A Critical Investigation of past and present methods of Control and Treatment of Diphtheria.

A THESIS.

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by

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Sections.

I N T R O D U C T I O N.

(Section 1.)

INTRODUCTORY.

During the last 30 years rapid advances have been made in our knowledge of diphtheria, both from the etiological, bacteriological, and clinical stand-point. Among the most notable landmarks in the rapid advance have been the discovery and isolation of the causal entity by Klebs-Loeffler, the isolation of its toxin by Roux and Yersin, and the elaboration by Behring of a specific antidote.

But notwithstanding the progress made we appear to be no nearer the solution of controlling the incidence of the disease as shown by statistics published from time to time, and by the continuance of seasonal epidemics in our midst.

The prime factor responsible for this appears to be the still unsolved problem of the carrier which not only in diphtheria, but in other zymotic diseases, constitutes the most difficult task of preventive medicine. In communicable disease our aim should be to reduce its incidence, prevent mortality, and cut short its course by attempting to eliminate all predisposing factors liable to give rise to complications.

Good nursing and proper management of each case is essential for success, while the free and early administration of the specific antitoxin with its well-known prophylactic and curative properties is of vital importance so far as the patient's welfare is concerned.

In/

In spite of our increased knowledge and improved methods of treatment, however, when we come to compare diphtheria with such diseases as scarlet fever and measles, whose etiology is still obscure and serum therapy still in the experimental stage, we cannot but regard the outlook as somewhat disappointing.

It is impossible to eradicate pathogenic germs but we can forestall them by adopting such measures at our disposal as the Schick test to search out the susceptible, and by actively immunising such individuals by toxin antitoxin treatment rouse the dormant and protective powers of the body into activity.

The mere education of the public as to the dangers of the disease does not suffice, hospital authorities should be urged to set aside observation accommodation for "doubtful" cases so as to encourage the general practitioner to secure their immediate admittance and early treatment without waiting for a bacteriological finding which oftentimes proves unreliable.

The carrier problem still remains obscure and we are as yet unable to explain why the organisms should persist in the respiratory passages of some convalescents and of healthy individuals.

Nasal carriers appear to be the worst delinquents of all, and this is not at all surprising when we consider the anatomical structure of the nasal chambers with their numerous ramifications and associated air sinuses any part of which may continue to remain infective, such infectivity only coming to light at/

at a future period by the occurrence of some accidental catarrhal process.

The present paper will attempt to deal with some of the more recent advances of control and treatment of this important disease, and is based on clinical observation and experience gained over a period of several years at the Park Fever Hospital, London, S.E. It is not my intention to undertake and discuss work of a purely laboratory or similar technical nature choosing rather to leave that aspect of study to those better endowed with special opportunities than myself.

The observations and deductions made are here collected and form the subject of this paper.

HISTORICAL OUTLINE.

(Section II)

HISTORICAL OUTLINE.

In all probability diphtheria is one of the oldest of the known group of infectious diseases but it is extremely doubtful whether Hippocrates or his contemporaries were aware of its existence. In the writings of these physicians repeated references were made to affections of the throat and air passages, but none bear any similarity to the disease under consideration, the assumption being that it neither occurred in a sporadic nor in an epidemic form during that period of history. The old Arabian physicians were apparently aware of its existence as it is referred to in various treatises and on account of its Eastern origin came to be known as the "Egyptian or Syrian ulcer."

The first accurate account appears to have been given at the end of the first century by Aretaeus[1], a Cappadocian physician, who lived in Rome and who described both benign and malignant types of angina, its common occurrence in children, the associated factor and its great tendency to spread down the respiratory tract with consequent suffocation and death.

Another observer, Aetius[2] of Amida, in Mesopotamia, besides outlining treatment was acquainted with paralysis of the palate, a somewhat common sequel of diphtheria. Only isolated or sporadic cases were observed however and the earliest mention of epidemics dates from the sixth century when diphtheria became the/

the scourge of Europe decimating the population in Spain and Italy.

In the latter part of the sixteenth century a similar pestilence occurred in Southern Europe under the name of "Garotello or Morbus Suffocans," and which from various descriptions given in the literature was undoubtedly true diphtheria. During these epidemics many were the clinical points of interest noted, such as membranous deposits on the pharynx, larynx and nares, a foetor associated with gangrene and suffocative death, while a suggestion as to its infective nature was put forward on account of several members of a family being stricken down almost simultaneously. After a prolonged spell of quiescence it again became rampant throughout European countries and, after spreading northwards, reached England and finally America where it became epidemic in New York.

About this time Samuel Bard[3] of Philadelphia, published an article postulating that angina and croup were akin conditions, but he erroneously included under the same grouping other anginose diseases such as measles and scarlet fever.

Another writer, Ghizi[4], of Cremona, in 1749, described a combined pharyngeal and laryngeal type of the disease and mentioned the occurrence of nasal voice and regurgitation of fluids as a sequel of the disease. Some years later Home[5], an Edinburgh physician, in his publication on croup gave to it the name "Suffocatio Stridula" on account of its most outstanding features,/

tures, the shrill voice and difficult breathing, and considered it to be not only a new but a rare disease.

He found it to be unusually common among children under twelve, damp and cold to be predisposing factors, and he advised treatment by bleeding, blistering and the inhalation of steam.

When the deposit once formed on the trachea he recommended its removal by tracheotomy in certain cases. His treatise stirred the whole medical world and research was further stimulated by the offer of prizes by the Société Royale de Médicine, of Paris, and later by Napoleon the First, for the best papers bearing on the subject.

These however led to little advancement of our knowledge, and so much uncertainty arose as to the nature of the disease, and the difficulty experienced in differentiating it from other infections, that no satisfactory classification was obtainable until the bacillary origin of diphtheria was definitely established.

Indeed it was not until the early part of last century that the clinical features of diphtheria were first clearly understood by Bretonneau[6], a French physician, during his investigations into a supposed outbreak of "scurvy" among the garrison of Tours.

In that epidemic he recognised there could be no connection between the two diseases as diphtheria developed suddenly in persons otherwise healthy, in some developing into the malignant type/

type of angina and, in others, the features of typical croup, the membrane in both cases being similar. He rightly assumed that all the cases observed were caused by one and the same disease and gave to it the name diphthérite (ἡ διφθέρα the skin). Trousseau[7], a pupil of Bretonneau confirmed his chief's observations but substituted the name diphthérie for diphthérite as he considered the specific changes encountered on the mucous membrane were but part of a general disease and not merely a local condition, a deduction which was afterwards accepted by Bretonneau himself. Trousseau further looked upon the disease as being capable of destroying life not only by asphyxia but also by the production of a general toxaemia.

Strong criticism of these deductions was offered by Virchow, the great German pathologist, who maintained that croup was a superficial inflammation, whereas diphtheria was a true interstitial change of a gangrenous nature involving the deeper tissues. He contended that both conditions were due to different causes, and so great was his influence in the scientific world that his opinion obtained many adherents and threw Bretonneau's observations for the time being into the background. It was not until bacteriological and clinical facts became more firmly established and linked together that these divergent views were finally disposed of.

At a later date further confusion arose when it was found that croup could be produced by injecting irritant substances, such/

such as cantharides and ammonia, into the trachea, but Bretonneau soon recognised that such cases ran an entirely different course.

Bacteriological investigation now began to take a prominent place in the scientific world, and the disease was variously attributed to the fungus Oedium Albicans, the leptothrex buccalis, and to various micrococci, but these erroneous findings can only be considered as of historical interest, while inoculation experiments carried out upon animals with the above organisms only gave rise to negative results.

Klebs and Letzgrich[8] were the first to cultivate diphtheritic material on solid nutrient media, and in 1883, at a Congress meeting held in Weisbaden the former described a short slender rod found in the superficial layers of the membrane and staining well with methylene blue, which is to-day recognised as the true causal agent of the disease.

His observations were confirmed by others, but as yet Koch's postulates had not been fulfilled, and it was not until the following year that Loeffler[9] published the results of his experiments, and finally satisfied these requirements.

By culturing material from the false membrane on peptone gelatine and serum this observer grew two types of organisms, cocci and rods, and on injection of the former into mice produced in some cases a general septicaemia, but no lesion suggestive of diphtheria.

He/

He therefore eliminated the cocci as not being the etiological factor, and by using solidified blood serum containing 25% of broth successfully isolated the rods, which on injection into guinea pigs gave most striking results. As the rods were however found at the site of inoculation only, and neither invaded the blood nor tissues of the animal, he concluded from their absence in the latter situations that the disease was the result of a poison elaborated locally by the organism and later taken up by the circulation.

Further investigation showed that in some cases rods were present in the mouth and throat of apparently healthy individuals and this for a time left him in doubt as to whether to proclaim them as the true causative factor, an observation which however is now-a-days more clearly understood.

During his experiments an interesting fact was revealed when two of the inoculated guinea pigs which survived developed at a later date severe paralytic lesions. He also drew attention to the presence of diphtheria-like bacilli in animals, especially birds, morphologically indistinct from the true diphtheria bacillus itself and only capable of differentiation by virulence tests on guinea pigs. The succeeding years brought many important facts to light as regards the life history, the effects of varying conditions, and of chemical agents on the virility of the organism, and Loeffler is credited with the important statement "that convalescents from diphtheria/

theria should not be permitted to resume social intercourse until the complete disappearance of the bacilli had been demonstrated by bacteriological examination", while at the same time he urged the vital importance of disinfection.

Neisser,[10] in the year 1897, described a special process of staining, which still bears his name, and is of undoubted value in differentiating the organism from the group of pseudo-diphtheria bacilli.

Much experimental work and research were also directed to a more comprehensive understanding of the nature of toxins and attempts towards their isolation, which study was principally carried out by the two French investigators Roux and Yersen,[11] who showed that the filtered toxin freed from bacilli when injected into animals was the potent factor in the production of paralytic lesions.

In the year 1891, Behring published a paper in which he made known his discovery of the antitoxin power of the blood of highly immunised guinea pigs, a condition brought about artificially by the employment of non-lethal doses of the toxin with the subsequent production of a non-fatal attack of diphtheria.

Thus a distinct advance was made in the discovery of an agent capable of neutralising the action of the poison responsible for all the manifestations of the disease, a discovery which has since led up to the preparation and adoption of antitoxin on a large scale as a therapeutic agent of considerable value.

Time has shown that serum administration has its drawbacks as/

as evidenced by certain clinical phenomena following its employment, but these have neither minimised its value nor have they proved a contra-indication to its universal adoption.

Of more recent date has been the introduction of the Schick test in order to determine the susceptibility of individuals to minute doses of the diphtheria toxin by intradermal injection. Subsequently immunisation of positive reactors by toxin-antitoxin or toxoid preparations can be produced, a procedure which is now being carried out on a large scale in the cities of New York and Aberdeen, with most encouraging results.

Such in brief is the historical outline of the disease. Without under-estimating the great value of bacteriological research one may say that it is the introduction of serum therapy which has to-day made diphtheria cease to be anything like such a menace as it was in former years.

BACTERIOLOGY OF DIPHTHERIA

(Section III.)

CRITICISM OF BACTERIOLOGICAL RESULTS.

Having dealt with the clinical aspect of the subject in the previous Section, a criticism of bacteriological findings is necessary in order to ascertain what assistance this department can offer in the control of the disease, and to what degree fallacies may arise by depending too much on the results obtained.

Once the disease is fully established clinical evidence speaks for itself, and diagnosis presents little difficulty, whereas in cases where the condition has not yet sufficiently developed or in the milder forms of infection we have to look to the bacteriologist for an expression of opinion on the material supplied.

He can inform us of the presence or absence of the diphtheria group of organisms and can differentiate between virulent and non-virulent strains by animal experiments, though the exact relationship existing between these forms has not yet been clearly defined.

Owing to marked variability in morphological characters, such as size and shape of the organism, considerable error must necessarily enter into attempts at identification but Westbrook Wilson and McDaniel[12] have made a morphological grouping which has to some extent narrowed the limits of error.

Neisser's stain, as a contrast stain, has likewise proved of invaluable assistance in distinguishing the true bacillus from pseudo-types/

pseudo-types showing similar morphological characteristics, but in all cases the skill and experience of the observer is a factor which cannot be disregarded.

One source of error in finding the specific organism is failure to swab the infected area; either accidentally or because the part involved is difficult of access, notably in the case of the nasal cavities and sinuses.

As regards the isolation of the organism from the nasal sinuses, a few cc's of normal saline previously sterilised and warmed would require to be introduced by means of an exploring syringe and the fluid subsequently withdrawn for examination.

Such a procedure could readily be performed through the inferior meatus in the case of the maxillary antrum, but exploration of the sphenoidal sinuses by reason of their anatomical situation and variation in development would prove a far more difficult task, and the possibility of injury to the fragile cribriform plate, leading to meningeal complications would be a very definite one.

No feasible plan seems to have been put forward to cope with these contingencies nor have the parts referred to received the consideration to which they are entitled as a possible nidus of the organism in the intermittent state of nasal carriers.

Possible errors in cultivation.

Sometimes considerable difficulty has arisen in obtaining a suitable growth of the Klebs Loeffler bacillus from culture media/

media within a period of twenty-four hours. Swabs taken, and smears made on such media, particularly during convalescence, have failed to reveal the presence of the organism within the time stated.

In consequence, this has led, in not a few instances, to the belief that such cases were free from infection, a conclusion, which on further investigation, was disproved. The question has therefore arisen as to whether the delay in cultivation could be attributed to unsuitability of media, the incubator having been maintained at the standard temperature of 37°C.

The media however can be absolved from blame if one out of every batch of a series of culture tubes is previously tested, before despatch from a laboratory, by inoculation from a sub-culture of the bacillus in order to find out whether a suitable growth can be secured in the given time. On the other hand the inoculation of a culture tube from a swab is apt to give varying results and repeated failure has been experienced in identifying the bacillus within a period of twenty-four hours, although subjection of the serum tube to a longer period of incubation, namely, thirty-six to forty-eight hours has given a positive finding.

This occurrence may be explained by the fact that a swab is necessarily contaminated with the bacterial flora of the throat and nose which, in growth and multiplication, have apparently outstripped the diphtheria bacillus, and so, for the time being, obscured the issue.

The/

The length of incubation in the case of a SWAB, as compared with that of a subculture, is therefore a consideration of practical importance particularly during the convalescent period when the specific organism is less vigorous.

Furthermore, the direct examination of a swab for diphtheria bacilli by reason of its contamination with other organisms and débris frequently leads to the giving of an uncertain opinion and cannot by any means carry the same weight as when the bacteriological examination is controlled by cultural methods.

Fallacies in the virulence test.

There is no reason to dispute the fact that virulent and non-virulent strains of the bacilli can exist in the same individual.

Should the latter type therefore be alone isolated and submitted to virulency tests it would naturally lead to a wrong conclusion, yet, the test must still be considered as our main stand-by in determining freedom from infection.

Estimation of virulence has long been a laboratory procedure and Wayson[13] was the first to suggest the use of field cultures in order to save time required for isolation of the bacillus in pure culture.

Further work on the subject was carried out by Force and Beatty;[14] Havens and Powell[15] and others who have since shown that the presence of contaminating organisms in the original diagnostic/

nostic culture does not interfere with typical results. This consequently saves time since pure cultures do not require to be isolated and permits of a determination in those cultures where it is not possible to obtain pure cultures.

But there appears to be two fallacies in this procedure as the possible presence of virulent haemolytic streptococci would cause rapid death of the animal long before the toxins of the specific organism had had time to exercise their characteristic effects on the suprarenals, while a slow growing and feeble toxigenic producing strain in the presence of pyogenic organisms might be similarly unproductive in its results.

Kolmer and Moshage[16] insist on the following requisites for a reliable virulence test:

(a) Delicacy in order to appreciate degrees of virulence.

(b) Representative sampling, i.e., the test should be made with a mixture of bacilli from several colonies of the culture in order to avoid danger of picking only one strain when virulent and non-virulent strains coexist in the same individual, and

(c) Specificity, i.e., the test should be made with pure cultures since "cultures contaminated with other micro-organisms may show no evidence of virulence because of alteration of the culture medium or the presence of products of the metabolic activity of the contaminating organism."

Variation in results.

From time to time a discrepancy has been noticed between results obtained by the hospital staff of the Boards hospitals and/

and those obtained by outside bacteriologists, and this is seen not only in the bacteriology of diphtheria but also to a lesser extent in Widal examinations.

Consequently a decided increase has been observed in the number of cases notified as diphtheria and diphtheria carriers admitted to hospital from the surrounding boroughs, which on later investigation have failed to corroborate the bacteriological findings.

In these cases one is inclined to suspect a difference in technique or interpretation on the part of two different investigators which leads to the suggestion as to whether it would not be possible to bring bacteriologists into closer touch, and so to reach a greater uniformity in their results, thus preventing unnecessary removal of such doubtful cases to hospital.

Again a negative report in diphtheria by no means excludes the possibility of infection any more than a proof of the presence of the organism gives confirmation of the disease.

There are undoubted cases of throat infections both with and without tonsillar exudate from whom a throat culture has revealed the presence of the organism of diphtheria, and yet the latter apparently plays no part in the pathological process. As regards the probability of conveying diphtheritic infection to others, such cases must necessarily be included in the Statistics of the disease.

In several instances this has occurred in patients who were/

were definitely known to be Schick negative re-actors and to whom further allusion will be made under the Section on treatment.

Bacillus of Hofmann.

A great deal of controversy has continually arisen in the past regarding the pathogenicity of this organism. On account of its uniformity in size and shape it is unlikely to be confused with the typical diphtheria bacillus, and it is only in those cases where the short atypical forms of the latter are in evidence that doubt should arise.

Hewlett and Knight[17] are inclined to the belief from experimental evidence obtained that the Hofmann bacillus is capable of conversion into the Klebs Loeffler bacillus and vice versa, and that it can replace the latter in the throats of convalescent cases.

Cobbett[18] however maintains that during the acute stage of the disease the diphtheria bacillus is most in evidence while the Hofmann bacillus is liable to be overlooked, and that only when the former has spent itself during the convalescent period does the Hofmann organism come into prominence.

Whether this be the case or not present-day bacteriological evidence strongly favours the view that these organisms are totally independent of each other and the Hofmann bacillus can be regarded as innocuous on clinical grounds as in no instance have we been able to associate its presence with "return cases" of diphtheria.

Summary.

The foregoing remarks serve to show that bacteriological evidence is often not so conclusive as one might be led to suppose.

The bacteriologist can indicate the presence of infection by informing us whether organisms are present morphologically identical with the Klebs Loeffler bacillus, and whose cultural characteristics on different media conform with it, but he cannot state whether they are harmless or otherwise without resorting to animal experiments.

Furthermore, his findings do not prove of any prognostic value, a factor which lies entirely within the province of the clinician.

His report must necessarily be looked upon as a means of coming to a conclusion, and bacteriological and clinical findings must in all cases be given only relative consideration.

THE EARLY SIGNS AND SYMPTOMS OF DIPHTHERIA.

(Section IV.)

The Early Signs and Symptoms of Diphtheria.

The symptomatology of this disease in its earliest stages is often so obscure, and the onset so insidious that the individual attacked may be going about with the disease well advanced before a diagnosis has been made.

Indeed, some of the prodromal signs at times are suggestive of other specific infections such as influenza, and this is more especially the case where the condition is ushered in by headache, backache or pains in the limbs. In the laryngeal form the very urgency of the symptoms and progressive embarrassment to breathing and circulation by the obstructive element should lead one to an early decision, but here again confusion may arise with measles if the buccal mucosa is not carefully scrutinized for the presence or absence of Koplik spots, and, particularly so, when the person has been exposed to that infection or an epidemic of measles happens to be prevalent at the time.

Again, through neglect to examine the throat, glandular swelling and oedema of the soft tissues of the neck have been the first outward manifestation of the disease giving rise to considerable facial disfigurement and leading to an erroneous diagnosis of mumps, valuable time being thereby lost in instituting early treatment.

In all cases where a child appears to be "out of sorts", even in the absence of difficulty of swallowing or sore throat, the/

the fauces should be examined as a routine measure so that the presence or absence of diphtheria can be early determined.

Temperature.

The temperature in diphtheria is as a general rule comparatively low as compared with other specific infections, and in a large number of charts examined did not exceed 100°F.

In those cases where the temperature registered 102°F., or more, other factors were involved such as an accompanying and well marked tonsillitis, or an unduly rapid extension of the infection, while in not a few cases there was a definite history of constipation of two or three days' standing. Neither the elevation nor the duration of the pyrexia can however be considered as of any special significance although in the more severe types of the disease it is usual to find it but hardly raised above normal.

Pulse.

Observations on the pulse rate showed that the occurrence and duration of the initial tachycardia were of no diagnostic value but at the same time any alteration either in force or abnormal slowing of the pulse are points to be carefully weighed as probable signs of an early implication of the heart muscle by the toxaemic process.

Vomiting.

Vomiting was found to be of less frequent occurrence than in/

in the case of scarlet fever provided the toxaemia was not of the severe type, the occurrence of this symptom being more commonly associated with the onset of grave myocardial change, and in a few cases it has proved to be one of the early manifestations of a commencing serum sickness at a later period of the disease. Both the incidence of vomiting and of early adenitis may however be taken as of some prognostic value as to severity, the former tending to aggravate heart weakness, and also by the mechanical act of straining to further add to the general exhaustion of the patient.

Albuminuria.

As this symptom can occur in any inflammatory throat condition it is of minor importance as a guide to diagnosis during the febrile period, but where the temperature is barely raised above the normal its presence is a strong point in favour of diphtheria as stated by Kerr.[19] Where persistent and copious it is quite uninfluenced by dieting and is invariably associated with the severer types of angina. In purely laryngeal cases the symptom is invariably absent.

Haemorrhage.

An epistaxis, or more commonly a sanguinious and irritating discharge from the nostril, must always be viewed with suspicion, but where the discharge is unilateral the exclusion of a foreign body from the implicated nasal chamber should be made.

Coffee ground vomit in the initial stages is of little moment/

moment as it may result from previous swallowing of blood during the process of separation of the membrane, but should this symptom occur after the angina has subsided, especially during the second week of the disease, it is always attended by a fatal issue.

The view may be accepted that haematuria is of exceptional occurrence in diphtheria, but in two instances during the past five years its presence appeared to have some connection with the onset of serum sickness, and subsided on the termination of the reaction.

Pallor.

Pallor as an early sign may be associated with any toxaemic process and apart from this has little significance.

Reflexes.

With regard to the reflexes Tirard[20] states that "one symptom which affords a certain amount of help in diagnosis of any form of diphtheria is the early abolition of the knee jerk", but this statement is open to criticism.

The knee jerk may be sluggish from disuse or even abolished but this does not usually occur until the third or fourth week of the disease or even later and may remain persistently absent for months.

Of the other reflexes that of the pupil is never involved the diphtheria toxin having a specially selective influence upon the oculo-motor and ciliary mechanisms.

Rolleston[21]

Rolleston[21] states that the Babinski sign is not infrequently obtainable during the early stage of diphtheria and is inclined to place a certain prognostic value on its presence as he thinks it invariably foretells the advent of complications later.

The Babinski sign, however, with few exceptions, is an INDICATION OF AN organic lesion involving the upper motor neuron, whereas in diphtheria which is essentially a peripheral neuritis the flexor type of reflex is invariably the rule. Its absence in diphtheria should therefore count more than its presence.

Querido[22] has recorded cases of haemorrhages into the central nervous system owing to changes in the vessel walls, emboli in the cerebral vessels, or encephalitis following diphtheria, and it is in such instances that we would expect to find the Babinski sign as of paramount importance.

Local Lesion.

The most characteristic features of the disease is without doubt the formation of a false membrane as a result of the toxic process acting locally.

Where present and accompanied by oedema of the soft tissues the condition is readily recognisable and any definite patch surrounded by a marginal zone of redness is highly suggestive. No stress can be laid on the colour of the membrane but the difficulty of removal, the rapidity of spread, its unilateral situation at first, and the presence of exudate either on the anterior or posterior/

posterior aspect of the uvula are points which must receive due consideration.

In some cases the peculiar foetor alone has in the hands of the experienced enabled a diagnosis to be made and even so prior to an examination of the fauces, while in not a few instances especially in adults where the initial attack has been so slight as to escape notice the nature of the disease has only been fully appreciated on the supervention of paralytic phenomena later.

THE PROBLEM OF ISOLATION.

(Section V.)

The Isolation Problem.

Certain circumstances militate against the attainment of complete success in eradicating the disease by hospital treatment. In times of stress, for example, consequent on epidemic outbreaks fever accommodation may become unduly taxed and temporarily bring about a relaxation of hospital regulations.

Convalescents released from hospital may contract a cold or catarrh and become infective after discharge from hospital, or previous discharges from the nose or ear may recur and form a fresh focus of infection.

Niven, of Manchester, has shown that return cases bear a close relationship to hospital treatment, and is of the belief that this is due to the recent association of discharged cases with acute forms of the disease, a comparatively rare event so far as home-nursed children are concerned.

Something may be said in favour of separating convalescents from acute cases in hospital in as much as we have the advantage of bacteriological investigation to guide us but this is not always feasible where accommodation is of a limited nature.

Some critics maintain that the cost of upkeep of fever institutions is no recompense for the benefits conferred by them as segregation increases the risk of complications and of secondary infection, and that in not a few instances infection has/

has had ample time to exercise its dire effects before removal of the infected to hospital. The development of the cubicle system has done much to obviate the risk of error or of doubt in arriving at a diagnosis and of eliminating the influence of cross infection but the question of expense is one which has to be faced if this is carried out on anything like a large scale.

Many factors seem to be involved in attempting to estimate the true value of hospital isolation by statistical evidence as the density of the population, the number of those exposed to infection, and those of susceptible age period have to be taken into consideration. Yet none of these factors are a constant quantity and this adds greatly to the difficulty of arriving at a true conclusion as to their utility.

VITAL FACTORS CONCERNED IN THE CONTROL OF DIPHTHERIA.

(Section VI)

Behring was the first to show that the blood serum from horses immunised by small doses of diphtheria toxin in gradually increasing doses possessed the power of neutralising the toxic factor of the disease, an observation which was later put into practice after the amount of antitoxin in the immune serum had been determined and expressed in units.

Dosage. Opinions, however, vary as to the appropriate dose of serum suitable for administration in individual cases and at one time the standard accepted was comparatively small as compared with present day conceptions.

There is no means at our disposal for accurately gauging what is an adequate dose in any one case as the quantity of toxin elaborated by the particular strain of the infecting organism is an unknown quantity and reliance must be placed on the degree of toxaemia as shown by the general condition of the patient, the extent and severity of the local lesion and the duration of the illness.

For mild cases I usually employ a minimum dosage of 8000 units, in moderate cases two doses of 16000 units each on consecutive days, and for severe types of infection not less than 24000 to 30000 units repeated on at least three successive days.

Park[23]/

Park[23] believes that one large initial dose of serum is sufficient to tide the patient over the whole course of the acute stage of the disease, but other authorities - e.g. Bie of Copenhagen and Friedemann consider that the repetition of large doses is an important factor in the cure of severe cases and with the latter opinion, I concur.

The use of subsequent injections must, however, in no way be considered as minimising the importance of the primary dose, but they should be rather looked upon as adjuncts in enhancing its value.

From a study of the statistics of various clinicians certain points of an instructive nature are revealed in relation to age, the first being the comparative rarity of the disease in the first year of life and secondly that the incidence is greatest during the 1 to 5 age period, while the mortality is apparently highest in children of from two to three years.

With the exception of infants, children display a high degree of susceptibility, their powers of resistance to the toxaemia being considerably lower than is the case with adults and so proportionately they require a larger dosage of serum.

Their greater liability to the laryngeal type of infection is also well known and calls for early control.

The/

The following table shows the mortality per cent, the cases being arranged in age periods.

	Under 5	5 - 10	10 - 20	20 - 30	30 upwards	Total
No. of cases	520	515	321	93	37	1486
No. of deaths	67	28	4	-	-	99
%age Mortality	12·8	5·4	1·2	-	-	6·6

Duration of Illness.

The history of onset has always had an important bearing on the prognostic outlook of a case as the earlier treatment can be carried out the more favourable will the issue be.

Unfortunately opportunities of recognising the disease on the first or even the second day of its inception are not always obtainable, its insidious character, the comparatively trivial discomfort associated with its earliest manifestations, and the extreme youth of the patient, oftentimes acting as factors which operate adversely to the patients' interests and thereby favour an increase in the mortality rate.

Yet no case, however desperate, should be despaired of, although with each succeeding day lost the prospect becomes less encouraging and the amount of antitoxin for administration must/

must be proportionately increased.

The following table shows the mortality from diphtheria the cases being grouped according to the day of disease on which antitoxin treatment was commenced.

Day of Disease:	1st	2nd	3rd	4th	5th	Total
Cases	25	127	135	123	90	500
Deaths	-	2	9	12	14	37
Mortality per cent	-	1·5	6·6	9·7	15·5	7·4

The Site and extent of the local lesion.

Of no less importance than age and duration of onset is the situation and extent of the membrane and the initial dose even in the apparently milder type of infection should not be less than 8000 to 16000 units of antitoxin. In some cases extensive formation of membrane has occurred before the disease was fully recognised and particularly so in cases where the primary seat of infection originated in the naso-pharyngeal space no visible deposit having as yet appeared on either the fauces/

fauces or tonsils.

The degree of oedema and swelling of the soft parts is also a feature for consideration more especially in young children as it is indicative of a high degree of severity.

SERUM THERAPY.

(Section VII.)

(a) Technique of serum administration.

MODES OF ADMINISTRATION OF ANTITOXIN.

Although promptness of administration and sufficiency of initial dosage are by far the most important factors for the successful treatment of diphtheria by antitoxin, there still remains open for consideration the mode of injection. Various routes have been employed or suggested namely the subcutaneous, intramuscular, intravenous and intraperitoneal, and while each has its advocates and opponents the first two named at least are probably more within the scope of the general practitioner.

(a) Subcutaneous Method.

For the milder types of infection even in hospital the subcutaneous method still retains favour by reason of the ease of administration and the usual site chosen for injection is the abdominal wall, an area which on account of the laxity of the tissues renders it most suitable for the reception of the serum in bulk.

Moreover for subsequent inspection and in unlooked-for circumstances where septic infection ensues it is a situation in which abscess formation can be more readily dealt with. Smith[24]/

Smith[24] and Park[25] have shown that when the subcutaneous route is employed the maximum amount of antitoxin is found in the blood stream only after a period of three to four days and in consequence where time is to be considered as a factor for safety one would naturally select for preference the more direct intravenous route especially in the graver types of the disease. Nevertheless the effects of some of the serum at least are shown to be operating long before the time stated by the above authorities, as evidenced by the clinical improvement in the patient's condition after a period of twelve to eighteen hours has elapsed.

The Intramuscular Route.

If antitoxin is given intramuscularly the period of time when the maximum amount of serum is available is still further shortened and therefore from the point of view of efficacy it may be taken as occupying a medium rôle between that of the subcutaneous and intravenous routes.

On the other hand the supervention of sepsis after intramuscular injections of serum, though fortunately rare, is a much more serious catastrophe as considerable destruction of the muscle tissue is liable to occur with subsequent crippling of the patient as an almost inevitable result.

An interesting point in technique has recently been furnished by the experiments of Zwick and Batson[26] on the cadaver. As/

As the result of their investigations these authors recommend that intramuscular injections should be made with the shaft of the needle parallel with the general direction of the muscle fibres and with the needle point directed towards the dependent part of the muscle, a recommendation which ensures freedom from injury to large vessels and nerves.

The Intravenous Route.

The importance of this method lies in the fact that as all the serum passes directly into the blood stream its full powers can be immediately exercised and in those instances where treatment has for any reason been unfortunately delayed and the patient's system is inundated with toxins it forms the most certain means of checking the ever accumulating toxaemia.

Originally suggested by Cairns[27] the method later received the support of such authorities as Bulloch[28] and Emery,[29] while Roehr[30] recommended that the serum should be well diluted with normal saline prior to its administration.

As regards its practical application the needle is fitted to a syringe charged with serum and introduced into an easily accessible vein, such as the Median Basilic at the bend of the elbow, the vessel having previously been distended by the application of pressure from above.

It is also advisable to guard against possible risks of air/

air emboli by ensuring that the apparatus has previously been freed from air bubbles before introducing the serum.

Difficulties in technique occasionally arise and are most likely to be encountered in young children especially those of tender years and with much adipose tissue, the insertion of the needle in such cases being often attended with considerable difficulty.

Osgood[31] considers that the injection of antitoxin by the intravenous route is contra indicated in organic lesions of the heart, blood vessels, and kidneys and in protein sensitivity unless the patient can be successfully desensitized.

The Intraperitoneal Route.

This method of administration has been enthusiastically urged of late in the journals of American literature and consequently it may be appropriate to comment upon it.

Tommy Goehle and Dauer[32] using commercial antitoxin undiluted with saline treated 168 cases of diphtheria intraperitoneally and claim that the rapidity of absorption is five times that of intramuscular injections and at least equal to the intravenous method in efficacy as regards disintegrating the membrane.

They further state that severe reaction with chill or rigor/

rigor is comparatively infrequent and for safety and simplicity they consider it the method of choice in severe cases of toxic myocarditis.

Nevertheless I am of the opinion that concentrated serum with the addition of normal saline is more appropriate for this purpose as the possibility of shock resulting from the injection and subsequent serum sequelae are thereby greatly minimised.

Before actual introduction however it is expedient to ensure that the temperature of the diluted or undiluted serum is at blood heat or slightly higher while the posture of the patient and the direction of the needle point should be such as to permit of the entering fluid gravitating towards the pelvic cavity.

Nor must the question of possible septic contamination and subsequent peritonitis be lost sight of, due precautions being taken to obviate this by careful technique in the practice of aesepsis.

In favour of the adoption of this route it may be conceded that a solution will run more readily into a cavity than into the cellular or muscular tissue as the adverse pressure is less and that once the actual passage of the needle point into the abdominal cavity has been successfully accomplished the patient will naturally experience a greater degree of comfort during the administration of the serum.

A further concession which may be granted in its favour is the ease and comparative safety of administration as no more difficulty/

difficulty is encountered in introducing a needle point into the abdominal than into the pleural cavity. Moreover provided that a suitable needle is chosen, there is no risk of local injury as the blunted point will readily glide off the glistening bowel without penetrating the latter, while time and labour involved in getting a needle satisfactorily into the vein of a young child by the intravenous route is not here experienced.

The method has, however, received no support in this country and in consequence it is difficult to offer an unbiassed opinion as to its therapeutic value.

The Oral and Rectal Method.

The administration of serum by mouth is not now practised either as a prophylactic or curative measure as it has been proved incapable of converting a Schick positive reactor into a negative reactor; while apart from the question of absorption the fact that the serum has to run the gauntlet of the digestive juices of the alimentary canal with possible changes in its composition and properties might be advanced as another drawback to its utility.

Nor have the experiments of Chantemesse[33] with serum administered per rectum been attended with any greater success and both these methods are now considered obsolete by present day clinicians.

(Section VII.)

(b) Varieties of Serum and their therapeutic value.

The phenomena resulting from the injection of a foreign serum has always remained a subject of great interest to the clinician and the beneficial effects of serum therapy, great though they may be, are to some extent marred on occasions by the production of sequelae of an undesirable nature. Such manifest themselves as a rule during the period of convalescence and are apt to embarrass temporarily the progress of the patient towards recovery.

Lublinski[34] and Scholtz[35] in the year 1894 described the occurrence of urticarial rashes not infrequently accompanied by joint pains after the injection of antitoxin serum and later Johannsen, experimenting with normal horse serum, met with similar phenomena, an observation which apparently implied that the sequelae resulting therefrom were due to deleterious substances in the serum itself.

At a still later date Hartung[36] basing his opinion on collected statistics expressed the view that something concerned with the individuality of the horse was the real causal factor in their production.

Therapeutic measures have proved of little avail in the treatment of serum sequelae and apart from the relief afforded to individual symptoms on palliative lines the course of serum sickness remains unchecked.

Calcium/

Calcium chloride has no doubt its advocates and has been recommended for internal administration during the first three days following injection, but the only apparent way to prophylaxis is the adoption of measures directed towards "perfecting" the serum by removal of the deleterious substances therein contained without in any way depreciating its antitoxin value.

By concentrating the product a distinct advance has been made in that direction and a comparison with the unconcentrated variety in the present thesis tends to show from the data recorded that not only does a reduced incidence of serum sequelae result but a definite amelioration of some of the more objectionable features of the phenomena.

Gibson[37] in 1905 found as the result of experimental research that if diphtheria antitoxin serum was treated with ammonium sulphate and the resulting precipitate dissolved in a saturated solution of sodium chloride the globulin dissolved in this solution contained all the antitoxin elements freed from the proteid non-antitoxin factors.

The soluble globulins were precipitated by acetic acid and placed in a parchment sac and dialysed.

The solution of globulins was then neutralised and sufficient sodium chloride added.

The refined and concentrated serum as supplied to us differs in a minor respect from the above procedure, sodium sulphate/

sulphate being substituted for the ammonium salt as the precipitating agent.

As the result of precipitation and brining the albumin and euglobulin fractions are removed and the final product consists mainly of a solution of pseudo-globulin and diphtheria antitoxin.

The specific antitoxin in the concentrated form was first issued to the Metropolitan Asylums Board's hospitals in 1927.

Prior to that date unconcentrated serum alone or with the addition of 25% of concentrated antitoxin serum was in use at a strength of from 300 to 400 units of antitoxin per cc. but with the subsequent adoption of the concentrated product only, the unitage rose to from 800 to 1000 units of antitoxin per cc.

Working in conjunction with White, Director of the Board's Antitoxin Laboratories, I was enabled to undertake a clinical investigation of the relative value of unconcentrated diphtheria antitoxin (natural serum) and of concentrated diphtheria antitoxin (solution of antitoxin globulins) and in order to make the test comparative specially prepared batches of each serum were supplied by him containing approximately the same number of units per cc. and a similar amount of protein per unit.

By this means the question of difference in volume and the amount/

amount of foreign protein injected was eliminated. In carrying out the test it was so arranged that patients admitted on alternate days should be treated one day with concentrated antitoxin and the following day's admissions with unconcentrated, each patient receiving only one variety of antitoxin throughout the whole course of the treatment.

1400 cases in all were treated in this fashion comprising 700 in each group and a statistical analysis of the results are herewith recorded.

	No of cases	Rashes	Pyrexia	Arthritis	Adinitis	Oedema	Albuminuria.	Vomitory	Serum Abscess
oncentrated.	700	218	39	3	1	2	3	1	0
	%	31·1	5·6	0·4	0·1	0·3	0·4	0·1	-
nconcentrated.	700	285	137	36	15	12	6	11	2
	%	40·7	19·5	5·1	2·1	1·7	0·8	1·5	0·3

Rashes

The rashes are subdivided into three groups according to the degree of severity as follows:-

follows:-/

follows:-

	Mild or Local	Moderate	Severe	Total	No Serum Reaction
ncen-rated.	174	44	0	218	482 (68·8%)
nconcen-rated.	198	77	10	285	415 (59·3%)

Type of Rash. Owing to insufficiency of clinical data it was found impossible to give an accurate classification of the different types of rash, but the urticarial variety occurred with the greatest frequency in both groups.

In one case out of 1400 the rash was recorded as haemorrhagic.

Degree. It is of some importance to differentiate between local and general serum rashes, as local rashes per se. are probably the least important feature of serum sickness.

General rashes on the other hand cannot be entirely neglected for apart from the discomfort and irritation experienced by the patient confusion may arise with those of the exanthemata particularly scarlet fever and measles.

General/

General rashes were more frequently met with following unconcentrated serum.

Pyrexia (Degree of Severity)

	Mild	Moderate	Severe	Total.
Concentrated	29	9	1	39
Unconcentrated	67	58	12	137

The degree of Pyrexia was classified thus:-

(a) Mild pyrexia 99 - 100° F.

(b) Moderate 100 - 102° F.

(c) Severe Over 102° F.

Analysis/

III Analysis of figures on the more objectionable features of serum phenomena.

		Mild	Severe	Total	Percentage Incidence
Arthritis	a.	Concentrated 3	0	3	(0·4%)
	b.	Unconcentrated 20	16	36	(5·1%)
Adenitis	a.	Concentrated 1	0	1	(0·1%)
	b.	Unconcentrated 9	6	15	(2·1%)
Oedema	a.	Concentrated 2	0	2	(0·3%)
	b.	Unconcentrated 9	3	12	(1·7%)
Albuminuria.	a.	Concentrated 2	1	3	(0.4%)
	b.	Unconcentrated 4	2	6	(0·8%)

Vomiting was recorded in 1 or 0·1% in the concentrated and in 11 or 1·5% in the unconcentrated group.

Serum Abscess occurred in two instances only and these were connected with the administration of unconcentrated serum. Different methods of storage, however, might account for this, unconcentrated sera being supplied in rubber stoppered bottles whereas the concentrated product was served up in ampoule form thereby ensuring a greater degree of certainty as regards freedom from contamination.

Type/

IV Type of Paralysis.

Concentrated (700 cases)		Unconcentrated (700 cases)	
Palate	26	Palate	21
Palate & Ocular	1	Palate & Ocular	2
Palate & Facial	1		
Palate & Pharyngeal	1		
Ocular	2	Ocular	4
Pharyngeal	1	Pharyngeal	1
Cardiac	10	Cardiac	5
General Paralysis	4	General Paralysis	3
	46		36
or		or	
6·6%		5·1 %	

Analysis/

V Analysis of Deaths.

	Concentrated (700 cases)			Unconcentrated (700 cases)	
	Cardiac Failure	14		Cardiac Failure	9
	General Paralysis	3		General Paralysis	2
	Croup & Br. Pneum.	4		Croup & Br. Pneum	3
X	Tuberc. Meningitis	1	X	Streptococce Pneumonia Empyema & Meningitis	1
X	Br. Pneum & Gangren Varicella	1	X	Whl Br. Pneum & Convulsions	1
			X	Infantile Diarrhoea	1
		23			17
	Mortality rate 3·2%			Mortality rate 2·4%	
	includes deaths not due to diphtheria.			includes deaths not due to diphtheria.	
N.B.	If these are deducted the corrected fatality rate becomes 3%			If these are deducted the corrected fatality rate becomes 2%	

Cases of Bacteriological diphtheria showing some degree of rhinitis and excoriation of the nostrils to whom serum was administered are included in the statistics and this would slightly influence the low death rate recorded.

The/

The rate of absorption was roughly gauged by introducing an equivalent amount of the two sera subcutaneously into the SAME individual but on opposite sides of the abdomen and comparing the time of disappearance of the local swelling in the two instances.

With concentrated serum the average time taken was from 2 - 2½ hours and in the case of unconcentrated serum from 20 minutes to half-an-hour.

Duration of Serum reaction.

The concentrated serum gave a reaction lasting on an average from 1 to 4 days and the unconcentrated from 1 to 7 days.

Form/

Form of antitoxin	Concentrated	Unconcentrated
Total number of diphtheria cases treated	700	700
Average dose per case of diphtheria	22000 units	22000 units
Incidence of paralytic complications: all forms	6·6%	5·1%
Case Mortality	Total 21 3%	Total 14 2%

Conclusions/

Conclusions.

From the figures recorded it will be seen that with unconcentrated serum:

(1) The percentage of cases inoculated which develop a rash was only slightly higher whilst the relative proportion of severe to total rashes observed was nearly four times greater than with concentrated serum. The types of rash appeared to be similar in both instances, the urticarial variety predominating.

(2) The incidence of pyrexia was three to four times greater with unconcentrated serum whilst the relative proportion of severe to total pyrexias was about three and-a-half times as high with the unconcentrated.

(3) Of the severer forms of serum sequelae joint pains occurred 12 times, oedema 6 times, and albuminuria twice, as frequently with the unconcentrated as with concentrated serum.

Therapeutic value of the two sera.

(1) From clinical observation there does not appear to be any appreciable difference in the clinical progress the/

the faucial signs diminishing at apparently the same rate and the severity of the cases has required equal dosage in the two groups.

(2) The severe forms of serum sequelae (pyrexia, arthritis etc.,) was decidedly more pronounced with unconcentrated serum.

The/

The general therapeutic action of serum.

From clinical experience cases of rhinitis and rhinorrhoea speaking broadly and seen particularly during the convalescence of scarlet fever, measles and occasionally whooping cough, have definitely improved in the great majority of cases by the administration of anti-diphtheritic serum; yet the cultural findings have failed to reveal the presence of the Klebs Loeffler bacillus although often showing diphtheroids and Hofmann.

The same improvement has, however, been noted with scarlet antiserum suggesting a general therapeutic action rather than a specific one. This also appears to suggest that ordinary horse serum may be as beneficial in this group of cases, but it has only been tried on isolated cases insufficient for any definite conclusions to be drawn.

Section VII

C. Drawbacks to Serum Therapy. Real and Alleged.

Great though its good points are yet antitoxin has its drawbacks and limitations.

Provided the toxaemia is not extreme, and the disease is dealt with in its earliest stages, nothing but good can accrue from the liberal use of antitoxin as the prognostic outlook is thereby enhanced.

Its inhibitive powers and capabilities of neutralising the diphtheria toxin in the uncombined state are indeed well known, but once the toxin has definitely attached itself to the tissues it is doubtful if dissociation can be brought about as some aver, nor can it rectify any damage sustained by the already absorbed and unchecked toxin.

One would naturally expect that so eminently a successful remedy would be devoid of criticism as regards its powers for good but notwithstanding a small body of the community - the antivivisectionists have from time to time launched vigorous campaigns against the adoption of any form of serum therapy and are apt to misconstrue facts in order to substantiate their opinions.

The percentage incidence of paralysis since the adoption of this important remedy and the dangers of anaphylaxis are but two instances which might favour their contention but yet the former can readily be explained by the fact that severe cases which would otherwise have succumbed are spared by its use, although perhaps permitting of the occurrence of paralytic phenomena at a/

a later stage of the illness, whilst anaphylactic phenomena are too infrequently observed to outweigh all the advantages which this important remedy bestows.

These propagandists by swaying the minds of a number of sympathetic members of the public have proved a distinct hinderance to the progress of medical and scientific research.

Serum Abscess.

The occurrence of a serum abscess at the site of injection is a comparatively rare event in serum therapy, but when it does occur should admit of some explanation.

The most likely cause would appear to be a faulty technique in administration but the serum itself cannot always be absolved from blame.

This has been particularly noted when it is put up in rubber stoppered bottles instead of in ampoule form, and in the few instances in which abscess was encountered subsequent bacteriological investigation of the sample concerned revealed the presence of a short chained streptococcus.

A third possibility difficult to foresee, and still more difficult to prevent, is the development of a serum abscess in a diphtheria patient where septic manifestations run coincidentally.

Air Embolism.

Air Embolism must be an accident of extreme rarity and has never occurred in my experience but, nevertheless, due precautions should/

should be taken especially in intravenous administration to ensure that the needle and syringe when charged are free from air bubbles, and in the case of the subcutaneous route that the site selected for inoculation is free from veins.

Anaphylaxis.

Frequent reference to the condition of anaphylactic shock has been made by various writers and Park and Bolduan[38] quoting two cases, one of which proved fatal, say: "It is probable that some of these cases are simply deaths from the slight shock of the injection in persons whose hearts are already seriously intoxicated." Others may be extreme cases of rapid onset of symptoms in hypersensitive subjects (allergy).

As the term shock is used in rather a wide sense it is perhaps desirable to differentiate between protein and surgical shock, the latter being a comparatively trivial affair during serum administration; and also from the shock associated with intravenous injections of serum.

Another form of shock is that described by Hale[39] as occurring after intrathecal injection of antimeningococcic serum, and ascribed by him as due to an increase in intracranial tension or to the presence of antiseptic (tricresol) in the serum itself.

Yet sudden death following the administration of serum must be extremely rare and particularly so after a second injection. Many of these fatalities cannot be accounted for, in others the asthmatical tendency, or the status lymphaticus have been recorded, but what the exact relationship is no one can satisfactorily/

satisfactorily explain.

At the same time, the presence of these abnormal states calls for early recognition if such tragic events are to be obviated.

It is common knowledge that severe types of diphtheria rarely show any serious manifestations of serum disease, and it would therefore appear to be the milder types of infection in which caution should be especially exercised.

It is a practical impossibility to desensitize all patients requiring serum, except perhaps those who show asthmatical tendencies, while the recognition of the status lymphaticus during life is an even more difficult problem. It is quite possible that the latter state is more common than is generally supposed as Osler[40] records 457 cases in 5,652 autopsies of all ages.

It is therefore reasonable to conclude that some of these cases at least may receive serum without mishap, and from clinical experience a large thymus has rarely given rise to any difficulty, except where the operation of tracheotomy was necessitated. Aschoff maintains that the status lymphaticus is not yet fully understood and although recognising a possible relationship with anaphylaxis regards it as a physiological rather than a pathological condition as its occurrence was noted in vigorous healthy young adults killed in the war.

Wolff Ersner[41] regards subjects of a highly neurotic tend-

ency/

ency with unstable vaso-motor systems as unduly susceptible to serum effects, but clinical experience has not always supported his contention.

Two cases of fatal protein shock have been recorded in our hospital statistics during the past 27 years, and are here given in detail:-

(a) A youth, aged 7 years, was admitted to the Park Hospital certified diphtheria on the evening of the 28th Jany, 1926. Four days prior to this a younger sister had been admitted with a mild attack of diphtheria and 12,000 units of anti-diphtheritic serum were given without mishap.

He himself had a previous history of both measles and scarlet fever, but in both instances had made a successful recovery without resulting complications and, so far as could be ascertained, no serum injections had been previously administered to him.

Although not complaining of feeling ill a throat swab was taken as a precautionary measure in view of the fact that he was a contact, and on bacteriological examination the day following the presence of diphtheria bacilli were detected culminating in his removal to hospital.

On admission he was found to be well-nourished and of good physique and his heart sounds were in all respect normal.

He displayed no abnormality nor were there any apparent/

ent signs of glandular enlargement.

The throat was somewhat congested and showed a few points of follicular exudate on both tonsils but no other local manifestations were evident. The same serum as had been given to his sister was administered into the abdominal wall, 8000 units in all, and no departure from the normal was noticed until his arrival at the ward ten minutes later when he became cyanosed, unconscious and breathed irregularly.

Despite the injection of adrenalin, ether, and the employment of artifical respiration he never rallied and after death his features and the whole body generally appeared swollen and oedematous.

The result of autopsy revealed the existence of status lymphaticus

(b) The second case was that of a boy, 2 years of age, with a previous history of measles and whooping-cough.

He further contracted scarlet fever without any subsequent complications but six weeks later developed a mild attack of faucial diphtheria and died within a quarter of an hour of the injection of 6000 units of anti diphtheritic serum.

His throat showed a small patch of membrane on the right tonsil and diphtheria bacilli were found in the culture examined.

No/

No previous injection of serum had been given. The fatal seizure was ushered in with cyanosis, slow irregular breathing and convulsions, and restorative measures in his case were likewise applied, but without avail.

Post-mortem appearances showed nothing abnormal.

The symptoms described in these two cases coincide with those already mentioned in the literature on the subject.

Gillette[42] gives details of 28 cases of protein shock following serum injection, 16 of which terminated fatally. All the fatal cases seem to have died after the first injection and nearly all were asthmatical subjects.

He says: "When death terminated the reaction only two of the cases lived longer than ten minutes after receiving the serum." In a few minutes after the injection they were seized with an intense dyspnoea followed by oedema and urticaria.

Netter[43] has classified the symptoms following a first injection into three groups - respiratory, circulatory, and nervous, such as "asthmatic crises", rapid fall of blood pressure, convulsions, vomiting and coma, and he attributes the stridor sometimes observed to a development of the rash on the mucous membranes.

The treatment of these conditions is fraught with considerable difficulty as symptoms supervene so rapidly and unexpectedly that little can be done beyond applying artifical respiration and/

and the hypodermic administration of adrenalin and strychnine.

Most of the cases, including the two recorded, have been confined to the male sex, and in the first case cited curiously enough the sister showed only a transient serum reaction even with the same batch of serum

(Section VII)

(d) Adjuncts to Serum Therapy.

There is no malady other than diphtheria in which symptoms of heart failure may occur so suddenly and unexpectedly; and similarly there is no ailment in which the clinician is so often deceived in the matter of prognosis.

Pathology has shown that the toxin produces marked degenerative changes in the heart muscle and in the nervous system.

Various drugs have been employed as cardiac stimulants but their use is comparatively restricted and in many cases they fail to yield the results expected of them.

Saline enemata are of value in some cases and patients may occasionally derive considerable benefit from them.

Every possible means should be adopted to keep up the body heat by hot bottles, and the foot of the bed raised in order to facilitate the flow of blood to the vital centres in the brain as there is a minimum blood pressure under which they will function.

It may be said, however, that the prevention of circulatory failure in severe types of the disease rests mainly on the early administration of the specific antitoxin and it is in such instances that intravenous administration is clearly indicated.

POST-DIPHTHERITIC PARALYSIS.

The occurrence of this complication is an ever impending danger to be guarded against in diphtheria and an analysis of 1400 cases showed a percentage incidence including all forms of 5.8.

As previously stated it is essentially a neuritis of the peripheral type implicating the lower motor neuron and rest is the first consideration in treatment. No matter how slight in degree it may be, it cannot be dealt with lightly in view of the possible implication of other muscles, including the heart at a later period.

For the palatal and pharyngeal types nasal feeding may have to be resorted to in order to avoid the risk of food entering the trachea during attempts at swallowing and setting up pneumonia, while accumulation of mucus in the still more serious type of respiratory paralysis is also fraught with danger and must be combated by postural drainage and the checking of fresh secretion by the administration of small doses of Belladonna.

Fortunately, the latter form of paralysis is comparatively rare and where present is invariably associated with cases exhibiting a multiple type of neuritis.

Massage as an adjunct to treatment is rarely necessary and its scope is limited to those cases with involvement of the lower limbs with some degree of muscular wasting.

Diphtheria/

Diphtheria must always be looked upon as a disease of serious import in view of the possible supervention of paralytic lesions and of cardiac trouble.

The absence of early recognition and prompt serum treatment often means a gloomy prognosis and if death does not ensue, the illness is likely to be a long and protracted one. Yet grave though the outlook may be, they are not permanent and the patient once better does not carry with him throughout life any sequelae which might later on hamper his well-being and efficiency.

LOCAL TREATMENT.

Prior to the introduction of antitoxin by Behring, local applications of various kinds to the fauces were the invariable rule and bulked largely as therapeutic agents in the treatment of the disease but of recent years such measures have fallen into disrepute and apart from attention to the toilet of the mouth, so essential in the management of all acute infections, no other local treatment is necessary or desirable. Even the act of douching or syringing of the throat is frequently attended with a great deal of resentment, especially in the case of young children and probably any advantage claimed for this procedure is entirely nullified by its disturbing effect on the heart and system generally.

The/

The specific action of large doses of antitoxin must, therefore, be our main stand-by in bringing about the local improvement desired.

THE DIET AND BOWELS.

The diet in diphtheria should be given in an easily assimilable form and in small quantities at frequent intervals, and even the presence of albuminuria is no contra-indication for interfering with the dietary regime.

The daily evacuation of the bowels is no less important and should be secured, if necessary, by enemata, as aperients are, as a rule, by no means well borne by diphtheria patients and may excite vomiting with consequent strain on the heart muscle.

ACIDOSIS IN DIPHTHERIA.

The state of acidosis or a diminution of the bicarbonate content of the blood in cases of diphtheria has been recorded by various authors, notably Peters[44] and Harding. The former considers it to be a possible cause of cardiac vomiting in severe types of the disease and Harding[45] has noted its association in diphtheria with coincident septic infection.

They therefore propose to deal with the condition by the giving of alkalies by mouth at an early stage of the disease.

In/

In the normal state 5-10 grammes of bicarbonate have been found sufficient to produce an alkaline reaction in the urine but in acidosis much more than this may be required to render it so, as the surplus alkali is used up in neutralising the retained acid products.

The ideal would therefore be to supply alkali in just sufficient an amount to bring the reaction of the urine approximately to that of the blood, in which case the acidosis state would cease to exist.

Yet alkaline therapy though a commendable measure merely counteracts an effect but does not deal with the cause.

If we are to accept the view that the acidosis state is dependent on a diminution of carbohydrate in the diet, it would appear to be a more rational procedure to supply a sugar of sufficiently high calorific value to meet the needs of the system and on this assumption it has been our custom to combat the condition by supplying glucose in a 5% solution at frequent intervals, freely diluted with water, either by mouth or, if this is impracticable, by rectum.

Glucose has further virtues in that it is a muscle food and therefore of vital importance in supplying energy to the heart muscle while by its stimulating action on the renal epithelium it is possessed of diuretic properties and aids the elimination of waste products.

BLOOD SUGAR RESEARCHES IN DIPHTHERIA.

Of recent years the administration of adrenalin in diphtheria, particularly of a malignant type, has been advocated by the French school. Thus Marie and Leprat[46] carried out blood sugar estimations on 9 cases of diphtheria, three of whom had a mild degree of angina and presented a normal glycaemia (0,90 to 1gr 13). The remaining six had grave angina with all the characteristic symptoms of malignant diphtheria, extensive membrane, foetor, bull-neck, and severe albuminuria and in only one of this series was the glycaemia normal (1gr 12) while in the other five it was clearly diminished, ranging from 0, 59 to 0, 74 centigrammes.

These researches were extended by Lerebouillet and Pierrot[47] who record the result of investigations on 40 patients. In 19 cases of malignant diphtheria, the blood was drawn off in the first few days of the morbid condition and in 13 a hypoglycaemia was revealed (less than 0,90), the remaining six showing a normal glycaemia, varying from 0,90 to 1gr 20.

In the milder types of the disease, on the other hand, their results were entirely reversed, 8 times a normal glycaemia and three times only a hypoglycaemia.

They conclude that in malignant types of diphtheria there exists/

exists a state of hypoglycaemia comparable to that which is noted in the course of cases of adrenalin insufficiency.

One of my colleagues more recently investigated 4 cases of angina in diphtheria and his results are as follows:-

3 of a mild type of angina : Readings: 0.142%: 0.13%: 0.12%

1 severe type of angina : 1st Reading: 0.05%

2nd Reading taken 1 hour after a carbohydrate meal 0.101%

From the above researches there would therefore appear to be some justification for the practice of adrenalin therapy in the graver types of the disease.

THE CARRIER PROBLEM

(Section VIII)

THE CARRIER

Science has demonstrated the fact that certain individuals of a community are capable of harbouring the bacillus of diphtheria in the throat and nose for varying periods of time without exhibiting any clinical features of the disease.

Such persons have been designated "carriers" and their discovery is often a matter of pure accident.

Although apparently in good health they act as human reservoirs for the spread of infection and their influence in this respect adds greatly to the difficulties of control.

It has been a debatable point as to whether the organism is pro tempore in an avirulent condition and that given appropriate opportunities it can assume a virulent character and perhaps create the disease in its host if he be not immune, or whether virulent from the commencement it can transmit infection to contacts should they happen to be susceptible. No subject offers a more perplexing outlook in the history of preventive medicine than that of the bacteriological carrier and it is a problem of interest which concerns the epidemiologist as well as the clinician. Moreover the solution is a doubly important one as it involves not only the art of bringing about the early discovery of such cases, but additionally the ability to cope with them successfully.

The detection of the carrier can be determined by a study of the cultural and biochemical characteristics of the organism isolated/

isolated and any such showing the characteristic arrangement and beading of the bacillus, coupled with the production of acid in glucose should be immediately submitted to animal inoculation as a final appeal.

The power of dealing with the carrier on the other hand is still beset with difficulty and no solution put forward has as yet been hailed with universal approval.

Our views of dealing with the carrier state have undergone a radical change of recent years, present-day effort being directed towards the securing of bacteriological control and segregation of those who alone harbour virulent organisms.

Kelly and Potter[48] in a bacteriological survey of some schools where diphtheria was prevalent found no fewer than 47% of carriers non-virulent, thus securing an early curtailment of their period of quarantine and consequently from an economic standpoint a matter of considerable importance.

TREATMENT of CARRIERS

In a certain proportion of recovered cases of diphtheria where bacilli have been unusually persistent enucleation of diseased tonsils and the removal of adenoids from the naso-pharanx as practised in some fever hospitals have been attended with varying success.

Yet a small group of cases show no pathological abnormality capable/

capable of correction by surgical means, nor are operative measures always feasible or permissible in the case of infection of the nasal sinuses.

Where the nasal mucous membrane is in a crusted and unhealthy condition Harvey [49] advocates regular and frequent douching of the nares with alkaline solutions, his contention being that the bacillus leads an extra-corporeal existence and measures directed towards the removal of its pabulum will at the same time eliminate the offender and bring about a more healthy condition of the nasal mucosa.

There is no doubt that nasal carriers are by far and away the most dangerous and most persistent, and they may linger in hospital for months despite every measure employed.

Various methods of treatment have been tried - vaccines, anatoxin to the nasal fossae and some of the more powerful antiseptics, including mercurochrome applied locally, but results obtained do not justify the expression of any opinion on their value.

From time to time the recovery of virulent bacilli has been recorded from skin lesions apparently intractible to treatment and the administration of the specific antitoxin combined with the application of ultra-violet radiation locally are measures which may commend themselves to some. Aural diphtheria does not apparently occupy so prominent a rôle nowadays as a fertile source of spreading infection as/

as at one time believed, the majority of organisms recovered from the auditory meatus having been proved on bacteriological investigation to belong to the diphtheriod group of organisms with non-virulent properties.

That school attendance has an important bearing on the incidence of the disease is unquestioned, the resumption of study after vacational periods permitting of the close association of children during school hours and enhancing facilities for spread.

Now that inspection and examination of school children has become a routine measure, the temporary abstention from school of contacts, if deemed desirable, and particularly the enforced isolation of those showing an almost trivial rhinitis, until proved innocuous by subsequent bacteriological investigation are but further means to a successful issue.

The persistence and perpetuating of the carrier state must depend in the main on the transmission of the bacillus from the apparently healthy and immune to the susceptible. Both are now capable of detection, the former as previously stated by cultural and animal methods, the latter by means of the Schick test, but herein lies the weak link in the chain of control, as our efforts to keep those two groups apart are practically insurmountable.

The liberty of the carrier has a right to consideration and from a health point cannot be subjected to prolonged and rigid/

rigid isolation, while the deprivation of his livelihood is a matter of considerable importance if an increased burden and expense of maintenance is not to be imposed on the community.

ULTRA-VIOLET RADIATION and CARRIERS

In these days when helio-therapy bulks so largely in the treatment of various diseases, its use in fever work has naturally become included, and with a view to this a lamp was installed at the Park Hospital about the beginning of 1925. Consisting of a portable mercury vapour lamp with a separate transformer it was used in different infectious diseases, several wards being specially wired for the purpose. Among the various pathological conditions treated an attempt to ascertain its value on throat carriers, both convalescent and healthy was made in the hope of shortening their stay in hospital.

The exposures were made on alternate days and subsequently daily, the rays being projected from a distance of three feet directly upon the fauces, each sitting consisting of a one-minute exposure, gradually increased to five minutes.

The following is an analysis of results obtained on 61 cases:-

61 cases:-

10	showed	negative	swabs	after	5 exposures
11	"	"	"	"	6 "
8	"	"	"	"	7 "
6	"	"	"	"	8 "
3	"	"	"	"	10 "
12	"	"	"	"	15 "
3	"	"	"	"	15-20 "
3	"	"	"	"	20-25 "
1	"	"	"	"	25-30 "
4	"	"	"	"	30-35 "

Thus 38 or 62% were returned as negative and discharged after ten exposures and a further 15 or 24% after fifteen to twenty exposures the treatment extending over a period of several weeks.

Although it cannot be claimed that ultra-violet radiation is by any means a certain cure for carriers it is possible that in some instances at least it may materially assist in hastening the elimination of virulent bacilli from the more accessible regions of infection.

THE SCHICK TEST

(Section IX)

THE SCHICK TEST.

Profiting by the valuable researches of Schick a skin test has been devised which offers a reliable guide to the degree of susceptibility or otherwise of an individual to diphtheria.

It is based upon the assumption that a minute amount of diphtheria toxin when injected intradermally is neutralised locally at the site of introduction by the antitoxin naturally present in the circulation of the individual.

When not so antagonised the toxin has free play to exercise its irritant properties on the dermal tissue and causes at first a local redness at the site of injection with the subsequent production of certain phenomena to be commented upon later.

Should, however, the individual prove to be completely immune, neutralisation of the toxin is brought about and in consequence no local manifestations are observed.

Such a result would be recorded as a negative reaction and the individual in these circumstances considered as possessing a natural immunity to the disease.

In the case of positive reactors, on the other hand, different degrees of susceptibility are met with as evidenced by a variation in the local redness and other changes. In its technique it is identical to that of the Dick reaction of scarlet fever although certain minor points are noticeable.

In/

In the Schick test the sequence of events is slower in development and the resulting phenomena are more lasting in their duration whilst local scaling of the superficial epidermis, so prominent a feature after a faded positive Schick reaction is much less in evidence, if at all, in that of the Dick test.

For the application of the test two solutions are employed, the one termed "Toxin" and the other "Control," the former consisting of a broth filtrate from a virulent strain of the Klebs Loeffler bacillus and the latter, though similar, differs in one important respect in that the toxic properties have been destroyed by subjecting the solution to a temperature of 75°C for ten minutes.

As the result of experiment and subsequent observation it has been shown that 0.2cc of the potent solution contains just the minimum amount of toxin necessary to produce a definite response in a positive reactor, a strength which is now accepted as a basis in practice and regarded as the unit for purposes of comparison between the immune and non-immune.

TECHNIQUE.

The apparatus necessary for the test and the mode of procedure for carrying it out efficiently are as follows:-

A/

A hypodermic syringe graduated in tenths of a cubic centimetre is selected and the needle should be of fine bore, of moderate length, and with not too elongated a bevel.

Both the toxin and control solutions are of similar strength and the diluent employed is normal saline to which has been added a minute amount of phenol (about 0.4%) just sufficient to preserve the sterility of the solutions, yet in no way liable to provoke local irritation of the tissues after injection.

The usual sites of selection are the abdominal wall or the flexor aspect of the forearms, although for ease of application and subsequent inspection the latter is perhaps the more preferable.

The injections are made intradermally, i.e. into the substance of the cutis, the skin of the forearm being held slightly taut with the fingers of the left hand while the syringe, previously charged, is held in the right hand in such a position that the bevel of the needle faces the operator.

A steady thrust is then made, the needle entering the cutis immediately beneath the surface epidermis and the test is/

is one which requires a certain amount of dexterity before the exact degree of penetration is attained.

The orifice of the needle will then be seen shining through the skin with the bevelled portion entirely covered by the tissues, after which 0.2 cc of the solution is ready for introduction.

Any slight resistance to the thrust of the piston is soon overcome and a raised blanched swelling or wheal about ten millimetres in diameter quickly appears if the test has been carried out with the proper amount of efficiency and care.

The absence of the wheal can be taken as unmistakeable evidence that the needle has been forced too deeply into the tissues or that leakage of the solution has occurred at the site of puncture, in consequence of which one is apt to place a wrong interpretation on the findings.

Occasionally pseudo-reactions are encountered, especially in adults, giving rise to a certain amount of uncertainty in the reading but these are mainly distinguished by comparison with the control and by their earlier appearance and shorter duration. Their presence is supposed to be due to some unknown constituent in the toxin broth.

THE VALUE OF THE SCHICK TEST.

The test has a wide range of usefulness in child communities, whether in schools or hospitals, and its diagnostic value in differentiating the immune from the non-immune has been fully established.

For example, where an outbreak of diphtheria has occurred in a certain class-room one can readily ascertain which of the scholars are in need of protection and passive immunisation can then be carried out in the hope that the incidence of cases will be considerably curtailed.

In view also of the somewhat frequent occurrence of cross infection in isolation hospitals during epidemic periods, there is considerable scope for the employment of the test in scarlet fever and in measles wards, the inmates of which are especially prone to contract the disease.

In the same way newcomers to the nursing staff of a fever hospital, if found susceptible, can have their safety assured by Toxin-Antitoxin inoculation.

There is no risk attached to the application of the test and any expense incurred as the result of its adoption is negligible as compared with the information gained. In the United States of America during recent years the Schick test and preventive inoculation have been employed on many thousands of cases with encouraging results, whereas in this country/

country neither have as yet been used on such an extensive scale, possibly through lack of knowledge or apathy on the part of the public.

The following table shows the percentage incidence of positive reactors among the probationer nursing staff of the Park Hospital:-

Schick tested	Schick +	Schick -
144	41 or 28.4%	103

ACTIVE IMMUNISATION

(Section X)

The state of active immunity produced by the injection of toxin antitoxin is but slowly developed and its use is precluded in cases of recent exposure to infection, consequently this form of immunisation although highly desirable has no immediate value in the protection of a susceptible contact which antitoxic serum possesses. Its immunising power, however, although not so rapidly induced is of a much more durable nature and more definite as a controlling factor in that it is capable of tiding one over that period of life when the incidence of the disease is greatest.

It has been claimed by Park that fully 90% of all susceptible children can be successfully immunised by a course of three injections and that the protection conferred lasts for years, if not throughout life. As a public health measure it can therefore be widely adopted, at least among the juvenile population on account of the powers which it exercises towards prevention or modification of the disease, and its use should be especially reserved for periods when epidemics are non-existent and the seasonal incidence of the disease has reached its minimum.

TECHNIQUE and PRACTICAL VALUE of INOCULATION

Toxin antitoxin immunisation consists in the injection under the skin of a few drops of standardised diphtheria toxin mixed with antitoxin, the amounts of each of which have/

have been carefully measured. The dose is usually 1 cc. irrespective of age, repeated at intervals of 10 to 14 days. The resulting reaction, especially in children, is comparatively insignificant, although severe reactions both local and general are not infrequently met with in adults.

As a prophylactic measure it has no place in the treatment of diphtheria, nor can it be adopted as an immunising agent in subjects recently exposed to the infection, while individuals who show a negative Schick reaction are exempt from a course of immunisation.

DANGERS

That the use of toxin-antitoxin as an immunising agent is not without danger is amply proved by three notable instances here recorded which led to unfortunate circumstances following its application.

The first of these happened in 1919 at Dallas (Texas) when 50 severe reactions with 6 fatalities occurred during the course of active immunisation and was ascribed to the presence of an excessive amount of toxin in the mixture, while at Concord and Bridgewater (Massachusetts) a similar accident happened, but fortunately unattended with fatal results. Subsequent investigation in the latter case showed that as the result of freezing the toxin-antitoxin/

antitoxin combination had become dissociated. A still more recent incident occurred at Bundaberg, Queensland, in 1928 during an anti-diphtheria campaign and involved the lives of 12 children.

It appeared that the cause of death was due to the contamination of the toxin-antitoxin prophylactic mixture by living staphylococci which had been permitted to grow freely in the absence of antiseptic in the sample employed.

Such calamities as these must necessarily alarm the general public, who are only too readily swayed by agitators desirous of exploiting its ill effects and at the same time it may create a hesitancy for the time being on the part of Medical Officers of Health throughout the country to submit schemes in its support to the local councils.

During the past six years a series of inoculations, having for their object the attainment of an active and lasting immunity has been carried out on the probationer staff of the Park Hospital.

The liability of these new members to contract the disease is always present, and it has been our custom since October, 1922, to extend the offer of this important remedy to any new entrant in order to increase her resistance to the infection. The figures recorded, though small, are nevertheless striking and it would appear that we are in possession of a valuable addition to present-day methods of control.

The/

The following table shows the incidence of the disease over a period of ten years, during the latter part of which active immunisation was in operation.

(A) Incidence of Diphtheria (1918 - 1928)

1918 - 18	staff	developed	diphtheria
1919 - 12	"	"	"
1920 - 12	"	"	"
1921 - 26	"	"	"
1922 - 22	"	"	"
1923 - 5	"	"	"
1924 - 8	"	"	"
1925 - 4	"	"	"
1926 - 6	"	"	"
1927 - 5	"	"	"
1928 - 4	"	"	"

Immunisation begun in October, 1922

(B) Mortality

There were no deaths.

(C) Severe Reactions

4 cases were warded in 1925 with severe local and general reactions.
None since.

(D) Immunising Material

Toxin Antitoxin first employed in 1922

Toxoid-Antitoxin (during the past 2 to 3 years).

There can be little doubt that the practice of immunisation for diphtheria brings about a modification of the deposit occurring in cases of so-called "diphtheritic sore throat" as it has been clinically observed that the exudation is/

is practically devoid of fibrin and the degree of inflammatory reaction comparatively mild.

On rare occasions an immunised member of the nursing staff will develop a sore throat which is diagnosed entirely on bacteriological grounds as diphtheria, but in which there is a definite lack of membrane formation, the deposit being patchy, granular-looking and pultaceous in consistence.

On swabbing the infected area the material comes away quite readily without leaving any raw or bleeding surface behind, an indication which points to its non-adherent character.

Whether this form of tonsilitis can actually be ascribed to the Klebs Loeffler bacilli, or whether their presence is a mere matter of coincidence it is indeed difficult to state.

In any case it has been deemed advisable under the circumstances to administer the specific serum in order to obviate any liability to subsequent complications and to regard it from a statistical point of view as a case of diphtheria.

From the clinical standpoint it would therefore appear that in some instances at least diphtheria prophylactic by interfering with the characteristic signs of the disease may add considerably to the difficulty of diagnosis, and a parallel to this is also met with in smallpox modified by previous vaccination.

The advances made in the prophylaxis of diphtheria during the past few years have been most encouraging, and as its field of/

of application is ever widening we may hope that its effects will still further lead to fruitful results.

It is to be regretted that the general public are as yet apathetic and not fully alive to the advantages which this protective measure confers, but in the course of time this lack of interest will no doubt be finally dispelled.

RECENT ADVANCES IN THE TREATMENT OF LARYNGEAL DIPHTHERIA.

(Section XI)

LARYNGEAL DIPHTHERIA.

As the toxaemic factor is not a striking feature in the laryngeal type of the disease we cannot expect to obtain the same beneficial results from the liberal use of antitoxin as in other forms of the infection and any new line of treatment directed towards the relief of the mechanical obstruction with which it is associated would naturally be favourably received.

A notable increase in the number of laryngeal cases largely influences the mortality rate and it is here that the bacteriological factor is often found wanting as many of them fail to give positive findings from throat swabs, while the urgency for operative measures is often so acute that no time is even granted for bacteriological investigation.

It is not my intention here to discuss the subjects of intubation or of tracheotomy as these procedures are a matter of every-day knowledge but to deal with some recent advances in the treatment of this form of the disease.

Such are

(a) Improvement in steam appliances

(b) Direct Laryngoscopy with

(1) Removal of membrane by forceps

(2) Removal of membrane by suction

A. IMPROVEMENT IN STEAM APPLIANCES.

To those who advocate the use of steam as a preliminary treatment for croup with a view to diminishing muscular spasm and oedema, a more modern and up-to-date method has been devised by Woodfield[50] entirely supplanting the various forms of steam kettle originally in use. The steam being directly obtained from the mains is constantly on tap and the apparatus consists of a brass nozzle telescoped into a gun metal socket, the latter being provided with a drip pocket and waste tube leading to the floor level to carry off water of condensation.

Being fixed, it is perfectly stable and working on a swivel can be directed to one or other side as desired.

No supervision is required as there is no possibility of boiling dry or risk of fire and its usefulness has amply repaid the initial cost of installation.

B. DIRECT LARYNGOSCOPY. (1) Removal of membrane by forceps.

Gover[51] has collected statistics on 189 cases of croup at the Willard Parker Hospital, New York, and claims the following advantages for direct examination of the larynx in croup.

(1) In cases with no faucial membrane it enables a decision to be made as to the administration of serum.

(2)/

(2) Confusion with croup due to foreign bodies can be avoided.

(3) A longer postponement of intubation is permissible with a catarrhal croup than with a diphtheritic one.

(4) Occasionally a large piece of membrane may be removed from the larynx with permanent relief.

(5) The question of quarantine Schick testing and immunisation can be satisfactorily settled.

His investigations showed that 112 out of 189 croup cases had membrane in the larynx, of which 36 were intubated and 11 died.

In 46 cases the membrane was loose and was readily removed by forceps.

The total number of deaths among the 112 cases was 22 of which one half had been intubated.

In 77 out of 189 cases of croup no membrane could be seen in the larynx; of these 5 died, one of whom had been intubated.

He does not claim that direct laryngoscopy and removal of the membrane by forceps is a substitute for intubation, but he thinks that the method diminishes the number of cases which ultimately come to intubation.

DIRECT LARYNGOSCOPY AND SUCTION METHOD.

Of recent years the Sorensen treatment of laryngeal diphtheria has to a certain extent supplanted the older method of intubation at the fever hospitals in New York and it is claimed that the number of cases of broncho-pneumonia are strikingly diminished with a reduction in the mortality rate of at least 50%/

50% since this measure was adopted.

Briefly expressed the principles of the treatment consist of a direct inspection of the larynx and subsequent aspiration of membrane and mucus lodged in the larynx and trachea giving rise to the laryngeal obstruction.

The equipment is a somewhat elaborate one and includes laryngoscopes of various sizes according to the age of the patient, light carriers, bulbs and batteries for illumination purposes, a Sorensen suction pump with rubber tubing attached and laryngeal tubes for aspirating the membrane from the larynx and trachea.

The mode of procedure is somewhat as follows:-

The patient is laid flat and secured in a manner similar to that of intubation, the head being fixed in the mid line, or a sand-bag may be inserted beneath the shoulders with the head drooping slightly over the edge of the table. The laryngoscope is then introduced past the tongue, towards the pharynx, and on viewing the epiglottis it is immediately covered with the lip of the laryngoscope, the instrument being firmly gripped in the left hand. The laryngoscope is now resting against the upper teeth in the mid line and by pressing upwards against the base of the tongue and epiglottis a good view of the larynx is obtainable.

At the same time the suction apparatus should be held in readiness with the appropriate size of aspirating tube attached, after/

after which the suction process is commenced. The tube is usually inserted again and again until the larynx is apparently clear and the final step is the application of adrenalin chloride solution locally on a cotton swab. It is emphasized that the cotton be put on with mucilage before sterilisation and wound tightly about the applicator, which is securely held by an artery clamp.

Suction is carried out through silk elastic catheters or preferably metal tubes attached to the motor driven suction pump.

The larynx should be exposed in a few seconds and the whole operation completed in a few minutes.

The relief is usually immediate and marked but the operation may have to be repeated in six hours or so and subglottic oedema may necessitate intubation or tracheotomy after all.

For the procedure it is claimed that no harmful effect results, apart from the occasional loss of a deciduous tooth in young children.

Gover and Hardman[52] give the results of 50 cases treated by suction instead of forceps in children whose average age was 3½ years. Only 4 deaths occurred, a fatality of 8%, whereas they put the fatality rate for intubation in hospital practice at 25-40%.

Of the 50 cases, 42 received small doses of serum 3,000 to 9,000 units intravenously, a point to which they attach the utmost/

utmost importance as the membrane will not reform 36 - 48 hours after this has been done.

The authors consider that the method is useful in certain cases but draw attention to the fact that in case of failure the operator must be prepared to do immediate intubation or tracheotomy. They consider suction superior to forceps and that the elastic catheter is safer though less effective than the metal tube.

Broncho-pneumonia in their opinion is less frequent than after intubation.

CONCLUSIONS.

There is no doubt that the method of direct laryngoscopy in cases of croup is scientifically sound and should be practised where possible, as it enables one to determine the exact nature of the obstructive process and apply treatment suitable to each individual case.

The value of the suction method, on the other hand, has its limitations, as many cases of subglottic oedema are unlikely to benefit from its use.

Gover states that the membrane in the larynx is much thinner and looser than that on the fauces and that it is often seen flapping about during respiration.

But this is not so in all cases, as I have seen instances where/

where the membrane was unduly tough and thick in consistence and where the dyspnoea was only partially relieved even by tracheotomy.

Further, I consider it to be contra-indicated in cases of croup immediately following a measles attack, as the larynx is more prone to damage by manipulative methods in these instances.

The method has not been adopted in this country to any extent, if at all, and until further work has been carried out we are unable to appraise its value over the more popular methods of intubation and tracheotomy.

THE ECONOMIC FACTOR

(Section XII)

The importance of immunological and serological research and the great benefit which accrues therefrom, not only to the State, but to the community and to the individual will be fully appreciated by the following remarks.

If we reckon the average expenditure of upkeep per patient per week at £3 per head and accept as a fair aggregate the treatment of 2,000 patients weekly at the London Fever Hospitals, we can readily realise that the total outlay per annum incurred by the country must reach a considerable figure. But not only the juvenile population suffer, but adults as well, and in the latter instance the period of temporary incapacity from work can only mean a serious economic loss of many working hours. The more widespread the adoption of schemes therefore towards successful immunisation of susceptibles the fewer the opportunities afforded for the outbreak and spread of infection as the smaller will be the numbers remaining who are capable of acting as a potential danger. At the same time there is bound to be a commensurate diminution of suffering throughout the country as a whole.

SUMMARY AND CONCLUSIONS

(Section XIII)

CONCLUSIONS

Antitoxin By the increasing use of concentrated serum a distinct advance has been made in serum therapy, statistical analysis having shown in the present thesis a definite reduction of the more disturbing sequelae associated with the administration of antitoxin.

Schick Test The claims advanced in favour of the Schick Test as a specific indicator of the immunity status of the subject tested have been fully justified and its clinical importance and reliability are such as to secure its adoption as a routine procedure, not only in institutions but also in private practice.

To limit the field of error in its interpretation, accurate standardisation of the toxin and duplicate estimations of the test are essential and no individual should be considered immune until these requirements have been definitely fulfilled.

Its value is undoubted in the detection of susceptibles, especially of school age and under, and in those who subsequently submit to a course of active immunisation it affords a proof of the success or non-success of that procedure.

ACTIVE
IMMUNISATION/

Active Immunisation

Consideration of the virulence of the diphtheria toxin and the number of non-immune indicate that the injection of Toxin-antitoxin as a prophylactic is a measure of very real value in controlling the incidence of the disease. Inoculated persons who subsequently contract the disease suffer from it only in a mild or attenuated form, a point of considerable importance in curtailing their residence in hospital.

The establishment of centres for the distribution of antitoxin and toxin-antitoxin would be a useful measure for controlling the disease during times of epidemic and non-epidemic periods respectively.

Opinion is also formed that inoculation, if widely adopted, would have a definite influence in diminishing the number of return cases.

The need for active immunisation as a means of control should be more fully impressed upon the public by propaganda work and schemes for its adoption should only be temporarily withheld until they become cognisant of the advantages conferred.

Decline in Mortality

Since the introduction of diphtheria antitoxin by Behring in 1894 the case mortality from diphtheria has shown a steady fall, and it might be claimed/

claimed that this is due not only to antitoxin treatment but additionally to a natural decline in diphtheria virulence. Infectious diseases do indeed at times undergo a change in character, a hitherto mild infection gradually or even suddenly becoming extremely virulent and vice versa.

But even allowing for this, other important factors are concerned, such as the admission of a larger proportion of cases of mild and moderate severity to hospital and the increasing habit of taking swabs by medical practitioners in all doubtful cases. Cases are also admitted to hospital at an earlier period of the disease as in 1928 only 9 deaths occurred at the Park Hospital within a period of twenty-four hours, whereas five years previous to this there were 22 such fatalities.

The increasing practice of injecting cases before admission to hospital without waiting for a bacteriological report is also a feature consistent with safety.

There is no indication that treatment after admission to hospital has contributed in any degree to a reduction of mortality, as no change in policy has occurred in that respect during recent years.

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