mislead the medical student.

2. FOWLS ETC., Experimental investigation[189] has shown the same to be true of fowls, pigeons, turkeys and horses, in spite of clinical observations to the contrary.

3. COWS. The occurrence, or otherwise, of the organism in cows and their mammary secretion requires

special consideration as it has close bearing on the preventive measures necessary in milk epidemics.

(a) Do cows really suffer from this disease?

The evidence is somewhat conflicting. Klein's[190] experiments lead to the conclusion that cows can be experimentally infected with diphtheria, and that as a result of the infection certain lesions may be produced on the teats and udders which contain diphtheria bacilli, and that diphtheria bacilli may be present in the milk apart from these lesions. The experiments of Abbott[191] and of Rilter do not, however, confirm Kleins observations, and most of those who have criticised these experiments hold that there is no evidence that diphtheria is a bovine disease.

(b) Infection probably superadded and of human origin. The general opinion appears to be that although very occasionally the organism has been isolated from naturally acquired lesions of the teats (2 recorded cases[192]) and from the milk (4 recorded cases[193]) the organisms are invariably of human origin, and introduced on to the teats by the milker, into the kits by the farmer or into the milk by the dairyman.

In view of the disgusting conditions under which the nations most important food is at present often obtained, there are plenty of opportunities for this to occur.

One has watched milkmen, for instance, at their work. A very usual procedure is for them to spit on their hands when they begin milking a fresh cow.

A farmer has recently informed one that several of his neighbours never dream of washing their hands before

milking, and that as they milk better with moist hands, they often moisten them with milk from their pail! This almost amounts to washing their hands in the milk - hardly a sanitary procedure. Doubtless milk is contaminated in some similar way, also, in the process of retailing it from carts, dairies or milkshops.

When one considers further that when investigation of milk epidemics have been made, diphtheria bacilli have frequently been found in the throats of those connected with the production and distribution of milk, (Chase[194], Littlejohn[194], Robertson etc[195]), and also that Eyre[196] has shown that milk at ordinary temperatures is a suitable nidus for the multiplication of diphtheria bacilli, - when one considers these facts, one is led to conclude that even in the case of milk epidemics the real culprit is not the cow but the carrier.

Eyre[197] has shown that organisms morphologically and culturally identical with b.diphtheriae are common in milk. The numerous observations affirming the presence of the organism in milk are due to virulence experiments having been rarely undertaken. As indicated above, the virulent organism has only been isolated on four occasions. But nevertheless the epidemiological evidence that milk is sometimes a cause of the spread of this disease is conclusive: Littlejohn[198] reported a milk outbreak in Edinburgh and Liberton.

At the dairy supplying some of the milk shops in these places, a young man was found assisting at the business suffering from unrecognised diphtheria. And the point is that as soon as the suspected milk was stopped,

the outbreak came to an end.

The literature abounds with similar cases.

That outbreaks due to this cause do occur, may therefore be taken as proven; one must remember, however, that compared to those due to direct contact with case or carrier, they are very rare.

(i) Features of milk epidemics. One would suspect the milk supply as a cause of an outbreak if no source of personal contact could be discovered, and especially if cases were arising, apparently, independently of one another.

Several features of milk outbreaks, given us by Dr. Graham-Smith in his Bacteriology lectures are:

1. They have a sudden onset. The milk may just be infected once, and so give rise to a small short outbreak, or the infection may be repeated and the outbreak lose its original character by secondary cases.

2. The route follows the milk track, if the milk is delivered by a cart as in most English towns, if from a dairy, the houses affected will be likely to be located round that centre. A "spot-map" might give an invaluable clue.

3. Better class houses are more attacked, because the tenants are more able to afford an ample supply of milk.

It is, of course, as useless to examine suspected milk for the diphtheria bacillus as it is to examine water for b.typhosus during an outbreak of typhoid fever.

(ii) Preventive measures: Having discovered a diphtheria outbreak due to a certain milk supply, the preventive measures to be adopted are obvious. - Course the milk to

be boiled before distribution, or, better, stop the supply, until the source of infection has been discovered, and removed from contact with the food as long as necessary (Infectious Disease Prevention Act 1890). This implies the bacteriological examination of those who are connected with the cows, the dairy, and the distribution of the milk, and the isolation and treatment of the infected person, when discovered, on the lines mentioned below.

B. LIFE OF THE ORGANISM IN MAN.

1. MAN THE GREAT RESERVOIR OF THE GERM. It will have become increasingly clear from a study of the foregoing that, in the author's opinion at least, the great reservoir of the causal organism of diphtheria (and probably the only one), is Man himself.

The fact that the disease is sometimes spread by milk, did seem to suggest that there was one exception at least, but even this apparent exception when it is studied more closely, is seen to vanish into thin air, and leave us with Man harbouring the Microbe. The principle of preventive measures must depend on this:- the enemy is within the gate.

We are led to this conclusion by a process of exclusion: air, water, soil, drains, sewers, cats, kittens, fowls, pigeons, turkeys, horses, cows - all have been examined for the organism, but, to all intents and purposes, in vain. On the other hand, one has shown the organism to be frequently present in the human subject, that this frequency increases with the proximity of the subject to a source of infection, and that cases of the

disease are rare except in people who can be proved to have been in direct or indirect contact with a previous case or a carrier.

It may, therefore, be taken as established that the disease owes its continuance to the presence (often undetected) of the causal organism in man.

2. A CONSIDERATION OF THE POSSIBLE INFECTIVE SOURCES.

By means of which secretion or excretion is the disease conveyed?

(a) The faeces might be thought a likely agent for the spread of the virus in view of the facts that diphtheria is an affection of the upper portion of the alimentary canal, and that present methods of attacking the cause of the disease meet with only modified success.

Such a hypothesis is supported, too, by a consideration of the fact that the incidence of the disease on rural districts has been greatly diminished since greater precautions have been taken re the disposal of excreta and the purity of water supplies. Any influence of sanitation on the incidence of the disease in towns may be masked by the increased opportunities of droplet infection.

Table 5 brings out the increased incidence in urban districts and the decreased incidence in rural districts, during the late years.

Furthermore Schoedel[199] observed diphtheria bacilli both in the lower ileum and in the freshly passed faeces of persons suffering from diphtheria.

There facts are in favour of the faeces being a possible mode of spread of the malady.

Süsswein[200], however, was unable to detect the

organism in either gastric or intestinal contents of 15 cases (examined during life).

The bacteriological evidence is conflicting and not sufficient for one to base any sound conclusion upon.

But the facts related of the equal frequency of post-scarlatinal diphtheria, in both sanitary and insanitary hospitals, is against infection through faeces. And then, too, there are no recorded outbreaks with the features of a water-borne epidemic, and such an epidemic would be likely to occur if faeces were infective.

(b) The evidence regarding the urine being a mode of spread is still stronger conflicting. The epidemiological evidence is, of course, the same as that for infection by faeces, and therefore unfavourable. The bacteriological evidence is still more so. Wildbagen[201] made examinations of 68 specimens of 14 diphtheria patients and on no occasion found the b.diphtheriae. It must be added, however, that Cassassa[202] claims to have found the b.diphtheriae in the urine in 85% of cases of the disease and states that the organism persists longer in the urine than in the fauces. He suggests that an examination of the urine may be necessary to detect carriers. If his statements are corroborated by others, we have been overlooking a probable mode of spread. But the epidemiological evidence, and the absence of reference to virulence, experiments, makes one sceptical.

(c) One has been unable to find any records of the examination of the other secretions-perspiration and milk. But seeing the urine gives a negative result, these are still more likely to do so.

(d) One may therefore conclude that for all practical

purposes, throat, nose and ears constitute not only A source of infection but THE source of infection, and that, therefore, this fact is the foundation on which our preventive measures must be based.

D. THE RELATIVE IMPORTANCE OF VARIOUS TYPES OF CASES AND CARRIERS IN THE SPREAD OF THIS DISEASE.

1. FREQUENCY AND SIGNIFICANCE OF VARIOUS TYPES OF CASES AND CARRIERS.

(a) Ordinary cases of the disease are, of course, a possible source of infection. That they should cause spread of the disease by in-direct contact will shortly be shown unlikely. Moreover they have little opportunity of causing spread of the disease by direct contact, because such cases are generally isolated. We need, therefore, to look elsewhere for an explanation of the sustained high incidence of this disease.

The explanation is that various classes of carriers, mostly undetected, are at large, spreading the disease amongst the community.

A study of their relative frequency and importance is essential to an appreciation of the relative value of various preventive measures.

These sources of infection can, of course, be divided into 3 main classes:

1. Convalescent Carriers.
2. Mild and Atypical Cases, and Carriers resulting therefrom.
3. Contact Carriers.

(b) Convalescent Carriers. Park and Beebe[203] in an extended research, made for the purpose of determining the persistence of the diphtheria bacillus in the throats of

convalescents, (2,566 cultures made), found that of 605 consecutive cases the bacillus disappeared within 3 days after the disappearance of the exudate in 50·25%, in 29·1% it persisted for 7 days, in 10·6% for 12 days, in 5·9% for 15 days, in 2% for 3 weeks, in 0·66% for 4 weeks, and in 0·33% for 9 weeks.

Guthrie, Gelien and Moss[204], found that of 159 carriers (virulent and avirulent), only 11(i.e. 6·9%) gave a history of having had diphtheria, and none within the previous 3 years.

Furthermore, considerable care is now taken not to discharge diphtheria convalescents so long as they are known to be harbouring the bacilli. And also, if the spread of the disease were due mainly to this class of carrier the preventive measures applied of late years against it would surely have met with greater success. In view of these facts, and further points considered under "Bacteriological Diagnosis", one feels justified in concluding, that the convalescent carrier is not the main source of infection. That he requires more attention than he is usually given will however be suggested later.

(c) The Mild and Atypical cases, and carriers resulting therefrom, appear to the author to be the great source of infection, and one has been led to conclude that the continued high incidence of this disease depends upon this fact more than upon any other.

The reason, of course, is that such cases of the disease are missed, and(unless bacteriological diagnosis is resorted to), necessarily so. They are generally

well enough to go about and, being undiagnosed, are uncontrolled. They thus scatter the virulent organisms wherever they go. Many of them become unknown carriers and so continue to spread the infection.

The clinical features of these mild and atypical cases have already been considered. The most important of all preventive measures is their detection by clinical and bacteriological observation. A slight sore throat, excoriated nares, or a running nose, or ears, may prove very important as a means of spread of diphtheria.

Thomas[217], writing of children, concludes from his large experience in London schools:

1. 80% of carriers are actual mild cases of diphtheria.
2. 12% are children from infected houses who presented symptoms.
3. 6% are cases of recrudescence after notified diphtheria.
4. 2%, only, are cases with no symptoms or demonstrable contact with diphtheria.

Also of the 159 carriers above mentioned, it was shown that only 6·9% had had the disease, and one's reasons for regarding contact carriers of minor importance will be given later. Therefore by a process of exclusion also, one is led to regard the mild and the missed case as the most important.

One has, however, already discussed the question in preceding sections of this thesis, so that no further mention need be made of it here.

(d) By "contact carriers" one means people who have come

in contact with ordinary or mild cases of the disease, and are harbouring the organism, although the bacillus has never even caused a mild sore throat or a slight nasal discharge in the individual.

The community must contain a fairly large number of carriers of this nature. This will be evident from a consideration of the conclusions arrived at by Graham-Smith[205] regarding the prevalence of the organism amongst various classes of contacts. "The statistics regarding close contacts, namely members of infected families, relatives, and attendants, show that amongst such persons 36·6% are liable to become infected, while the mean infection amongst inmates of hospital wards and institutions is 14% and amongst scholars of infected schools 8·7%. Of the latter classes, anyhow, 66 - 81% of the strains were virulent. In the throats and noses of healthy persons who have had no opportunity of acquiring them by contact, virulent diphtheria bacilli are very rarely found".

There must therefore be a big number of these carriers amongst the community. If all were to convey the disease to others, the incidence of the malady would be much higher than it is. So sure are they in Germany that the Healthy carrier does not constitute a menace to the population that it has recently been decided regarding even convalescents, that no diphtheria carrier, if otherwise healthy, is to be excluded from school longer than eight weeks after clinical recovery.

Reference has already been made to the fact that eight American workers[206] had their throats sprayed with virulent diphtheria bacilli. 7 became carriers. 4 of them

later developed diphtheria. The remaining 3 healthy carriers had ordinary intercourse with other members of the community, but no cases of diphtheria occurred in the town (Baltimore) which could be traced to them. Moss, Guthrie and Marshall[206] as a result of this and other work on HEALTHY carriers conclude "In a few words may be given our impression concerning the relation of the healthy carrier of virulent Klebs-Löffler Bacilli to the health of the community:- Although the results of our experiments indicate that the virulent organisms from the throats of healthy carriers are capable of causing clinical diphtheria, when the proper opportunity is afforded, we have not obtained evidence either from this work or our previous study of carriers that diphtheria is spread by their agency under ordinary conditions. It is our belief (1) that such carriers constitute a potential menace to the health of the community but (2) that their opportunity for dissemination of the disease among their associates is quite limited, owing to the relatively small number of persons susceptible to infection and (3) that the actual part which they play in the spread of diphtheria is probably quite small".

3. THE PREVALENCE OF THE CARRIER STATE.

The question of how many diphtheria carriers there are amongst the population is difficult to answer. The number varies according to the prevalence of diphtheria, partly. Then so many workers fail to carry out virulence experiments that their statistics are not always comparable with others.

Parkes and Kenwood[207] state that, even in non-epidemic

times, 1% of the general population carry the diphtheria bacillus (mostly avirulent) in their throats. As mentioned elsewhere Sholley[129] examining the noses and throats of 1000 children attending the out-patient department of a New York Hospital and suffering from various minor maladies, found 1·8% of them harboured the virulent Klebs-Löffler Bacillus, and 3·8% the avirulent.

Guthrie, Gelien and Moss[130] examining 1217 school children found 0·66% harboured the virulent organism and 2·94% the avirulent.

The same workers examining 1290 people in the city (Baltimore) at large, found the organism present in 3·61% of the population, but performed no virulence experiments in this case.

Diphtheria is less common in this country than in America so that probably British figures would not run so high as most of those quoted.

It would appear likely however that in this country some 2% of the general population harbour avirulent diphtheria bacilli, which matters to no one, save a misguided health official, and that some 0·4% harbour the virulent organism. This means that in Edinburgh, say, 1400 people infected with the virulent organism, are let loose upon the community daily - yet only about 2 people take the disease each day. This supports one in one's belief that only a small number of even the virulent carriers are actually spreading the disease at any one time, and that the healthy carrier and the convalescent carrier (being generally isolated or supervised) are largely guiltless, but that the

mild and the missed cases are largely responsible for maintaining the high incidence of the disease.

Owing to the neglect of virulence experiments, probably most of the people termed carriers are not really carriers of the virulent organism at all. Of these that are, it would seem that when they are perfectly healthy the virulent organisms are generally buried in the crypts of the tonsils, and often not even the rubbing and the prodding of the bacteriologist and his swab are able to bring them out. One can easily understand, therefore, that such carriers are generally of little danger to the community. But if such a carrier should develop, say, a catarrhal condition of throat or nose, there is evidence to show that these organisms multiply and swarm out of their hiding places, and so he who harbours them may become a source of danger to his associates. It might be argued, indeed, that he has become a mild case of the disease.

In any case, let it not be understood from what one has said, that one regards the healthy carrier as of no importance. Potentially, at least, he is dangerous and so needs some supervision. He may become unhealthy.

E. METHOD OF SPREAD FROM PERSON TO PERSON. Having concluded that Man is the source of the infection, and that the disease is spread, for the most part, by missed (mild and atypical) cases, one's next enquiry is: How is the organism conveyed from one person to another?

Many facts bearing on this question one has already considered, under the heading "Life of the organism in

the world". These, therefore, we shall take for granted.

There are two methods of spread viz:- by indirect contact. i.e. from one person to another through fomites, and by direct contact. i.e. from one person to another directly, as by kissing.

1. INDIRECT CONTACT. Regarding the indirect, much stress used to be laid upon fomites as a mode of spread of infectious disease. During late years we have come to regard this means of spread as of comparatively little importance in most of the Zymotics.

It is only fair to say, though, that in diphtheria there is fairly strong evidence to show that fomites not infrequently convey the disease. For instance Carstairs[208] records the case of a father and son, who were cornet-players, being attacked with diphtheria. The instrument was put away, but a few weeks later a younger member of the family, having found the cornet, played it, and developed diphtheria within a week.

Bugbee[209] describes a case due to supposed infection through a library book, which after being read by a person suffering from the disease was fumigated and returned to the library. The book was borrowed eleven months later and the borrower took the disease.

Warry[210] describes an epidemic of 23 cases occurring amongst 26 occupants of a workroom. He cites the mouth-pieces of speaking tubes used in common as the mode of spread.

These facts are suggestive. It is left to the individual to decide whether or not we are dealing here with things that are post hoc or propter hoc. Personally one would like information regarding all the other

possible means of spread before giving an opinion.

Bacteriological evidence suggests the possibility of indirect spread from A CASE of the disease. Thus Park[211] was able to demonstrate living diphtheria bacilli in a bit of membrane no larger than a pin's head, 4 months after its removal from the throat. And we know that patients frequently cough out, with considerable force, small pieces of membrane which may become attached to any fomites near - bed-linen, handkerchiefs, crockery, furniture, linoleum etc., It has been shown, too, that the organism in membrane is fairly resistant to disinfectants, unless they are strong, and applied thoroughly.

Trevelyan[212] gives an instance in which diphtheria bacilli were cultivated from a handkerchief 11 weeks after it had been used by a diphtheria patient. All these facts carry their own moral regarding the importance of adequate disinfection in this disease.

When we consider the possibility of the occurrence of the disease in an individual, due to the spread of the virus from a CARRIER, by indirect contact, we are on different ground. Here the organism is not protected by membrane, and it has been shown that without such protection it is short-lived, a matter of hours only, especially in presence of sunlight - another argument for adequate lighting of schools and against the housewife drawing down the blinds to prevent the carpets fading.

We have probably been too much afraid of the indirect spread of the bacillus from carriers in the past. There is a certain germ of truth in part of Shaw's[213] gibe:

"Doctors have suddenly concluded that the whole art of healing can be summed up in the formula "Find the microbe and kill it". And even that they did not know how to do. The simplest way to kill most microbes is to throw them into the open-street or river, and let the sun shine on them. But doctors instinctively avoid all facts that are reassuring, and eagerly swallow those that make it a marvel that any-one could possibly survive three days in an atmosphere consisting mainly of countless pathogenic germs. They conceive microbes as immortal, until slain by a germicide administered by a duly qualified medical man. All through Europe people are adjured, by public notices, and even under legal penalties, not to throw their microbes into the sunshine, but to collect them carefully in a handkerchief; shield the handkerchief from the sun in the darkness and warmth of the pocket; and send it to a laundry to be mixed up with everybody else's handkerchiefs, with results only too familiar to local health authorities"!

As usual, the picture is disgustingly overdrawn, but it would be as well if we would all actually realise that the sun is our greatest germicide, and instil the truth into the laity.

One concludes, therefore, that indirect spread from case to individual is a possibility to be guarded against, but that indirect spread from carrier to individual is probably rare.

2. What of spread by DIRECT CONTACT? There is ample evidence to show that this is not only A mode of spread but THE mode of spread. This, one will now need to consider.

There are many records showing that surgeons have contracted the disease through attempting to aspirate a piece of membrane through a tracheotomy tube in cases of laryngeal diphtheria. Such incidents form striking instances of infection by direct contact.

Then there are many recorded cases which show that the disease is conveyed by kissing, - people expressing their affection at the expense of children's health. Dawson[214] records the case of two children, brother and sister, who went to a party at the house of a woman who had a tendency to suffer from "sore-throat". Both were kissed by her, 2 days later the boy took nasal diphtheria, and 2 weeks afterwards his sister was found to have the same affection. They recovered, but 5 months later their mother, after kissing the boy to quite an unusual extent, developed diphtheria. It was then found that the boy had membrane in his nose again.

There could hardly be a more direct form of spread. Mention has already been made of the fact that diphtheria is more common amongst girls than boys. One very likely explanation of this is that whilst school girls indulge in the practice of kissing one another to a considerable extent, indeed it enters into many of their games, school boys would be ashamed of such a practice. Such stories carry their own moral!

Another example, of spread by direct contact, is an individual receiving droplets on his person when his infected neighbour coughs or sneezes. It has been demonstrated experimentally that on such occasions the

droplets expelled (possibly containing the organisms) travel several feet. It has also been shown that diphtheria is most common between September and December, the period of the year when coughs and colds are very common. As has been already shown, such a catarrhal process is likely to bring the organisms out of their safe hiding places, e.g. the tonsillar crypts, and then a sneeze or a cough will scatter them broadcast. The seasonal incidence of the disease is, therefore, in favour of spread by direct contact.

This also receives support from the fact that, when means of spread by direct contact are diminished, much fewer people become infected. Thus Graham-Smith was led to conclude that where cases of diphtheria are nursed at home, the number of householders who become infected with the b.diphtheriae, varies from 100% to 10% of the whole, according to the absence or varying degrees of efficiency of attempted methods of isolation.

Although droplet infection, as by coughing and sneezing, does occur, it would seem clear that rather close and intimate contact is generally necessary for the spread of the virus of this disease. And this fact is of considerable importance. It is illustrated by the statistics given on page 135 from which it will be seen that the mean infection amongst inmates of infected houses is more than four times higher than amongst scholars of infected schools. (36·6% and 8·7% respectively). The explanation, of course, is that contact is even more intimate in a home than in a school.

It will now be clear that an adult carrier, pursuing

his ordinary occupation does not come into intimate contact with his associates, relatively speaking, for few people in their work are housed as closely together as people inhabiting a house or even attending a school. The ordinary carrier, for instance, does not go about kissing his fellows!

This fact, therefore, needs to be borne in mind when considering why those 1400 carriers of virulent diphtheria bacilli in Edinburgh only give rise to 2 fresh cases of the disease a day, a partial explanation of which one has already given, when considering the healthy carrier.

3. RELATION OF DIPHTHERIA TO SCHOOLS. A study of the relation of the disease to schools bears out the same fact, that spread is by direct contact, and that the contact generally needs to be fairly intimate.

There is much statistical evidence to show that the sustained high incidence of diphtheria is due, in part at least, to the segregation of children in schools. In this connection Reid[215.] makes an interesting observation "While in Scotland, where practically every child has attended school voluntarily for generations, there was a steady fall in diphtheria mortality in each quinquennial period, with one exception, from 1861 to 1913, the English rate, which had steadily fallen to below the mean in the period 1876-80, rose and was maintained above the mean until the period ending 1900. Coincident with this rise, education became compulsory in England by the coming into operation of the Education Act, and the consequent bringing of the child population into intimate contact in schools, in numbers which progressed as school facilities increased".

The same facts are brought out graphically in Chart 6.

It has also been pointed out that each year there is a fall in the incidence of the disease, in the summer holidays, but a rise when the children return to school in September. But one has suggested that climatic changes account for part, at least, of this increase.

And of course it is just those people of school age who are most susceptible to the disease; or is the fact that the disease has its highest incidence at school age due more to great opportunities of infection, than to special susceptibility at that period?

At any rate, we do know that the tonsil of the child at that age is more liable to receive the organism and harbour it than at any other period of life.

It will be clear that there is much evidence to show that the spread of diphtheria is intimately associated with school attendance.

One only needs to observe children at school, both at work and play, to realise that there is any amount of opportunity for infection by direct and intimate contact to occur.

Reference has already been made to the rather perilous practice of kissing. School authorities ought to give this their attention!

The great difficulty of a subject such as the prevention of diphtheria is that possibilities are so many, it is difficult to assess their relative importance.

It is one thing to give a list of the possible modes of infection in this disease, but quite another to put one's finger on those with an outstanding

significance, and so separate them from many others of which are, more or less, only of academic importance.

There is great need to view things in correct perspective, and there are those of us who think that one of the most important factors in the spread of this disease is the habit, children have, of passing numerous articles from ~~one~~ mouth to mouth. For all practical purposes this is direct contact and is therefore classed here.

It is well nigh incredible, to one who has not observed children at play at an elementary school, how many things pass from mouth to mouth; whistles, mouth-organs, marbles, chewing-gum, sweets - anything. Probably sweets are the greatest offenders. Fruit also plays a part. Scores of times, one has seen one child, observing another eating an apple, ask him for the "stump" (core); commonly he gets it, and often, no doubt, it is complete with a whole army of diphtheria bacilli.

School discipline ought to be set against such procedures. Such facts as these often seem too homely for the scientist's notice, but they must be fraught with dangerous meaning to the health of the community.

Spitting is another of their habits; they often rival each other in the distance they can project their saliva! When spiteful they not infrequently spit at each other.

There are also opportunities for infection to occur at work. Slates must have played an important part till recently, and as they are still used in some

places, must still be a factor. The child spits on the slate to clean it. Later it is passed from one child to another to the end of the desk - practically speaking, direct contact. Pencils and pens etc are now used; the children commonly suck the ends of these implements; a little later they are used by another child who also introduces them into his mouth. Cristioni[216] claims to have found b. diphtheriae in considerable numbers on pencils which had been sucked by carriers and then put away in boxes for 15 days. It must be added, however, that he only used morphological tests and that other observers have failed to corroborate his claim.

In any case, however, it seems likely that the virus could remain alive for a few hours, and it would accordingly be safer for children to have separate writing materials.

The use of drinking cups in common is another factor likely to favour the spread of the disease. Two or three cups are often used for the whole school. Schools should employ drinking fountains such as the "Crystal Stream" where no cups are necessary, the scholars directly taking water as it issues in weak upward jets from the fountain.

That we have a right to hope much from the improved hygienic conditions in schools, is suggested by the fact that in Higher Grade and better class schools, the incidence of the disease and of carriers is less than in elementary schools.

F. THE ROLE OF THE TONSILS.

The throat of man has been shown to be the great reservoir of the diphtheria bacillus, but our attack can be more intensive than even this knowledge would allow, for we can track the organism down to the special part of the fauces involved - the tonsils.

1. PALATINE TONSILS. An appreciation of the anatomy and pathology of the tonsils is the key to successful preventive measures against this malady.

If it were not for the 10 - 20 deep, sinuous crypts in those organs, it is scarcely too much to say that diphtheria would be a rare disease. It is in these long and narrow crypts that the virus lies hidden; local applications may destroy the organisms on the surface, but the majority of the bacilli are out of harm's way, safe in the depths of the crypts. And so they came out of their lairs when the effect of the antiseptic has passed off.

Hence the carrier problem.

That this is the case has been shown repeatedly. Thus Feefer, Friedberg and Aronson[218] found, from a study of 686 carriers and 461 cases, that pre-operation cultures from tonsils which later proved positive were negative in 22·8% of cases.

Also Hartley and Martin[219] studied the rate of the apparent disappearance of the diphtheria bacillus from the throats of patients and carriers. They found the average case took 45 days, three swabs being taken. But if they were content with 2 negative swabs the time was reduced to 31 days, and if with 1 negative

swab the time was reduced to 21 days.

These findings must mean that very commonly the organisms, though apparently absent from the fauces, are in reality hidden away deep down in the crypts. They also carry their own lesson regarding the importance of obtaining at least three negative swabs from a carrier before allowing him to mix freely with the rest of the population.

Furthermore Brown[220] made a microscopic examination of the tonsils of 7 carriers. He found that the organisms were chiefly located within the crypts and amongst the tissue lining the crypts.

Similarly Ballantyne and Cornell[221] explained their failure to cure, (by local applications), several cases upon which they operated, by demonstrating that sections of the removed tonsils showed the organisms to be in the very depths of the crypts, in 4 out of 6 cases.

It has already been noted (Chart 5) that diphtheria is most prevalent when "colds" are commonest, autumn and spring. This is doubtless explained by the histology of the tonsil, the organisms emerging from the crypts in the presence of a catarrhal condition of the fauces.

It seems likely, also, that the histology and development of the tonsil has a bearing upon the age incidence of the malady.

Hett[222] from a study of "The Anatomy and Comparative Anatomy of the palatine tonsil and its role in the Economy of Man", concludes that normally at the 5th. or 6th. year the tonsil begins to atrophy gradually,

until by middle age there is a flat, hollow space between the pillars of the fauces consisting mainly of fibrous tissue; often, though not invariably, a few crypts remain.

Now it will be seen from reference to Chart 7, which gives the age distribution of the cases investigated at Blackburn, that the incidence rate begins to fall sharply at about the 6th year - when the tonsils are commencing to fibrose. It is true that general immunity (as shown by the Schick reaction) becomes more frequent after the 6th year, but not to so great an extent as to account for the marked fall in the incidence which commences at that age.

This suggests that in this disease we have not only to deal with a general and serological immunity, but also with an immunity which is local and cellular— depending upon the histology of the tonsil.

This is also supported by the fact that many people who possess no general serological immunity, as shown by the Schick Reaction, harbour the diphtheria bacillus in their fauces, and yet (through this local cellular immunity) do not take the disease. Thus Leete[223] found that, of 32 carriers, 14 gave a positive Schick Reaction.

Now if everyone were physiological, their tonsils becoming fibrosed and well-nigh devoid of crypts by the time they reached adult life, diphtheria would be likely soon to become a rare disease.

Unfortunately this is not so— witness the fact that the most common operation in Surgery is tonsillectomy. There is abundant evidence to show that it is the enlarged ragged tonsil, with its many and deep crypts,

which, having once become inoculated with diphtheria bacilli, retains these organisms for long periods and often stubbornly resists all efforts to free it from these organisms.

So it is that such individuals become carriers, and remain so for long periods.

It is granted that people with healthy tonsils may become carriers but, as one has already shown, they are of relatively small importance as agents of spread of this disease. Part of the explanation of this fact is that healthy carriers free themselves of the organisms fairly rapidly. Thus Ledingham and Arkwright[124] state that average healthy carriers remain infective for 30·0 days.

Many are so convinced that the morbid tonsil alone is of importance in this disease that they do not even examine individuals with healthy throats, when searching for carriers.

Further evidence, in support of the crypts of the morbid tonsil being an all-important factor in this disease, is afforded by the fact that conservative methods of freeing carriers of the organisms, (gargles etc), are almost always fruitless (V.infra), as they only affect the surface of the tonsil, whilst in reality the organisms are safely hidden in the depths of the crypts.

In striking contrast to this is the success which attends tonsillectomy, a measure which, in the author's opinion, is one of the most important in the prevention of the disease under consideration.

2. PHARYNGEAL TONSIL. Much the same is true of the pharyngeal tonsil. According to Quain's Text-book of Anatomy[225] "The pharyngeal tonsil increases in size, in infancy and early childhood. Possibly it normally attains its maximum development by the 6th or 7th year, after which it gradually atrophies". But here too, the organ often fails to fibrose and diphtheria bacilli become lodged in the crypts of the adenoids which often result.

Thus Pilot[226] made cultures from the tonsils and adenoids excised from 100 children, not known to be carriers. In 12 of the cases he proved diphtheria bacilli to have been present in the crypts of both tonsils and adenoids. (In 3 cases the organisms were virulent).

Another effect of adenoids is to cause nasal obstruction and nasal discharge. When the vegetations are infected with Klebs-Löffler bacilli, a nasal carrier results - and, according to Lewis[227], even apart from infection adenoids are a factor in the spread of diphtheria, inasmuch as the permanency of any nasal carrier depends on the degree of nasal obstruction.

The treatment of infected adenoids by local applications is less likely to be successful than the treatment of infected palatine tonsils. And here again, in persistent cases, surgical removal of the infected tissue would seem the only rational course.

That adenoids have an importance which is far more than academic is suggested by the fact that Keefer,

Friedberg and Aronson[228] found, from their study of carriers, that in 26% of cases the nasal culture was positive and Kelly and Bathgate[229] found, in a school outbreak they investigated, 72% of the carriers detected gave positive nasal cultures, but only 28% gave positive throat cultures.

Amongst other causes of the most persistently positive carriers must be mentioned acute or chronic infections of one or more of the accessory sinuses, and septal deformities with erosions.

It will be clear therefore, that in one's own opinion, the cause of the great problem in diphtheria, the carrier problem, is found in the existence of the tonsillar crypts, especially in these crypts as they exist in certain morbid conditions of the tonsil.

We know that one great cause of enlarged tonsils and adenoids is the too early addition of starchey foods to the diet of infants. And therefore an indirect method of prevention of diphtheria might well be more universal breast-feeding of infants, or, failing that, the witholding of starch, or the many patent foods which contain it, till the 8th.month.

IV. METHODS OF CONTROL.

Several preventive measures against diphtheria have already been fully discussed.

Evidence bearing on some other methods, now to be mentioned, has also been given; upon it many of the conclusions to which one has come, (and which are found below), are based.

A. NOTIFICATION, of all cases of the disease, is an essential measure. Carriers whould be classed separately as otherwise statistics are falsified and often healthy carriers, as a result of their notification as victims of diphtheria, are removed to hospital, where they may stay to the exclusion of persons urgently requiring treatment.

B. ISOLATION OF PATIENTS. The sustained high incidence of diphtheria has been shown to be due, not to the spread of the disease from frank cases, but from mild cases and carriers. It has also been shown that the number of infected contacts in a house varies from 10% to 100% according to the amount of care taken to isolate the patient. Both these facts point to the need of early isolation of the infected person. This almost always means sending the patient to an isolation hospital, for there are few houses which allow of the patient being looked after by a special nurse in a separate wing of the building.

Despatch to hospital should not await bacteriological diagnosis, for the patient's sake, and for the sake of the community; the sooner he is isolated, the less likely are carriers to result.

Before isolation was practised, e.g. in Bretonneau's time, it was a tragically common occurrence to have several deaths from the disease in one household, within a few weeks of each other.

If the members of a household are known to give a negative Schick reaction, the need for isolation is accordingly diminished.

Nurses of diphtheria patients should give a negative Schick reaction.

Regarding the duration of isolation necessary in a case of diphtheria, one must be guided by both clinical and bacteriological examination (glucose broth cultures).

If the bacteriological examination were negative, one would allow freedom after an isolation of at least four weeks, provided that convalescence is completed, that there is no longer any sore throat or any abnormal discharge from the throat, nose, ears, or eyes, no sores and no albuminuria. The danger of, e.g., a sore throat, (even if it give a negative swab on occasion), one has already considered.

One has also fully entered into the bacteriological standards considered necessary (p.80). Both nose and throat should be negative on three successive occasions.

Since avirulent organisms tend to replace the virulent, during convalescence, a virulence experiment should be performed at the end of say 10 weeks, or preferably 5 if the person continues to be a carrier in spite of treatment.

All isolation hospitals ought to have facilities for making virulence tests. As things are at present, much time and money is wasted through prolonged isolation of avirulent carriers. One has given ample evidence to show that such carriers are not even potentially dangerous.

A difference of opinion exists as to whether local

applications hasten the disappearance of the organism from the throat of the convalescent.

This matter will be dealt with later.
But one thing seems clear - the earlier antitoxin is exhibited in the disease, the earlier is the patient free from the bacilli.

C. DISINFECTION.

The evidence given as to the life of the organism outside the animal body, and instances cited as possible cases of spread by indirect contact, go to show the importance of adequate disinfection in this disease. Plates, crockery, towels, linen etc. should be reserved for the use of a patient or carrier, and be boiled or otherwise disinfected after use.

It is customary to strip the paper from the walls and fumigate the room occupied by an infected person. Such procedures impress the laity considerably, but one doubts their value. One has already cited cases of the organism remaining alive in a book, and in the crevices of a floor, in spite of fumigation. On the other hand, however, one is a firm believer in sunlight, and soap and water.

Liq. Cresol Saponatus (1%), makes a good antiseptic soap. It would seem wise to pay special attention to a scrubbing of the floor, for it is here the shreds of membrane, enveloping the organisms, are likely to be.

If the evidence regarding the presence of the organism, in faeces, and urine, is confirmed, it will become necessary to disinfect these excretions.

From references given, it will be evident that the disinfection of such things as telephone mouth-pieces, drinking cups of public fountains, slates, pencils, pens, school furniture etc are desirable measures.

Mention may be made here of the importance of sanitary habits - thus indiscrimate kissing, especially in schools during an outbreak, is dangerous. One's belief in the importance of sweets ~~re~~ etc. passing from the mouth of one child to another has already been mentioned.

Reference must also be made to the wisdom of "screening the sneeze" - it has been shown that otherwise, organisms may be propelled long distances.

The importance of boiling milk during certain epidemics has been indicated.

D. THE DETECTION OF CARRIERS.

One has shown that about 10% of contacts become carriers. One of the most important preventive measures in diphtheria is, therefore, the examination of contacts, with a view to discovering ~~contacts.~~ carriers.

From the evidence given and the work of Cobbett[230], one concludes that it is generally only necessary to examine direct contacts. During an epidemic, however, a search for carriers through an ever-widening circle

must be made; therein lies the secret of successful control. This involves the swabbing of the scholars and teachers of schools.

Every member of an infected household must be examined, but in the event of cases occurring in a school, for reasons given, one is of the opinion that only certain scholars need be examined the friends and immediate contacts of the patients, and those who show obvious general or local signs of ill-health, such as pallor, sore throat, nasal discharge, excoriations about the nares, whitlows or sores. Special attention must be paid to children with enlarged tonsils or adenoids.

One has already stressed the great importance of the mild case and the probable safety of the healthy carrier. (p.136).

Negative evidence should not be accepted as final until at least two negative swabs, from throat and nose, have been obtained at several days interval,- witness the fact that Graham-Smith obtained a negative swab in 40% of individuals which, later, were proved to be carriers. Other evidence one has already given.

But the most difficult and important step consists in finding whether an individual is harbouring the virulent diphtheria bacillus or merely a harmless organism. Buchanan[232] says "In essence, the chief difficulty in the choice of appropriate methods of prevention lies in assessing the infective ability of the different individuals who collectively are classed as "carriers" of the diphtheria bacillus."

But this difficulty is not insurmountable.

The methods of bacteriological diagnosis one favours have been fully discussed, and the standards necessary under varying circumstances laid down. (p.80).

33% of the population harbour the b.Hofmanni, or diphtheroid organisms. 3·0% of the population harbour avirulent diphtheria bacilli. The diagnosis of "diphtheria carrier" is made ~~for~~ far too readily. If all such were to be isolated our fever hospitals would be full of healthy people.

Their number is so great that it is impossible to carry out correct treatment in all these cases. As it is, the energy of local authorities is diffused over a large number of "carriers". If thorough bacteriological diagnosis were carried out, the number of "carriers" would be much smaller, the result would be that proper supervision and treatment could be given to these members of the community, whose presence amongst us is the cause of the high incidence of diphtheria.

We cannot hope for Parliament to grant legal powers to isolate the numerous people now classed as "carriers" - nor indeed would it be desirable. If people were proved to be harbouring the virulent diphtheria bacilli, before being diagnosed as carriers, we might be more hopeful of being able to compel isolation of such carriers, and so largely prevent the spread of the disease. One has shown that even true carriers with healthy fauces are probably not infective; these individuals need not be isolated, and so isolation of all actually infective carriers comes still nearer the realm of practical politics.

One corollary of all this is the routine employment of the glucose-broth culture in the bacteriological examination of close contacts. No person should be pronounced a carrier till the action of pure cultures on glucose media has been determined.

A second, and equally important, corollary, is a wider use of guinea-pigs in bacteriological examination of other suspected individuals.

E. THE ISOLATION OF CARRIERS.

Having definitely found individuals harbouring virulent diphtheria bacilli, the next step is to isolate them all, or at least supervise them, until they are free from infection. This commonly means removing the individuals to a fever hospital or quarantine home.

Unfortunately, at present, many such carriers are not isolated, often they are not even supervised.

Isolation causes much inconvenience and pecuniary loss both to the carrier and to the State. It is an ideal measure, but we live in a practical world and there are certain types of cases in which, under certain circumstances, one feels it is not absolutely necessary. These one will now mention.

If the carrier be perfectly healthy, both generally and locally, he is not likely to infect others and therefore may remain at home. If, however, there are children in the home who give a positive Schick reaction he ought not to associate with them.

If all the members of a carrier's family give a negative Schick he may be safely isolated at home.

Any carriers who remain at home should be carefully supervised and bacteriologically examined just

as are those in isolation hospitals. They should be warned to exercise the preventive measures considered under "Disinfection", and to avoid catching "cold" as much as possible, for there is evidence to show that a "cold" may make them infectious. They should also be advised to spray their throats with an alkaline lotion, so as to cleanse the mucous membrane of adherent mucus, and then to gargle with an antiseptic such as a solution of carbolic acid, or iodine. There is no proof that such a procedure shortens the duration of the carrier state but it does kill the organisms on the surface of the fauces, and so lessens the chance of such incompletely isolated carriers spreading the disease. Thus Cobbett[233] examined 17 children in an isolation home. 8 of them were virulent carriers and 5 avirulent. Sprays and gargles, and sterilisation of cups etc. were employed. After several weeks he examined them all again - no cross infection had taken place.

Especially in the case of dairymen, and others concerned with the handling of foodstuffs, efforts must be made to prevent the carrier following his employment, indeed we have legal power to prevent such class of workmen following their trade, so long as they are infective.

In the case of children who are carriers, - since their time has no monetary value, there will be less hesitation in isolating them. Objections may be raised, however, and if removal to hospital is impossible attempts at isolation at home, with the precautions suggested, must be made. Most large towns have Open-Air schools, Copeman[234] suggest that carriers might attend

such schools, under special supervision, stating that under such conditions the health of the child would be likely to benefit, while danger of transference of infection would be reduced to the minimum. The probability of infection through such things as sweets, however, would still be great. One feels the procedure would be fraught with danger to the other children.

The loss to the cause of education, and the loss of grants to school-boards, resulting from the prolonged isolation of convalescent and contact carriers is considerable . One would suggest however that this could be partly obviated by forming classes of children, who give a negative Schick reaction, and allowing the carriers to attend such classes. This might become worth while if diphtheria carriers were numerous, but the negative Schick reactors would be liable to become carriers as already mentioned (pp.116 & 117).

But the "home-isolation" of the virulent diphtheria carrier is at best a makeshift, and often becomes a farce. Moreover the type of carrier most anxious to be at home, the chronic, is generally the most infective, because he probably has diseased fauces. The healthy carrier on the other hand, who would be fairly safe at home, would not need to be isolated in hospital long before he would become non-infective (30 days is the average time for such a type of carrier).

One is of the opinion, therefore, that, wherever possible, hospital isolation of virulent diphtheria carriers should be resorted to.

Nothing furthur need be said, as to the duration

of isolation, since the same standards hold true for contact carriers as for convalescent carriers (q.v), - guinea-pig inoculation should be resorted to if an individual continues to give positive faucial and nasal swabs after an isolation of more than say 10 weeks (more or less according to his occupation).

The various methods of treating carriers, with a view to freeing them of bacilli, one is to consider presently. Meikle[234] states that, of local applications, "no one antiseptic seems to be much better than another" in hastening the disappearance of the organisms, and Ledingham & Arkwright[235] are led to conclude that no one antiseptic produces more rapid disappearance of the organism than another.

Carbolic acid, iodine, alcohol, chlorine, menthol, thymol, pyocyanase etc have all been tried.

It is advisable to use the spray and gargle as suggested however for two reasons. In the first place it acts as a placebo. Patients are never satisfied without some overt act. The use of spray and gargle makes them feel something is being done, and so they are more amenable to prolonging their stay in isolation than they otherwise would be. In the second place such a procedure prevents cross infection - as already shown.

The difficulty of estimating the value of local applications lies in the fact that in the vast majority of cases the throat clears itself within a few weeks without any medicament. Thus Weaver[236] states that of 52 patients admitted to the Durand Hospital, Chicago, as carriers-and kept under observation until free from

bacilli without operation - 55·8% were free from bacilli after 2 weeks, and 80·8% after 4 weeks. In 10 of the 52 cases the bacilli persisted longer than 4 weeks. In 4 of these the cultures were obtained from the pharynx only, in 1 from the nose alone, and in 4 from the pharynx and nose. The persistent pharyngeal cultures were associated with abnormal tonsils, usually enlarged, with deep crypts and roughened surfaces. In the nasal cases there were discharges associated with adenoids and chronic rhinitis, usually secondary to accessory-sinus disease.

These facts serve to illustrate points one has already endeavoured to bring out and contentions one is about to make.

Weaver's observations are confirmed by others. 80% of carriers are in isolation for a matter of only 1 to 4 weeks, and the remaining 20% almost invariably present some abnormality in throat or nose, which requires attention. The question of how to free this 20% of virulent diphtheria carriers from infection is still one of the most pressing problems in this disease and to a consideration of this problem one will shortly proceed.

SCHOOL CLOSURE. It will be convenient to interpolate here, however, one's views on the question of school closure in diphtheria. One has shown that schools are actively concerned in the spread of this disease. A study of the records of various epidemics, in some of which the schools were closed, and in others remained open, leads one to the conclusion that school closure, during outbreaks of this disease is an unwise

procedure. The reason would appear to be that when schools are closed the scholars are lost sight of, whereas when they remain open they can be medically, and if necessary bacteriologically, examined daily. In this way mild cases and carriers can be detected and excluded from school, and so the spread of the disease can be controlled. Furthermore when schools are closed the children spend their days playing with each other. This commonly involves close contact and so the ends of school closure are defeated, the carriers and mild cases being quite well enough to play amongst their fellows and so infect them.

F. A CONSIDERATION OF THE METHODS OF FREEING CARRIERS OF THE ORGANISMS.

One has given one's reasons for concluding that, regarding practical measures for the control of diphtheria, one hopes more from an attack upon the seed(the diphtheria bacillus), than from attempts to modify the soil (i.e. the human organism).

One has shown further that little good can be expected to result from an attack on the organism as it exists in the world (for it is short-lived there), or in the bodies of animals (since they rarely if ever harbour it).

One has endeavoured to show that the most rational method of preventing this disease consists, in the author's opinion, in attacking the organism as it exists in the body of man, and more particularly in the tissues of pharynx and nasopharynx of various kinds of carriers. The desirability of preventing access

of the organism to other individuals, by isolating the persons harbouring it, has been indicated.

We cannot isolate these persons indefinitely and so one is brought to a final problem in the prevention of diphtheria - how to free these individuals from the organism. If we can solve this we are in a fair way to eradicate this disease, since.it is the few chronic carriers in the world who are largely responsible for keeping up the life of the organism.

In the vast majority of carriers the organisms disappear spontaneously within a few weeks of infection. Those individuals who remain carriers do so because of some abnormality in throat, nose or ears. In most cases the organisms lie hidden in the depths of the tonsillar crypts, evidence for which one has already given. On a recognition of this fact depend successful efforts to free a persistent carrier of the bacilli. One will now consider the various forms these efforts have taken.

1.Local applications.

Reference has already been made to the doubtful value of ordinary antiseptics. Every year some new medicament is suggested for freeing carriers of infection, and many are the claims made for them. Amongst them are the following:.

(a). Iodised phenol. Ott & Ray [237] recommend the following.

Phenol 60%.
Iodine. 20%
Glycerine 20%.

Ft. pig.

They claim that 60% of 16 carriers were freed of bacilli after 2 applications of the paint, and that 15 of the carriers became negative after 6, or less, applications. One subject required 9 applications to free him of the organisms.

They examined their patients 1 to 3 weeks after leaving hospital; all were still negative. The process is rather painful but they had no bad results.

(b)Kaolin. Hektoen and Rappaport[238] recommend the frequent insufflation of Kaolin - swallowing as slowly as possible 1/3 of a teaspoonful of Kaolin 4 or 5 times an hour during the day. This substance has great absorptive powers. Others have claimed good results.

(c)Chloramine-T (Chlorazene) is recommended by Mc.Cord, Friedlander and Walker[239]. They advise its use as a gargle 3 or 4 times a day, the gargling being followed by an oily spray of Dichloramine - T (2%). By these means they found it possible to reduce the stay in hospital, of contact carriers, from 55 to 16 days.

(d)Hypochlorous Solution, electrically produced from hypertonic saline, is advocated by Beattie, Lewis and Gee[240], as being very efficacious in ridding the fauces of diphtheria bacilli.

(e)Hot Air, directed on to the fauces from a nozzle is recommended by La Rivière[240a].

(f)Mercurochrome (a bisodium salt of dibrom - oxymercury -fluorescin) is advocated by Gray and Meyer[242]. By dropping into the noses and painting on the tonsils

a 1·2% solution of this salt, they freed 88 out of 90 carriers from B. diphtheriae, after an average of 19 applications, in an average of 12 days. Their criterion of cure was 3 consecutive negative cultures taken at 2 day intervals, but while treatment was still applied. The third negative swab was taken 24 hours after the last treatment.

The great number of medicaments, recommended for the freeing of carriers, makes one inclined to doubt the value of any one of them. It is the same in diseases, if many remedies are used it suggests that no one of them is specific. Furthermore the evidence regarding at least some of the drugs mentioned is unconvincing. Take for instance the last cited - Mercurochrome. One negative swab, 24 hours after the last treatment, is not satisfactory evidence that the patient is bacilli free. Organisms probably remain in the crypts and come out in a few days time - maybe not until the carrier takes a "cold". One has already considered the anatomy and pathology of the tonsils - the facts recorded there are fundamental to successful procedures for freeing carriers. Local applications merely affect the surface. Moreover adenoids are commonly infected - here local measures are practically impossible.

Not only chemical substances but bacterial agents have been employed for the purpose under consideration:

(g)Cultures of Staphylococcus Pyogenes Aureus, sprayed on to the fauces, were first advocated by Schiotz;[243] Cattin, Day & Scott[244] regard it as a valuable measure.

Lake,[245] Rolleston[246], and Alden[247], however, found the method less satisfactory.

A difficulty in estimating the value of all these various matters lies in the fact that the bacilli disappear naturally, after a few weeks, without treatment.

The staphylococcal treatment is evidently of doubtful value. Furthermore Davies[248] and others have shown it is sometimes dangerous, since an acute follicular tonsillitis not infrequently follows its employment.

(h)Cultures of Bacilli Acidi Lactici are recommend^ed by Woods[249]. He only reports 4 cases however, too small a number on which to base any conclusion.

(i)Cultures of Pneumobacilli. Lesbre[250], in a recent paper, claims success far treatment by this method. He inoculated living pneumobacilli on to the tonsils of four diphtheria carriers and found that in each case the number of bacilli diminished rapidly and disappeared completely in 7 to 12 days. Similar success followed the treatment of a convalescent case. The method is open to objections already raised, however, and the cases too few to allow of generalisation.

(j)Not only has the effect of the local application of various organisms been tried ~~by~~ but also the effect of antitoxic serum.

Benard[251] claims that the insufflation of dried and powdered antimicrobic serum is more efficacious than any other method in quickly rendering the nasal passages and Pharynx

free from bacilli: Others advise the sucking of lozenges consisting of dried antitoxic serum in a gum basis.

2. TREATMENT OF CARRIERS BY GENERAL MEASURES.

Local applications having proved of such doubtful value, attempts have been made to attack the organism from within, through the blood stream.

(a) Injections of antitoxic serum have been given with this end in view.

Both experimental and clinical evidence are against this method however.

Moss, Guthrie and Marshall[252] sprayed avirulent diphtheria bacilli into the throats of healthy people and so produced the carrier state. They then sprayed the organisms into the throats of persons who had previously received an injection of antitoxic serum. The carrier state again resulted.

Moreover Gelien, Moss and Guthrie[253] found that the occurrence and duration of infection of cats, rabbits, and guinea-pigs, (produced by inoculation of the nares), were wholly unaffected by the previous administration of antitoxin.

Clinical findings lead to the same conclusion, indeed one has shown that one of the objections to a routine administration of antitoxic serum in contacts is the danger of producing unknown carriers.

(b) Diphtheria Endotoxin, by subcutaneous inoculation at intervals of 7 to 10 days, has been recommended by Hewlett and Nankivell[254] and by Hewlett[255]. The results, however, were admittedly not invariably successful, though Hewlett considers them sufficiently promising to warrant a trial in obstinate cases.

(c) Diphtheria Vaccines have been employed on the same principle as endotoxin. The results are somewhat conflicting.

Forbes and Newsholme[256] record 3 cases of nasal diphtheria treated with autogenous vaccines. They state that while the local membrane and discharge were lessened and finally stopped, (because of vaccines or in spite of them?), bacilli were still present in the mucous membrane at the end of several weeks of treatment.

Wood[257] treats cases of the disease with a vaccine, as well as antitoxin, and claims that by this method he prevents the formation of carriers.

Weil[258] records 24 carriers he has treated with vaccines. All cleared up with large doses. But one finds that whilst not less than 9 of these cases had none of them had been carriers for more than three months. been carriers for more than 3 ~~months~~ weeks. Our difficulty is not so much the eradication of the organisms from transient carriers however, but from those who have been carriers for more than 2 - 3 months.

Brownlies'[259] work is more promising. He treated 50 carriers with vaccines in doses ranging from 10 to 200 millions. From 1 to 8 injections were given. 44 of the carriers, which received not more than 3 doses were discharged with 2 consecutive negative cultures on the 11th day. The vaccines were not autogenous. No bad effects were observed.

He calculates that by ordinary methods the convalescent carrier is 4 weeks longer in hospital than the non-carrier, and that the method he recommends will, therefore result in a great saving of the time of the patient, and of the money of the state.

The evidence regarding the value of vaccines in the treatment of carriers is, therefore, conflicting.

A priori considerations hardly support their use, for in the carrier state the organisms are merely leading a saprophytic existence upon and within the tonsils, and therefore would appear unlikely to be affected by an attack through the blood stream - as by vaccines.

3. TREATMENT OF CARRIERS BY TONSILLECTOMY ETC.,

All these various methods of treating the carrier state one has shown to be unreliable and, in some cases, useless. There is one method left, to which we are led if only by a process of exclusion, - enucleation of tonsils and removal of adenoids.

A consideration of the facts one has set out, regarding e.g. the histology and pathology of the tonsils, will show that such a method is a rational procedure, for the organisms, in the carrier are in the depths of the crypts.

Moreover in nearly all chronic carriers the palatine or faucial tonsils are diseased, so that even apart from their being carriers, such surgical interference might be a wise measure; and Hett[260], and others, have presented a strong case to the effect that the function of the tonsil is over at an early age, (5-6 years), and that thereafter it is a source of danger to its owner - by presenting a channel of infection, involution does not take place. And so the patient, apart from ceasing to be a carrier, will be no worse in his general health, and may, quite well, be better.

Of course, one does not advocate a wholesale removal of the tonsils and adenoids of carriers. One has shown that in the majority of cases (80%) the organisms die out within 4 weeks. In the remaining 20%, of proved virulent carriers, at the month end active measures should be taken to free the individual of the organisms. Various methods have just been named. The administration of vaccines, combined with the local application of iodised phenol, would seem as good as any. If this fails, other medicaments may be employed. If, however, at the end of three months the individual is proved to be still a carrier of the virulent diphtheria bacillus (animal experiment), one would advise operative measures on tonsils, adenoids, septum, antrum of Highmore - or whatever morbid condition there may be keeping up the infection. One has shown that some morbid condition is almost invariably present in these persistent carriers, and by far the most common, are pathological conditions of palatine or pharyngeal tonsils. These therefore one considers specially here.

Since only 1 to 2% of carriers harbour the organism for more than 3 months, the routine employment of the procedure indicated, is not so formidable a matter as might first appear. If more care were taken to detect carriers and isolate the transient ones, till they are bacilli-free, and then exterminate the diphtheria bacilli from the remainder, by operative procedure if needs be, diphtheria would be likely to become a rare disease.

That tonsillectomy is a wise procedure and is much more than a theoretical probability is shown by

the following facts:

Graham Brown and Hughes[261] enucleated the tonsils and removed the adenoids of over 100 persistent carriers. All ceased to be carriers, and on an average, 10 days after operation, 3 negative swabs throat cultures were obtained.

Tilley[262] quotes 3 of his cases who sought treatment having found prolonged isolation irksome. One girl of 18 who had been isolated by the M.A.B for 14 months, was discharged 3 weeks after removal of tonsils, having given 2 negative throat cultures at intervals of 5 days.

Ballantyne and Cornell[263] report similar successes after removing tonsils and adenoids from a number of persistent convalescent and contact carriers.

Details of 6 cases are given, all of which gave 3 negatives on 3 consecutive days, within 2 weeks of operation. In all their cases saline irrigation and gargles had been used continuously until the time of operation - but without benefit. Living cultures of staphylococcus pyogenes albus had also been employed - they also had failed in their purpose.

Keefer, Friedberg & Aronson[264] conclude from a study of 686 carriers that in persistent carriers, in whom the focus of infection is the tonsils, enucleation offers the only certain procedure for terminating the carrier state. Of 294 carriers operated upon, they found that only 1, i.e. 0·3%, was still positive at the end of four months; 96·3% were negative 3 weeks after operation.

Several precautions, however, should be taken. In some cases, diphtheria has followed the operation

and therefore it is advisable to give a prophylactic dose of antitoxic serum before the operation. Also operation should not be performed in the presence of any acute local infection.

Attention[265] has also been drawn to the fact that occasionally individuals become nasal carriers after the operation, and are apt to be overlooked. Nasal discharge is generally present in such cases.

One concludes, therefore, that the removal of enlarged tonsils and of adenoids, in persistent carriers, is a most important preventive measure in this disease.

Preventive measures necessary in milk epidemics, and the question of prevention by Immunisation, one has already discussed.

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S U M M A R Y .

An outline of most of the various sections of this th thesis will be found to precede those sections.
It will be fitting to close this thesis with a statement of the conclusions to which one has come .

Diphtheria is as prevalent as ever, in spite of all the preventive measures now in force.
The disease has been known since about 400.B.C. The first account of its presence in this country is found early in the 18th. century. It has been endemic since then and frequently epidemic.
Many writers confused it with croup, thinking the latter a separate affection. Bretonneau (1826), finally and conclusively proved croup to be merely a form of diphtheria.
Löffler discovered the causal organism in 1884. Behring discovered antitoxic serum in 1891. This is still bacteriology's greatest gift to curative medicine.
An early diagnosis is more important in this disease than in almost any other. A case diagnosed on the fifth day is five times more likely to die than one diagnosed on the 2nd.
Failure to make the diagnosis is ,perhaps, more often due to criminal negligence than lack of skill.
One is convinced that an accurate early diagnosis is generally possible from a careful inspection of the fauces. One has not, however, come to place full reliance on Drinkwater's standards.
One has found glandular enlargement absent in almost 1/3 of cases.
The chief thing to remember about nasal diphtheria is not to forget it. It may simulate a "cold" and is easily missed.
A comparatively low temperature and a high pulse rate, one has found in the cases investigated. These constitute a valuable aid in diagnosis.
The marked asthenia one regards due to the degenerative changes wrought by the toxin on the suprarenals.
The alleged value of absent knee-jerk and albuminuria, in the early diagnosis of the disease, one has come to regard as fictitious. The latter sign was only present in 34% of the cases one investigated, although the average case had been ill for three and a half days ,when the examination was made.
Examinations of neither blood , nor cerebro-spinal fluid are of value in diagnosis.
The view that a negative Schick test is of value in diagnosis, one has not found tenable.
On the contrary a priori considerations lead one to think a positive Schick reaction would be of value in the diagnosis, excluding the disease.
Many cases are doubtful and bacteriology is our "final court of appeal", but therapy must not await bacteriological diagnosis. One believes b.Hofmanni and b,pseudo-diphtheriae and diphtheroid organisms are generally distinguishable from the Klebs-Löffler bacillus by ordinary cultural methods,(especially by their effects on glucose broth). An account of one's morphological standards has been given.
The above organisms never acquire virulence or become transformed into b.diphtheria.

These organisms are present in about 33% of healthy people.

The avirulent b.diphtheria are indistinguishable from the virulent organism , except by means of animal experiment.

They are present in about 3% of healthy people.

The avirulent forms never become virulent.

The majority of ,so-called, carriers are merely harbouring the avirulent organisms. The isolation, therefore, is a useless and expensive procedure which often causes great inconvenience. This would be obviated if animal exoeriment were used.

Animal inoculation is still far too rarely practised. The author is of the opinion that the State should provide central laboratories at which even the smallest hospitals and practitioners can have virulence experiments performed [redacted] before deciding to isolate any individual for a long period.

One has pointed out that bacteriological methods are not infallible: clinical observation , in the detection of both cases and carriers, is of the greatest importance. Bacteriological methods,however, find their greatest use in the diagnosis of mild and atypical cases, and in the detaction and isolation of carriers. Here ,indeed, they are indispensable , through reasons given.

Regarding etiology and preventive measures, one has concluded that an attack against the organism is likely to be more effective than attempts to modify the "soil" i.e. the human organism, although more success will attend our efforts to control the disease if efforts are conducted along both these lines.

Regarding "the soil", one has shown that more benefit is likely to result from attention to the health of the pharynx and nasopharynx than to the general health. Consideration should be given, therefore to such matters as defectively ventilated or draughty schools., to the ventilation of drains and sewers,etc., and the prevention of dampness in houses.

One has remarked also upon the influence of fear upon susceptibility.

One has expressed the opinion that careful supervision of contacts is more desirable than routine administration of prophylactic doses of serum , for reasons shown. hands

The Schick test is fairly reliable in competent ((1-2% of errors). It has shown us that only one third of the population is susceptible to diphtheria.

The value of the test in various circumstances has been indicated. It has an important bearing on the isolation of carriers. The isolation wards of institutions need not be used in diphtheria, because carriers, or even cases, can be safely housed in a ward of negative Schick reactors

The most important use of the test however is in the determining of the susceptibles, with a view to Toxin-Antitoxin inoculation. This method is now recognised as of great importance in the prevention of the disease, but sufficient time has not elapsed to allow of a confident statement as to the place which it should take in Public Health measures against diphtheria. One has cited various objections to the routine employment of this method of control, as chief among which the author regards the fact that there is a danger of producing an increased number of undetected carriers. This is of importance since immunisation of the whole population is not practicable in this country. If the

measure makes us less vigilant regarding the detection and isolation of carriers , it does harm.

Toxin-Antitoxin inoculation however, promises to be of great value in the control of diphtheria in institutions, and in the protection of nurses exposed to infection.

For reasons given, one is of the opinion that the most effective method of controlling this malady consists in an attack upon the diphtheria bacillus. This organism one has shown to be practically non-existent in the world generally and even in the bodies of animals other than man.

When once the organism leaves the human body, its death-knell is rung. Evidence has been given ,from the work of bacteriologists, regarding the life of the organism in air, water, soil, drains, and sewer gas. The bacillus has been shown to be short-lived. From a consideration of the evidence one has given regarding the relation of defective drains etc, to the disease , one has concluded they are a negligible factor.

Reference has been made to the practical importance of the bactericidal power of sunlight.

The facts one has given regarding rainfall and the incidence of diphtheria have led one to regard Newsholme's theory as untenable.

One has reviewed the evidence regarding the occurrence of Klebs-Löffler bacilli in cats, kittens, cows, etc, and concluded that for all practical purposes they may be regarded as not occurring in these animals. Milk epidemics do occur and have their own peculiar features , but the milk is infected by a human carrier and not by the cows. Preventive measures must be based on this fact. Reference has been to the disgusting conditions one has found to prevail oh some farms.

Man, however, is the great reservoir of the organism, if not the only one. This fact must be the basis of our campaign against it. The evidence given goes to show that the fauces and naso-pharynx are the sites which harbour it. Some writers hold that the faeces and urine are also infective. This is not proven, but one is of the opinion that these agents shoud be regarded with suspicion until bacteriology gives a more unanimous verdict upon the subject.

The fauces and naso-pharynx, however, are the chief infective sources. Cases of the disease are generally isolated ; those mainly responsible for the spread of the disease are carriers. For reasons given, one is of the opinion that healthy carriers are a potential menace to the health of the community, but that some 80% of carriers are mild or atypical cases and special care is necessary in detection of such cases. Here again clinical observation will be of value as most virulent carriers show either some general or local abnormality- pallor, enlarged ragged tonsils, adenoids, discharge from nose or ear etc.

Bacteriological methods are essential in this work of detection of carriers.

Disease is spread from person to person, chiefly by direct contact. One has given bacteriological and epidemiological evidence, however, which suggests that indirect contact is so much a possibility that preventive measures , such as disinfection, are desirable.

By far the commonest mode of spread , however, is direct

contact. Various examples have been cited and attention called to one's opinion that one of the most important factors in the spread of this disease is the habit children have of passing sweets, and so forth , from mouth to mouth. Indiscriminate kissing amongst schoolgirls is another important factor. School- discipline ought to be directed against such procedures.

Statistical and other evidence has been set forth to show the relation of diphtheria to schools.

One has expressed it desirable that more care should be taken ~~that more care should be taken~~ regarding the ~~dis-~~i disinfection of such things as pencils, pens, drinking-cups and school-furniture.

We can not only say that the fauces and naso-pharynx are the chief infective sources, but particularise still further and say that the disease largely owes its continued high incidence to the presence of crypts in the tonsils, and especially to their deep and sinuous nature in diseased tonsils. One has endeavoured to demonstrate this point by reference to the development, anatomy, and pathology of both palatine and pharyngeal tonsils.

Regarding methods of control , mention has been made of notification and disinfection; one is of the opinion that sunlight , and soap and water are more efficacious than fumigation.

Emphasis has been laid on the importance of immediate isolation prolonged until three negative swabs have been obtained. One is of the opinion, however, that no one should be isolated longer than ten weeks, and preferably five, without virulence experiments having been performed.

The examination of contacts in order to detect carriers of the virulent organism, and isolate them , is one of the most important preventive measures. But one is of the opinion that the diagnosis of "carrier" is made far too readily. Virulence experiments should be more mumerous.

One has discussed preacautions necessary where hospital isolation is impracticable, and the doubtful value of ordinary medicaments for freeing carriers of bacilli.

School closure is not desirable.

One has concluded that the most promising method of attacking the problem consists in attacking the bacillus as it exists in the human fauces.

One has reviewed the evidence regarding the value, for this purpose of, in persistent carriers, of local applications, such as mercurochrome, etc., and also of general measures sush as the injection of vaccines and antitoxin. One has concluded that these agents are of doubtful value. Finally one has given evidence for one's belief in the efficacy of such measures as tonsillectomy, and expressed one's opinion that these measures should be resorted to in the treatment of individuals who have remained virulent carriers for more than three months.

A P P E N D I C E S.

1. TABLES.
2. CHARTS.
3. BIBLIOGRAPHY.

T A B L E S.

TABLE 1*

England and Wales.

Death-rates, per 1000 of population, from Principal Infectious Diseases.

Name of Disease	1871-1880 Average.	1911-1920 Average.	1921
DIPHTHERIA.	0·12.	0·141.	0·126.
Enteric Fever.	0·32.	0·035.	0·016.
Influenza.	0·01.	0·599.	0·237.
Measles.	0·38.	0·276.	0·059.
Puerperal Septic Diseases.	0·07.	0·033.	0·031.
Scarlet Fever.	0·72.	0·047.	0·034.
Small Pox.	0·24.	0·000.	0·000.
Tuberculosis (Pulmonary).	2·13.	1·079.	0·884.
Tuberculosis. (Non-Pulmonary)	0·75.	0·351.	0·243.
Typhus Fever.	0·06.	0·000.	-----
Whooping-Cough.	0·51.	0·184.	0·121.
Totals.	5·31.	2·745.	1·751.

* Figures abstracted from Annual Report of the Chief Medical Officer of the Ministry of Health for the year 1921.

TABLE 2.

Case Mortality of Diphtheria based on cases notified in London.

	1890-1894 Average.	1917
Case Mortality. %.	28·8.	7·1.

TABLE 3*

Notifications of Diphtheria and Scarlet Fever in the years 1911-20. Rates per Million. England and Wales.

Year.	Diphtheria.	Scarlet Fever.
1911.	1,324.	2,900.
1912.	1,239.	2,980.
1913.	1,329.	3,575.
1914.	1,592.	4,445.
1915.	1,514.	3,592.
1916.	1,428.	2,194.
1917.	1,284.	1,447.
1918.	1,305.	1,439.
1919.	1,496.	2,287.
1920.	1,857.	3,192.
Average.	1,436.	2,705.

* Figures abstracted from Annual Report of the Chief Medical Officer of the Ministry of Health for the year 1920.

TABLE 4.

Schick Test.

Percentage found positive, by various workers, at various ages.

Observer	Zingher.	Copeman[x]	Dickinson.	Leete[y]
Total number of Cases tested.	1,200.	132.	213.	500.
Age				
6 months-12 months	50.	16·7.	---	---
1 - 2 years.	68.	20·0.	50.	100.
2 - 4 "	66.	36·4.	51.	78.
4 - 6 "	53.	16·7.	46·5	59.
6 - 8 "	37.	13·3.	39.	58.
8 -15 "	28.	20·0.	36.	56.
15 "	24·5	15·0.	19.	37·5.
Average.	43·3	18·9.	38.	57·2.

x. In wave of an epidemic in the institution.

y. Scarlet fever patients only.

TABLE 5.

Death Rates from Diphtheria per Million living in different parts of England and Wales.

Years.	1855-60.	1861-70	1871-80.
Densely populated districts.	123.	163.	114.
Medium.	182.	164.	125.
Sparsely populated districts.	248.	223.	132.

C H A R T S.

To show maintained High Incidence of Diphtheria (England & Wales)

Death Rate (per 1000 living)

.6 .5 .4 .3 .2 .1

1871 - 1880
1881 - 1890
1891 - 1900
1901 - 1910
1911
1912
1913
1914
1915
1916
1917
1918

— Scarlet fever Death Rate
— = Diphtheria " "

Chart 1.

Showing Effect of Early Administration of Antitoxic Serum, in Edinburgh City Hospital (8,591 consecutive cases).

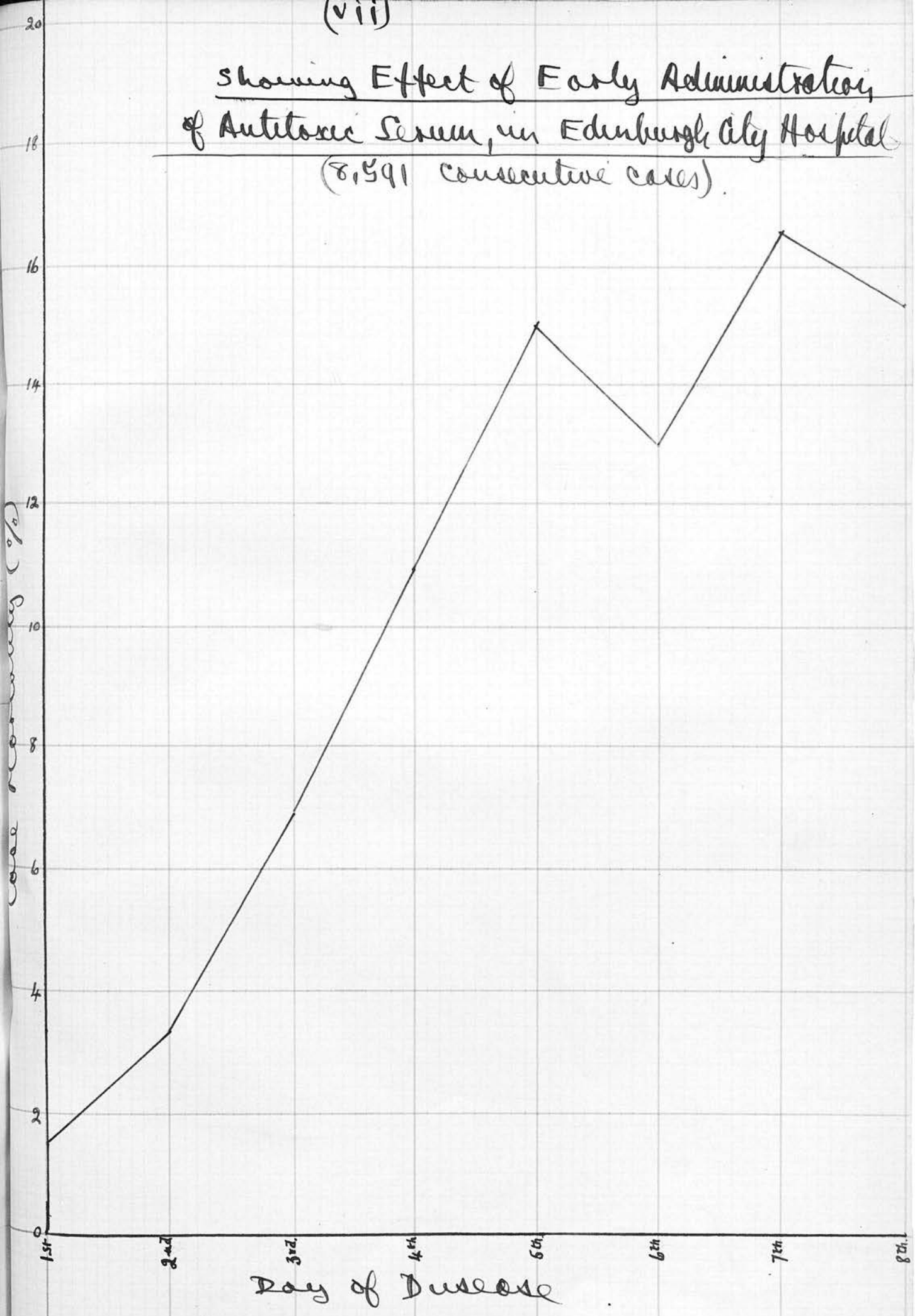


Chart 2.

Showing Average Temperature of early cases of diphtheria, at various days of disease.
(Drawn from temperature, on admission of Blackburn Fever Hospital Cases (55).)

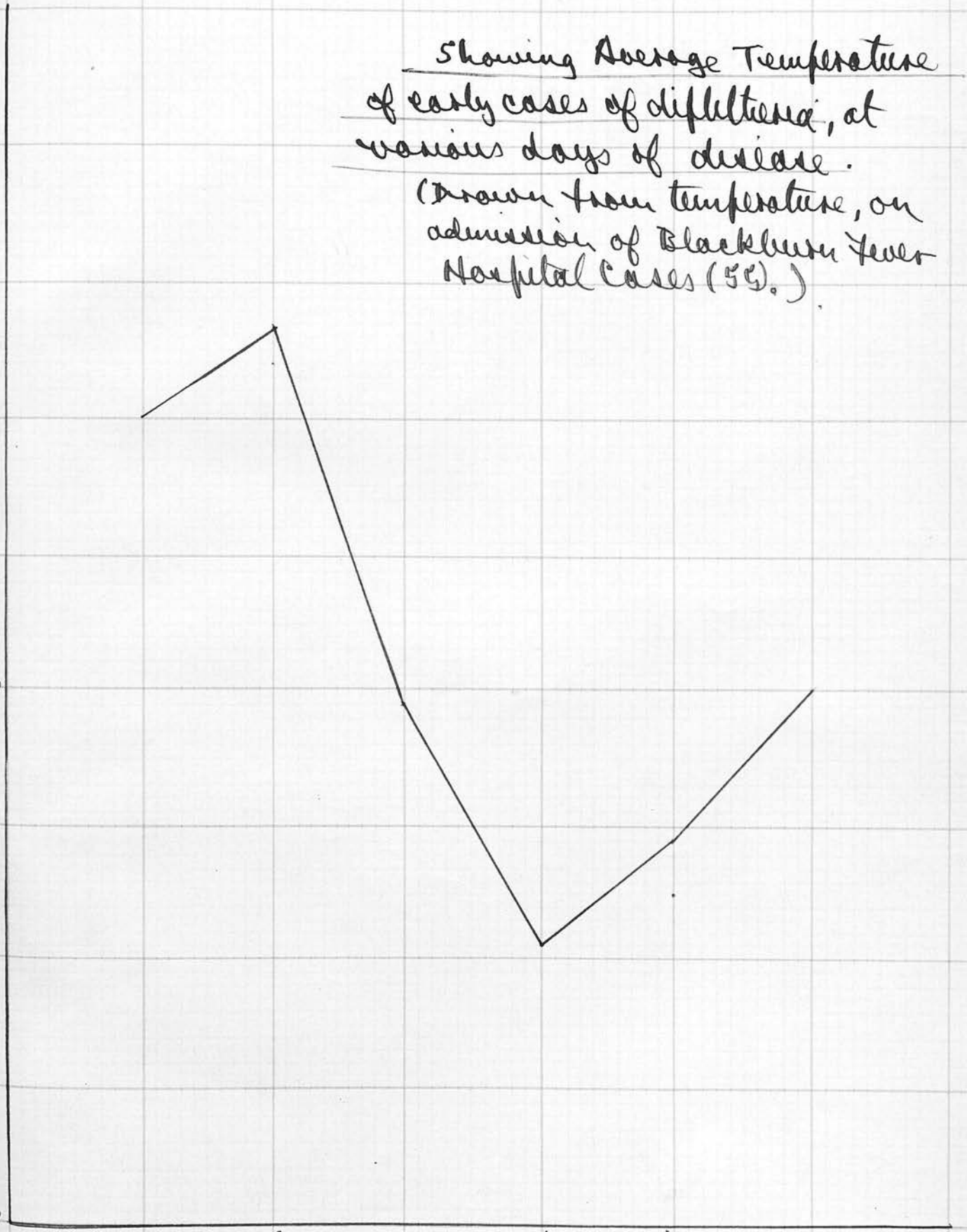
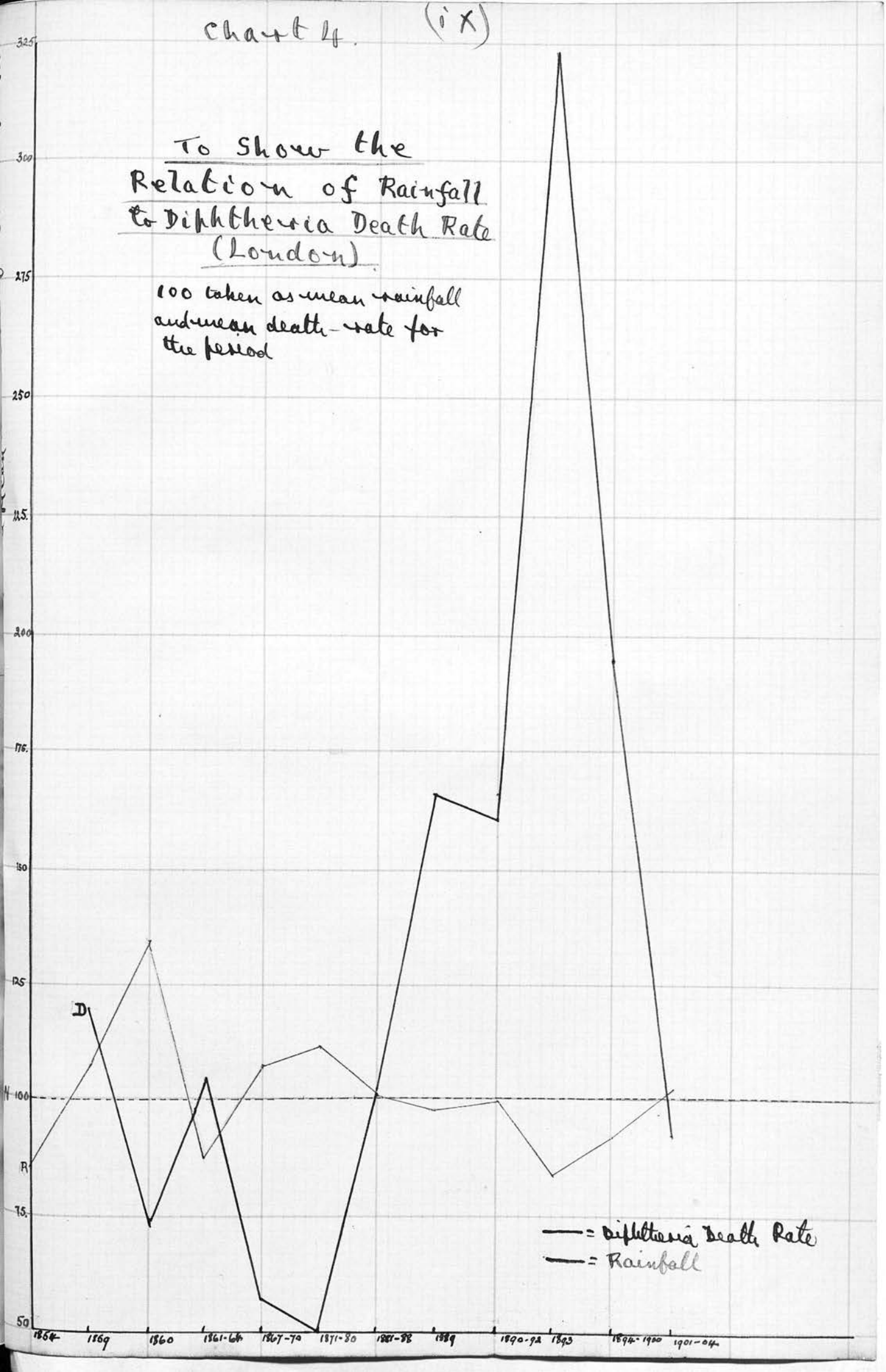


Chart 3.

Chart 4.

To Show the Relation of Rainfall to Diphtheria Death Rate (London)

100 taken as mean rainfall and mean death-rate for the period



(X)

Showing Monthly Incidence of Diphtheria (Blackburn Cases).

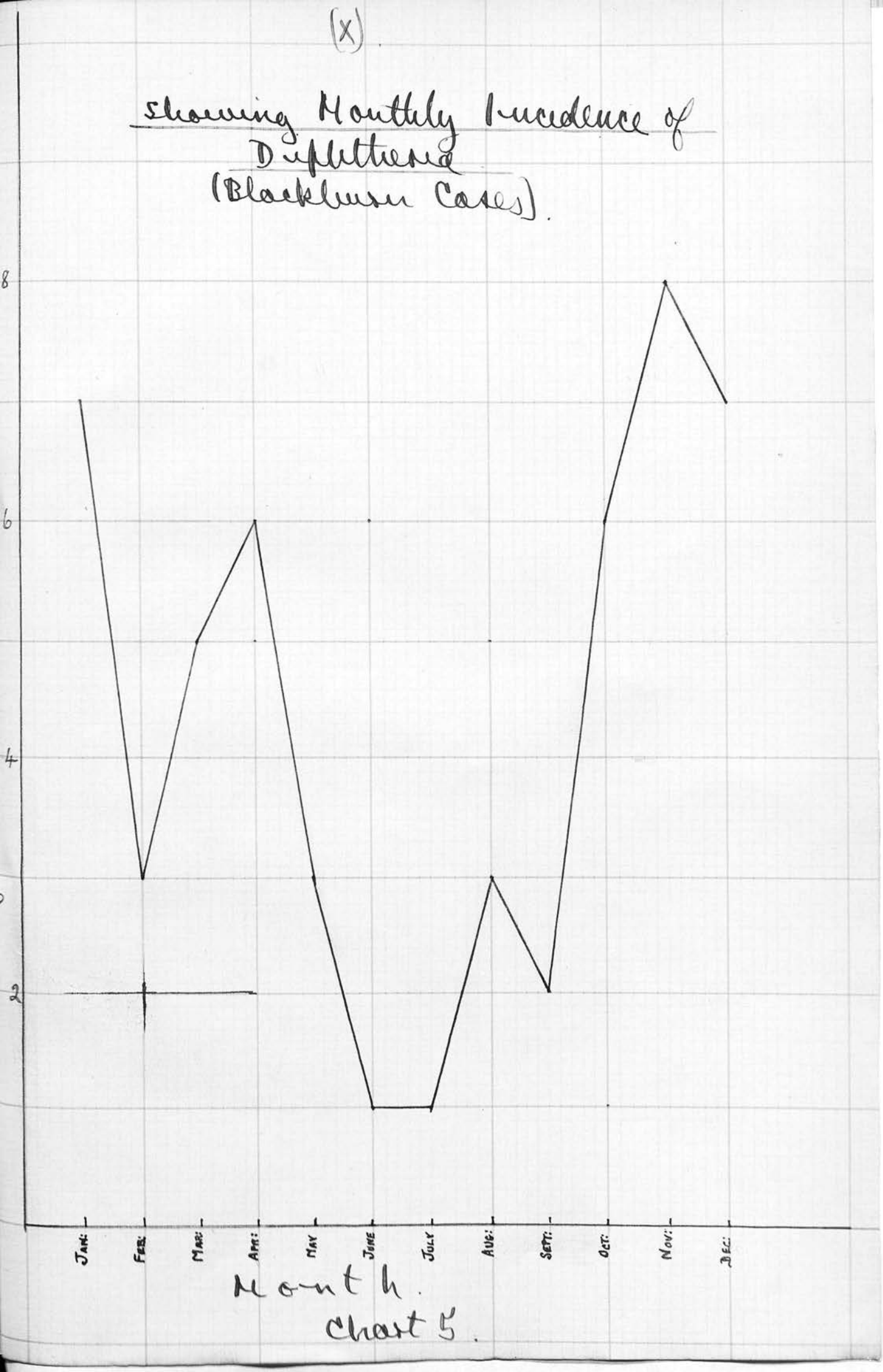
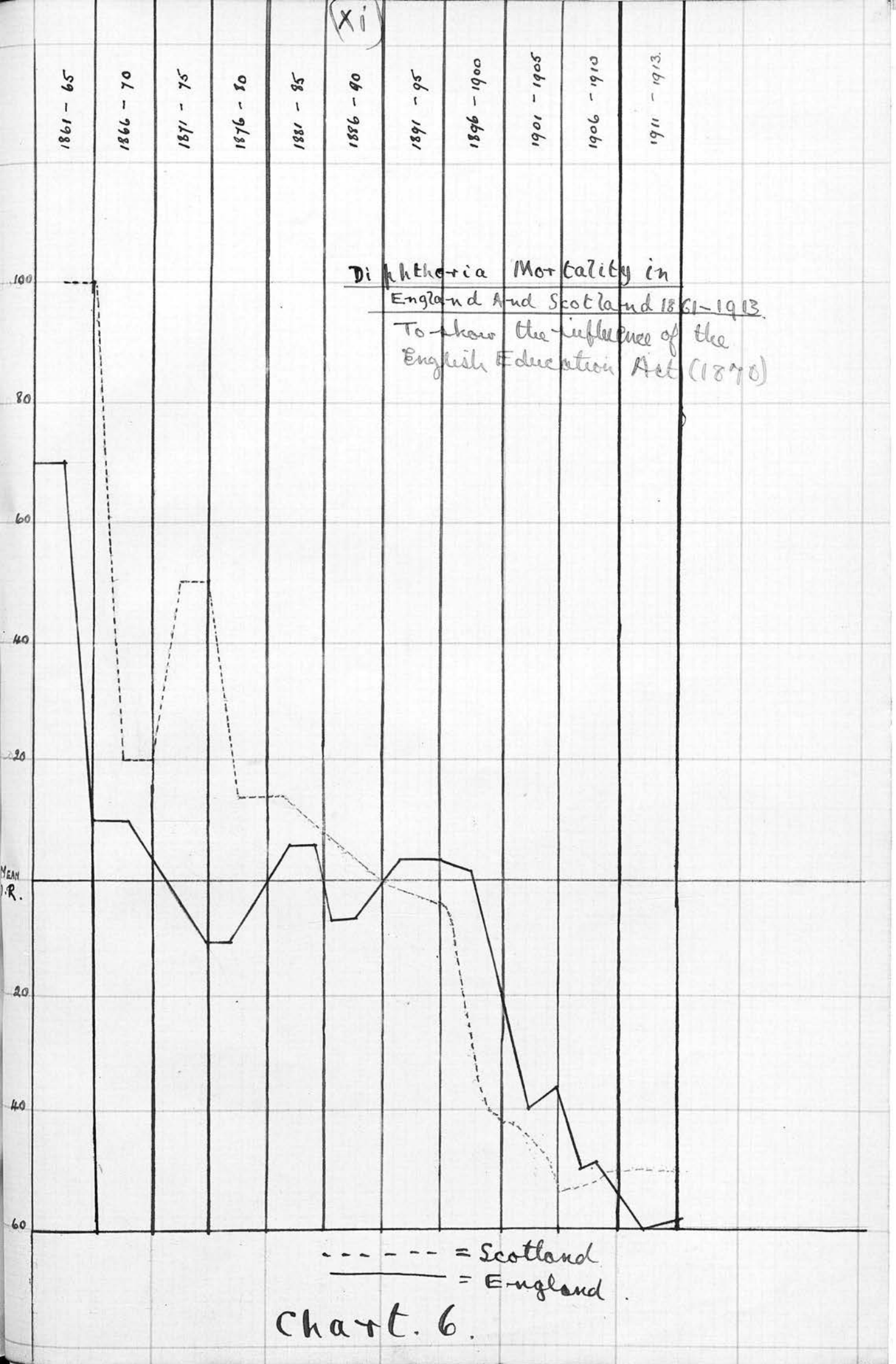


Chart 5.



Diphtheria Mortality in England And Scotland 1861-1913.

To show the influence of the English Education Act (1870)

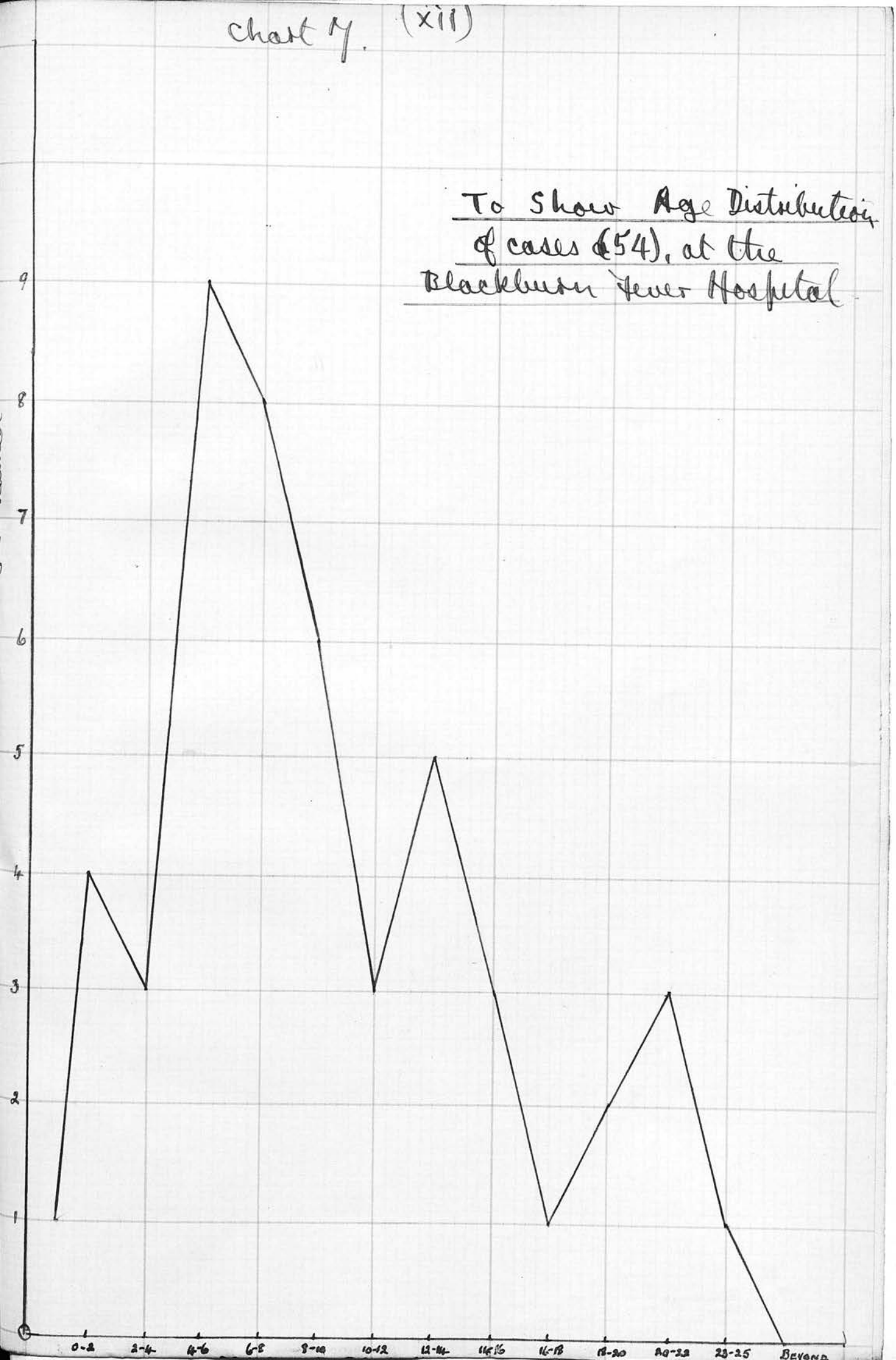
- - - - - - = Scotland

——— = England

Chart. 6.

Chart 4.

To Show Age Distribution of cases (54), at the Blackburn Fever Hospital



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