DIPHTHERITIC TOXAEMIA,

- Modification under Antitoxic Equivalent -

Phagocytosis.

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Diphtheria is an acute infectious disease due to the presence of a specific micro-organism — the Klebs-Loeffler bacillus — characterised by a local fibrinous exudation, usually upon a mucous surface, and accompanied by constitutional symptoms due to the absorption of toxins produced at the seat of the lesion, and also other complex metabolic products in the blood, and within certain cellular units. The clinical and bacteriological conceptions of this treacherous disease, however, are at present, not in full accord. On the one hand, there are cases of simple sore-throat, which bacteriologists, finding the Klebs-Loeffler bacillus, pronounce "true diphtheria"; and there are again another group, even membranous sloughing anginas, diagnosed by the physician as diphtheria, and which, in the absence of the Klebs-Loeffler bacillus, are called by bacteriologists "pseudo-diphtheria".

Moreover, little is definitely known regarding the precise chemical composition of the toxines produced — even the toxines obtained in culture-media, from absolutely pure

cultures of the Klebs-Loeffler Bacillus, are not yet known in a state of chemical purity. What then must be said of the complex cultures that occur in the throat.

Very closely allied to the Klebs-Loeffler bacillus are, the so-called "Pseudo-diphtheria Bacillus", which very nearly resembles the pathogenic organisms; and the "Bacillus Xerosis", which according to some authorities is identical with it.

Associated with the Bacillus diphtheriae in throat affections, complicating and masking their pathological phenomena, and rendering these enormously more difficult to follow minutely, we have various combinations of Streptococcus, Staphylococcus, and diplococcus & others.

Lennox Browne in his admirable treatise on "diphtheria and its associates", gives a record of illustrative cases of some typical combinations of malignant exudative throat affections, due to the association of Streptococci, Staphylococci, and diplococcus, with, and apart from the true bacillus diphtheriae, in one or other of the varieties mentioned in Chapter VIII. This series of cases are of extreme interest, and well illustrate the complex nature of many of the cases we meet with in practice, these cases being illustrative both of the true diphtheritic process, and also of the Pseudo-diphtheria forms.

I enumerate the combinations in this order —

Class I Bacillus diphtheriae.

II " " with Streptococcus,

III " " with Strepto- & Staphylococcus.

IV " " with Streptococcus & Diplococcus.

V " " and Diplococcus.

VI Streptococcus.

VII Streptococcus and Diplococcus.

VIII Staphylococcus.

IX Staphylococcus and Diplococcus.

X Diplococcus.

XI Diplococcus and a mycelium.

XII Intermediate.

The same author assigns all cases under one of four distinct types thus —

1. Simple, pure, or Simple Bacillary Diphtheria, when the specific Bacillus constitutes the sole organism.

2. Complex, impure, or Coco-Bacillary Diphtheria, when the specific Bacillus is associated with other micro-organisms (chiefly cocci).

3. Pseudo, false, or non-Bacillary Diphtheria, when there is an entire absence of the specific Bacillus.

4. Non-virulent Bacillary Diphtheria, when characterised by the presence of a Bacillus identical in every respect with the Klebs-Loeffler Bacillus, except in virulence.

This last type is often erroneously classed by Clinicians amongst the pseudo-diphtheritic forms.

When one comes, however, to consider the morbid process of Diphtheria itself, in relation to its Etiological Criterion, we observe the morbid influence manifested mainly in three distinct directions.

I. The Local condition, the Special inflammatory process with the fibrinous Exudate characteristic of the disease. This Exudative membrane being nearly always on the fauces or tonsils; but sometimes found in other situations also as a primary seat eg. nares and larynx, or sometimes even in wounds on Skin Surface.

II. The Systemic intoxication produced by the entrance of very highly toxic bodies into General circulation, these Soluble complex poisons so lowering the vitality, and depressing the very sensitive vital centres, that rapid death may ensue from paralysis of their vital functions; or at a later stage of the disease bringing about degenerative changes of a very definite type, from altered conditions in certain nerve cells belonging to the higher centres, and also in the nerves themselves. whether also in the fibres of Striped and non-Striped muscles we shall see later.

III. Certain characteristic phlegmonous & pyaemic processes, which are caused by the introduction of associated

organisms, more particularly the Streptococcus Pyogenes.

It will, however, be mainly with the details of the second group, that will form the subject of this Thesis. Their modification under an Antitoxic Equivalent - the mode of action of Antitoxins on diphtheral toxines - and the theory of Phagocytosis.

The Bacillus Diphtheriae was first described by Klebs of Zurich in 1883, and cultivated in the following year by Loeffler, called therefore "the Klebs-Loeffler" or simply "Loeffler's Bacillus".

Klebs described its characters in the false membrane but made no cultures. It was first cultivated by Loeffler from a number of cases of diphtheria, his observations being published in 1884. It is to him we owe the first account of its characters in cultures, and of some of its pathogenic effects on animals. By experimental inoculation he was able to produce false membrane on damaged mucous surfaces, still he hesitated to conclude definitely that this organism was the cause of the disease, for he did not find it in all cases of diphtheria he examined. And this point was, he obtained the same organism from the throat of an apparently healthy child.

This organism became, therefore, the subject of

much enquiry. The subsequent brilliant researches of Roux and Yersin, however, definitely established its relationship to the disease. Their experiments were published in 1888-90. Much further elucidation has been thrown on this subject by the labours of many earnest workers in this field of experimental research, notably by Behring and Kitasato, by Brieger, Sidney Martin and others. With the exception perhaps of the Tubercle Bacillus, there is probably no organism which has been the subject of so much routine examination, and in which the opinion of competent bacteriologists may be said to be so unanimous.

The diagnosis, then, of true diphtheria depends on the detection of this specific bacillus in the false membrane, or secretions from the mouth and nose. This must be regarded as the only certain means of diagnosis. Distinctions formerly drawn between true diphtheria and non-diphtheritic conditions, from the appearance and situation of the membrane, have no scientific value.

The means at our disposal for identifying the bacillus are either by microscopical examination, or by making cultures. Each of these, as well as the microscopic characters of the bacillus diphtheriae itself,

and also of the so-called pseudo-diphtheria Bacillus, are very minutely given in many books on this subject.

Suffice it to say that the specific bacilli are slender rods, straight or slightly curved from 1·5 to 5 micro-millimetres in length — usually about 3μ —; in thickness 0·5 μ to 0·8 μ; being, therefore, slightly longer and much broader than the Bacillus of tubercle. There is a want of uniformity in the appearance of the bacilli when compared side by side.

Their differences in length and calibre probably represent various stages in the development, or may be varying exuberance in growth. As the present time definite evidence is wanting to show that variations in the size of the Bacillus, either in length or thickness, represent differences in the degree of their virulence. The tendency, perhaps, is towards attributing greater virulence to the longer and often branched varieties. Certainly, many observers have asserted that the bacilli examined during convalescence are almost invariably of the shorter varieties.

Bacilli diphtheriae stain deeply with methylene blue, often exhibiting fine granules more deeply stained in their substance, so that a dotted or beaded appearance is sometimes presented. Sometimes the ends are more swollen and more darkly stained,

instead of being tapered, these swellings & granules often taking on a violet tint, in methylene-blue staining. The bacilli usually lie irregularly scattered, or in clusters, the individual bacilli disposed in all directions. They never form true chains, however. Occasionally, longer forms are met with in the spaces between the fibrin. Very often these bacilli are found within the leucocytes themselves.

The bacillus diphtheriae may be present alone in the false membrane, but more frequently we find associated with it, one or other of the pathogenic organisms. The streptococcus pyogenes being the most common. Staphylococci, however, and occasionally the pneumococcus or the bacillus coli may be present.

Streptococci are usually found side by side with the Bacillus diphtheriae, often, however, penetrating more deeply into the tissues. In cases where a gangrenous process is superadded a great variety of micro-organisms may be present. Against such complications it is questionable how the anti-diphtheritic serum may act. In such cases, I consider that the bacteriological examination of the parts affected may throw valuable indications regarding treatment. In such mixed cases, the anti-streptococcic (polyvalent) serum has been used along with the anti-diphtheritic.

The Bacillus diphtheriae is very resistant; dried diphtheria membrane kept away from direct light, and at the room temperature, has been proved to contain diphtheria bacilli still living and virulent at the end of several months. In cultures, these bacilli possess long duration of life. Even when kept at 37°C. for two months, they may be shown by sub-cultures to be still alive. Under moist conditions they have a low power of resistance. In membrane which is perfectly dry, however, they can resist a temperature of 98°C. for an hour.

Following an attack of diphtheria the bacilli may persist about the tonsillar crypts for weeks, even months, after all trace of the membrane has gone.

Given, then, a deposit of Bacillus diphtheriae membrane in the fauces, the toxic action of the bacilli quickly depresses the vitality of the subjacent epithelial cells, which very early show active proliferation of their nuclei. These change to refractive hyaline masses and soon break down. The primary lesion is a superficial necrosis, and degeneration of the epithelial cells. The bacilli developing in the necrotic tissues. One of the most striking of the early phenomena, is the enlargement

of the blood-vessels, which occurs after a short period of incubation. From the deeper structures a rich fibrinous exudation is poured out, and fibrin at once is formed, whenever that secretion comes into contact with the necrosed epithelium. The membrane is never formed primarily on an intact surface. It may spread over it, however. The underlying connective tissue, and the smaller blood-vessels, undergo a hyaline fibrinoid degeneration. The degeneration in the mucous glands of the tissue affected is constant.

The membrane differs somewhat both in structure and in subsequent behaviour, according as it is formed on stratified squamous epithelium e.g. pharynx, or on a surface covered with ciliated epithelium e.g. trachea. On squamous epithelium, local necrosis is uniformly present, and also very pronounced inflammatory reaction in the subjacent connective tissue, with abundant exudate. The necrosed epithelium becomes raised by the fibrin, and the interstices are also filled with it. The exudate extending around the subjacent blood-vessels and other tissues — the membrane becomes very firmly adherent. On ciliated epithelium, the cells are freely and rapidly shed, and the

membrane, which is almost exclusively of reticulated fibrine lying on the basement membrane, is much less firmly adherent, and therefore more readily shed.

Necrosis may extend deeply into the tissues; but in the purer forms of true diphtheria, there is little tendency either to deep ulceration or abscess formation.

Extremely poisonous toxins being produced at the seat of lesion, they readily gain entrance to the systemic circulation. The temperature first rises, then sinks below normal. This being due, according to Arloing and Laulanie, to the decrease in the vital energy and the oxidising processes.

The whole metabolism now suffers, one of the very striking phenomena is an extensive decomposition of albumens. General symptoms of poisoning supervene. There is marked and progressive muscular weakness, a tendency to syncope, and albuminuria. Late, striking paralyses manifest themselves, it may be of the pharynx, larynx, the eye, less frequently the lower limbs. All these paralyses appear late in the disease, and are together grouped under the term "Post-diphtheritic paralysis".

All these symptoms have been experimentally reproduced by the action of the Bacillus diphtheriae, or by its toxins.

Other bacteria, however, are concerned in producing the various secondary inflammatory complications in the region of the throat e.g. the deeper ulcerations, gangrenous and suppurative conditions.

There are characteristic changes in many of the organs, but especially in the circulatory system - heart - and in the nervous system.

Special interest attaches to the question whether diphtheria toxin has a directly injurious effect upon the heart or not. Collapse of the heart ultimately takes place, and the cardiac muscle remains arrested in diastole; but it is not known whether this is not the secondary result of a primary paralysis of the vasomotors. On this point, different views are expressed by observers.

Heart: Fatty degeneration is commonly found in the sarcous elements, this may precede the more advanced hyaline degeneration. Also there is a primary interstitial myositis, and a secondary form following the degeneration in the cardiac elements. Pericarditis and endocarditis have been found much rarer than formerly regarded.

Endocarditis was found only in 7 out of 220 cases at the Boston City Hospital (McCollum).

According to the same authority about one death in 5

in diphtheria is due to heart failure, and being more frequent during the second week of the disease. A slow pulse in those cases being indicative of more serious danger than a rapid one. Frequently the fatal collapse appears during convalescence, even as late as the 6th week after apparent recovery. The syncopal attack may come on abruptly, perhaps following a sudden exertion, Generally however, there have usually been symptoms pointing to disturbed cardiac rhythm. Formerly, such symptoms were commonly ascribed to thrombosis or to endocarditis. At the present state of our knowledge, however, the majority of such cases are due to a neuritis of cardiac nerves, only a small percentage to an infectious myocarditis.

Kidneys: Albuminuria is present in all severe cases. The nephritis frequently sets in quite early in the disease. Occasionally it sets in with complete suppression of urine. It is only when the albumin is very excessive in quantity and accompanied by renal casts, that the condition indicates parenchymatous nephritis, and is alarming. There is no specific type of lesion. Sometimes one encounters nephritis in its most intense form. Such lesions, it is quite clear, are due to the action of the toxins, not to the presence of the specific bacillus.

Lungs: Broncho-pneumonia is the most common and fatal complication. It was present in 131 of the 220 cases quoted by Mc Collum: Boston. The pneumococcus is the etiological criterion. Acute Lobar pneumonia is rare.

Nervous System: Paralyses are by far the most important - even up to 15% and 20% in certain types. Though strictly regarded as a sequel, there is evidence to support the view that the initial process in the cell unit must begin very early - perhaps with entrance of toxines into blood stream. Occasionally, the paralysis appears as early as the 7th day of the disease - and it may follow what appear to be very mild cases. - e.g.

In one case of my own - a robust girl of four years, with only slight faucial exudation which completely cleared up within 24 hours, and in which no antitoxin was given. So slight indeed were the initial symptoms, that the mother disputed that the condition had been diphtheria. Having warned her of the grave attendant dangers, I insisted on the child being kept in bed for the customary period. This was not done. I did not visit the child again. Four weeks later I was urgently called to see the same little girl. This time, there was marked post-diphtheritic paralysis. The child was totally unable to swallow - the liquid foods returning through the nose. There was cardiac dulness with a

gallop-rhythm. This child suddenly expired early the following morning. This case occurring early in my professional experience has remained an object-lesson, and has forced upon me the desirability of administering diphtheria antitoxine used in the simplest-types. Perhaps in this case the result might have been different- had I neutralised what-poison was in the system by antitoxine.

Usually however, the paralytic symptoms appear about the second or third week of convalescence.

A common site is the palate, which is seen to be relaxed and motionless, with impaired sensibility. Often there is extension to the constrictors of the pharynx.

Any of the ocular muscles may be involved - ptosis, loss of accommodation, strabismus, &c.

Facial paralyses, some of them of a very persistent-type, with or without analgaesia. Neuritis may attack either the upper or lower extremities - sometimes confined to one side, more commonly both however are involved - sometimes taking the form of paraplegia in the lower extremities.

Frequently I have observed a pronounced weakness in the legs, apart from any condition of paralysis. This also coming on late in the disease, and frequently accompanied by the loss of patellar reflex. Such pitiful patients often walking better earlier in convalescence than at a later period.

The multiple form of diphtheritic neuritis is fairly common. All these are toxic in nature. The toxines have a most pernicious effect on the more highly developed nerve cells, and also on the nerve fibres themselves. Often there is a striking change on the peripheral nerves, manifesting itself early by disintegration of the medullary sheaths.

It is disputed, however, whether these nerve lesions are of a primary nature, or secondary to changes produced within the substance of the nerve cells.

As regards the site and frequency of the different post-diphtheritic lesions, Prof. Dins Woodhead collected 494 cases. In these, he found the ocular muscles involved in 197, the palatal muscles in 155, other muscles 10. Of these 494 cases, 91 died.

Speaking generally of the systemic infection - the main features of a case bear pretty much a definite relation to the intensity of the local lesions. This is not always so however. Cases have been accurately recorded in which there was extensive local disease, without corresponding grave constitutional symptoms. On the other hand appear rare cases in which from the very outset, prostration is extreme. Escherich endeavoured to explain such discrepancies by assuming degrees of susceptibility to the specific

bacillus - and to its toxins — e.g. with high local susceptibility to the bacillus, and only slight susceptibility to the circulating poison, there naturally would be extensive local necrosis and exudation, with mild general symptoms - and of course the reverse.

In cases of diphtheria, the bacilli remain for the most part confined to the false membrane in the fauces. No general affection of the blood as a rule takes place, though in severe cases, a condition of septicaemia may perhaps occur.

The bacilli manufacture a substance, probably of the nature of a ferment - at least the main poison in the toxine being so regarded - which is absorbed and carried throughout the body.

This ferment, by its action on the tissues, gives rise to other poisonous materials, or secondary toxines. The bodies of the bacilli themselves, after washing and filtering, have been proved to be not so poisonous, as their soluble products. Wassel showed that if the actual bacteria were washed free from their attendant poison, the dead bodies had very little toxic effect, when injected into the blood-stream of certain animals.

The casual relation of the specific bacillus

of diphtheria to the disease having been established, it remains now for me, to investigate more thoroughly, some of the many difficult problems presented in this connection. The whole subject of immunity being still enshrouded amid many profoundly difficult and obscure phenomena.

After Koch had established the principles of bacteriology, very early it came to be recognised that the living micro-organisms were only indirectly harmful, and that it was to the products of the specific bacillus, that attention must be directed.

Brieger early recognized this. Much exceedingly interesting and instructive literature forms expression about this time - detailing the patient and laborious work of many investigators, as the bacillary products, originally known as "ptomaines" and "toxalbumins", came to be better understood in a clearer experimental light.

Diphtheria toxine is the most important of all the bacterial poisons, both as regards its theoretical importance, and also on account of its relations towards artificial immunity and serum-therapy. It represents the fundamental type of the true toxin; and moreover it has been used in most of the experimental work, that has helped to elucidate the mode of action of toxines in relation to disease and the formation of antitoxines.

Roux and Yersin were the first to demonstrate the presence of diphtherial toxines in broth cultures of the bacilli. They found that a cultivation of the Bacillus diphtheriae in calf's bouillon of 7 days' growth, when filtered through porcelain, produced typical symptoms of diphtherial poisoning.

Further they found that the toxicity increased with the age of the cultivation. A culture 42 days old, killed a rabbit in 6 hours with toxic symptoms analogous to those of a severe attack of diphtheria; while 6 days was necessary with an equal dose of the same cultivation of 7 days' growth.

Roux recognising that the poison was destroyed by heat, concluded that it was akin to the enzymes. Gamaleia considered that it was not a secretion-product of the bacilli, but a constituent of their cell contents; and that when the bacilli died, the poison was extracted from their decomposed cells.

That it was not so, however, Roessel conclusively established in a series of careful experiments, in which he filtered Bacillus diphtheriae-cultures of different ages, collecting as a residue the dead bodies of the bacilli, and which after careful washing, were found to have almost no toxic effects when injected into the blood of living animals, and proved that

Kitt toxin was left within the bacillary cells. He concluded therefore that the toxin was a secretion product. He further observed that young cultivations produced a very plentiful supply of toxine, which decreased in amount according to age of cultivation, after a certain period had been reached.

Diphtheria toxine therefore must be regarded as a metabolic product, not a constituent of the cell contents. The purest preparations of it do not give the proteid reaction. It is a very complex body. Roux and Yersin considered that the main poison was of the nature of a ferment. Of its exact chemical composition little is definitely known. It is not known at all in a state of chemical purity.

The production of this poison shows marked variations, and its amount cannot be estimated beforehand, even in the case of a similar cultivation in the same nutrient-medium. With our present knowledge it is difficult to explain these variations.

The essential conditions for the production of the diphtheria toxin are —

1. A suitable culture which grows on the surface of the bouillon, using for preference a flattened vessel, less than half full, so as to admit abundance of atmospheric air.

2. Alkalinity of the bouillon, to which is added a suitable peptone (2%). e.g. Chapoteaut's peptone.

3. A period of growth at 37° C. – the length of time depending upon culture. Tests must be applied to each variety to ascertain maximum production.

A stage has been reached in the preparation of the toxine of the Bacillus diphtheriae, that for immunising purposes we now use only poisons – 0.02 c.c. of which will kill with acute symptoms guinea-pigs of 250 grms.

Properties of diphtheria toxin – Not being known in a state of chemical purity, all the known characteristics of it relate to the preparations that contain it in admixture with other substances.

It is exceedingly sensitive to outside influences. It is rapidly destroyed by boiling, and under sun-light – and adversely affected by acids and oxidising agents.

Sterilised solutions of it injected into the peritoneum produce in detail the toxaemia of diphtheria, just as in the disease, except the membrane.

Guinea-pigs receiving the toxin subcutaneously, present symptoms of toxaemia, varying with the dose.

1. A very large dose of toxin may produce death in twenty four hours.

2. With a moderately strong dose, oedematous swelling

at the seat of injection is observed, accompanied by enlargement of the nearest glands. The animal gets weaker and weaker hour by hour and dies in about four days.

3. With doses insufficient to cause rapid death, one observes again the same local swelling, and if the guinea-pig lives for a couple of weeks or longer very pronounced paralytic symptoms may appear, and death ultimately results from asthenia.

According to Ehrlich and others - at least three separate poisons exist in the toxine —

1. One producing the local oedema and necrosis.
2. And this instrumental in bringing about the paralyses.
3. The chief poison - in all probability a ferment (at least of that nature) - causing death by a general intoxication.

All however are more or less hypothetical substances.

The toxones appear to be responsible for the production of the local oedema. It is not known that free toxones form primary decomposition products and exert distinct toxic effects. They possess the least affinity for their specific antitoxine, but whether they are true haptines, and are able to throw off receptors or "side-chains" and thus produce immunity it is extremely difficult to say. Bordet, however, looks upon toxones as molecules of toxine incompletely saturated with antitoxine, being a different and less active substance than true toxine.

In Bordet and Gay's "Studies in immunity" page 278. Its words - "This toxon seems to us to be simply our

complex – toxin incompletely saturated with antitoxin. Such a complex has all the characteristics attributed to toxones: it is by definition less toxic than free toxin and also less avid of antitoxin, since its affinity for it is already partially satisfied. It is evidently related to toxin as far as origin and composition are concerned, but still is a new substance and therefore gives rise to different symptoms than a small amount of diluted toxin."

Nothing definite is known of the properties of the Toxoids or Protoxoids. They occur especially in old cultures, and possess the greatest affinity for antitoxine. Probably they have no poisonous properties, but we have not the slightest idea of the chemical process which induces the probably inert nature of the toxophore group.

The toxines proper however, are known to be the poisons mainly concerned in producing death, and possess an affinity for their specific antitoxin intermediary between the toxones and toxoids.

It is pretty generally held by observers that nearly all toxines are absolutely without action upon the system from the stomach or intestines, unless perhaps the mucous membrane of these surfaces is depressed or injured. They either pass through with the excreta being unchanged, or are completely destroyed.

The fate of the toxines within the body: Toxines disappear with extreme rapidity after injection into susceptible animals. In quite a short time, the blood

is absolutely free of them, as has been proved by experiments of Bonstein and Brenner on diphtheria.

The virus seems to enter into close combination somewhere or other in the latent stage of its activity, (Donitz's experiments). Donitz found that he could not save infected animals by the injection of Antitoxins, even when only a few minutes after the injection. He concluded that the toxine was no longer in a free condition, when it encountered the antidote. He found further, that it was only by the injection of very large doses, that it was possible to break up the combination of the toxine with the cells of the body; and so destroy the effects of the latent poisoning. In such cases the poison had become firmly attached to the cells specifically susceptible to it.

This however is more apparent in the case of Tetanus, in which the ~~at~~ initial poison, chemically transformed, becomes attached as molecules of complement to the receptors of the cellular units, deep in the central nervous system, where the antitoxin cannot easily follow. Such at any rate would be an explanation of the fact, according to the hypothesis advanced by Ehrlich in his "side-chain" theory of immunity.

It is extremely questionable whether the lesions of the nervous system are to be attributed to the diphtheria toxine as such. So far as these changes have to do with the diphtheritic secondary paralysis, they must, I think, be attributed to the toxones.

Whether the pure toxine can also produce secondary paralysis, or whether it is only a function of the toxones cannot yet be ascertained with any degree of certainty. The latter hypothesis, however, is the one generally held; and it seems to me the more probable.

The whole question of the precise relations of the component constituents of diphtheria toxine is, at the present stage of our knowledge in these matters, extremely vague and most difficult to determine in anything like definite terms.

Antitoxines: Behring and Kitasato published the results of their important researches in 1890. They proved that it was possible, by injecting animals first with infinitesimal doses of toxine, and gradually increasing the amount, to render such immune to the disease to which the specific poison belonged. Animals so treated were able to bear large doses of the particular toxine with impunity — many times as great as could be borne by non-immunised animals of the same species.

Further, they were able to prove that if a measured quantity of serum, drawn from an animal thus rendered immune, be mixed with an equivalent amount of the toxin originally used, and injected into a non-immune animal no ill effects were produced.

Also that the injection of immune serum into a non-immunised animal rendered the latter resistant to that specific toxin. They likewise demonstrated the astonishing fact, that if a dose of immune serum was given within a definitely short time to an animal already inoculated with the same toxin from which the serum was obtained - the disease did not develop at all. In short they proved that in animals treated with diphtheria toxine, a serum could be extracted from their blood, which was capable of neutralising the diphtheritic toxin. And at the same time, there was exhibited a pronounced curative effect on the disease itself.

The same was proved of some other toxines - notably that of the Tetanus-Bacillus. However, the serum drawn from the tetanus case had no effect on the animals treated with the diphtheria toxins, and vice versa. Each serum was found to be specific, neutralising only the toxin of its corresponding disease.

This peculiarity was found to exist in all subsequently prepared antitoxins.

The demonstration of such facts stimulated afresh interest in this subject, and with it, research came to be established in different directions.

In 1895, Bordet, to whom a very great deal of our knowledge of the phenomena of bacteriolysis is due, discovered that if the blood of one species of animals were injected into another species, the serum of the latter acted upon the corpuscles of animals of the former species, destroying them. This haemolytic power being more pronounced in certain species of serum from self blood. Thus this study advanced on such special lines until Antitoxin became an established factor in treatment.

Further experiments demonstrated that blood serum, even when all formed elements, such as the corpuscles, had been removed, still exerted in many instances an inhibitory action on the growth of micro-organisms. There must be present in the plasma, therefore, some substance of a protective nature — and to this hypothetical quantity Büchner gave the name "Alexines".

It is in all probability by means of such alexines that destruction of bacteria is brought about; and it is by this chemical products circulating in the blood that the poisonous products of the organism are neutralised.

Diphtheria antitoxine, per se, has no effect in preventing the growth of the bacillus diphtheriae, indeed, it is actually a favourable culture-medium for that bacillus. It is evident, then, that some special substance is produced in the bodies of immunised animals, which acts as a solvent of the bacterial protoplasm.

As the result of these discoveries, and much painstaking investigation along such lines, a whole series of peculiar properties possessed by the serum of immunised animals have been brought to light.

Chief among these being the recognition of a special group of substances - "Opsonine". The influence of the serums having been studied specially by Wright and his collaborators. The name of opsonins being given to the chemical substances at work. (Wright & Douglas Proc: R. Soc: London 1903)

French observers, studying the phenomena of phagocytosis, on the lines of Metchnikoff, early discovered that the activity of the leucocytes was greater in the presence of blood serum. The presence of normal serum increasing the activity of the leucocytes in ingesting all kinds of bacteria.

When, however, infection with a pathogenic organism has occurred, and been successfully resisted, the opsonic power of the serum is found to be increased

towards that particular organisms.

The exact nature of opsonins, and their relation to the substances concerned in immunity is doubtful.

Grüber regarding them as complements.

Grey Smith, as allied to agglutinins.

Verney, that all immune substances can act as opsonins e.g. complements, copulas, autotoxins.

Their action is manifest enough, however, and has served, as nothing else has done, to reconcile the two great opposing schools with regard to the resistance and the cure of disease, viz - the "Phagocytic" and "Humoral" theories of immunity. The action of opsonins probably in some way renders the bacteria less resistant to the attacks of the special phagocytic cells - the existence of opsonins inducing or facilitating the process of phagocytosis.

So far as it is understood, it would appear that both phagocytosis and bacteriolysis take part in the destruction of bacteria within the body.

Certainly, the older theory of phagocytosis, modified a little from Metchnikoff's earlier account, is again finding greater acceptance amongst scientific observers of the present day. The more, and the deeper I go into the study of the behaviour of the leucocytes, and the more minutely I follow the very careful experiments of Bordet and others on this subject, the more

I am convinced of the importance played by Leucocytes in the warfare against microbes and their products; not only in contagious diseases and in those of a particularly infectious nature; but in those that are preeminently toxic and in which bacterial invasion is extremely limited, such as in diphtheria.

The assemblage of Leucocytes which takes place at any focus of irritation is almost certainly protective in character; and it has been shown by Hankin and others that the granules contained in the protoplasm of the Leucocytes consist of substances which in themselves tend to combat the bacteria and to arrest their development.

M. Jules Bordet working on Leucocytes and the bactericidal power of serum ("Studies in Immunity", Bordet and Gay.) pages 24 & 82., concludes that the bactericidal substance present in the serum, comes from the Leucocytes. He says, "we were forced to the conclusion that during life the bactericidal substance is present in the Leucocytes and that when the white blood cells are removed from the blood-vessels they liberate into the surrounding serum those bactericidal substances which they normally retain".

Others supporting the phagocytic hypothesis, have satisfactorily proved also, that in many important

affections the serum alone was ineffective in destroying bacteria, and that the action of the leucocytes was essential for the purpose of defence, maintaining likewise, that the precise chemical bodies held by their opponents to constitute the basis of immunity, were none other than the secretions from leucocytes in the blood.

Bordet attributes an important part to the leucocytes in the elaboration of those substances which endow sera with their activity. He has proved that leucocytes respond to stimuli in various ways, and are capable of reacting in several different manners. These different reactions being often all exercised in the course of a given phenomenon.

The fundamental facts of the "Phagocytic theory", as advanced by Metchnikoff and his followers, have been frequently dealt with in articles and other writings, on various phases connected with problems on immunity. So that it will only here be necessary for me to touch on one or two points, which may be cited in confirmation of this doctrine.

This important theory of resistance to disease was advocated early by this celebrated Frenchman. He studied the behaviour of the white blood corpuscles in many of the lower animals, and attributed the destruction of bacteria in the body to the activity of these cells.

This was the well known theory of Phagocytosis.

Metchnikoff taught that the Leucocytes attack & devour invading organisms which they meet, and thus rid the body of these parasites, just as they may be seen to take into their substance particles of any foreign matter met with. When they had swallowed and destroyed all the existing bacteria in the body, the disease came to an end.

This phagocytic function belongs essentially to the polynuclear and large mononuclear leucocytes, and also to a certain extent to certain endothelial cells in the capillaries of liver and spleen - and may be of their parenchymatous substance.

Phagocytosis has been found in all animals that have been carefully studied. It occurs in all diseases of an infectious or contagious nature - wherever there comes to be an invasion of micro-organisms or their products. Phagocytes not limiting themselves to the taking up of living and dead microbes, but capturing also their spores, and preventing further germination. Their activity is also utilized against other foreign bodies, and against the other cells of the same animal when such have become useless or harmful and are destined to disappear. Body scavengers therefore.

The protoplasm of phagocytes has been found to take up soluble substances introduced

into the blood stream, as was shown by Samoiloff in his researches, on the distribution of soluble silver and iron compounds in the body.

The surprising rapidity with which the engulfing of organisms may be accomplished — often, the almost-instantaneous occurrence of this phenomenon — proves the very fundamental function of phagocytes in the destruction of bacteria. The intensity with which phagocytosis occurs in infected animals has been shown to be always proportionate to the resistance of the animal, being decidedly more active in immune animals, and in those previously treated by a preventive serum.

The proved existence of a peculiar reaction on the part of the leucocytes to chemical substances secreted by bacteria offers important evidence of the part which these cells take in the defence of the body. Whenever bacteria find a lodgment in the tissues, their presence is evident from the fact that their diffusible products bring about chemiotaxis on the part of the leucocytes, so that when these phagocytes have approached the infecting bacteria to the point of contact — the tactile reaction of these cells permits them to send elongations about the infecting bacteria and engulf them.

The rapidity with which these various phenomena follow each other, especially in animals rendered immune, shows how very active phagocytic intervention is.

Leucocytes may, however, be actually repulsed by very virulent organisms. Whether this is due to a paralysing influence of the very highly toxic bodies themselves, so preventing the leucocytes feeling the attractive influence of the bacterial products, or to some repellant action of the bacterial secretions, or simply to not being attracted. It is not an easy matter to determine.

Bordet recognises that leucocytes have a 'negative' as well as a 'positive' chemiotaxis, as will be seen from the following experiment. (Bordet "Studies in immunity" pages 13. 14 & 15.) — Where a normal guinea-pig was given an injection of 1 c.c. of a two-day culture of a very virulent streptococcus into the peritoneal cavity.

After three hours it was found that the exudation was very rich in polynucleares, far more than required to take up all the organisms present. Only a certain number of the cocci becoming the prey of the whole corpuscles.

At the end of six hours the exudate was found to contain very large numbers of phagocytes. Likewise streptococci, but after staining & under the microscope, it was found that these phagocytes were empty. — in other words — the phagocytosis of the cocci, which was noted at first, is no longer present. The cocci and phagocytes must be still in intimate contact, however, as before. What of their tactile reaction now?

It must be that some active influence prevents

the phagocytes from taking up these organisms scattered about them. What is this influence?

Bordet offers two explanations; either the leucocytes are paralyzed by the toxin secreted by the streptococci in multiplying, or that the leucocytes have been subjected to a negative chemiotactic influence from the streptococci, and so preventing them taking up the bacteria.

At the end of 8 hours, the peritoneal exudate was found literally alive with cocci; also very rich in phagocytes. He gives now a second injection — this time, 1 c.c. of a rich bouillon culture of the Proteus vulgaris, which under normal conditions is easily destroyed by phagocytes — being only slightly virulent. Now note what happens.

Bordet says, "A few moments later, if we take out a little exudate, we find that the cells which refuse to take up the streptococcus have eagerly taken hold of the new organisms offered them. Within half an hour almost the entire culture is within phagocytes. It is extraordinary how these phagocytes have chosen between the two varieties of bacteria. With greatest delicacy they have reacted to a new chemical substance and each one takes up numerous Proteus organisms, recognizable by their

rod shape, but still refuses the streptococcic which remain scattered throughout the preparation outside the cells. The protoplasm of the phagocytes acts rapidly on the bodies of the bacteria that have been engulfed".

It is right to conclude, therefore, that the leucocytes of the peritoneal exudate have neither been killed nor paralysed by the toxin from the streptococci, their faculty of engulfing bacteria having remained intact. They refuse to enter into contact with the streptococci owing to the fact that they have received a negative chemical stimulation from the strepto-cocci. This interesting and instructive experiment illustrates the elective properties of the phagocytes, which seize first the organisms that are most attractive and the least dangerous to themselves. This characteristic was found in many the experiments. This phenomenon of selection is an important and far reaching one, and we have yet to learn how very slight an alteration in environ-ment may predestine even the most recalcitrant bacteria to rapid phagocytosis. Bordet attributes to phagocytes a most important function, and considers that the theory of phagocytosis is capable of explaining the problem of immunity.

In vitro, he found a very marked phagocytosis against the Bacillus diphtheriae, (page 35 of Studies in immunity) he writes "the shape of the organisms is not changed (at least in 4 hours), but the reaction to dyes is extraordinarily modified.

"The majority of the diphtheria bacilli
"taken up by phagocytes are colored a deep red or violet. Outside the leucocytes, on the contrary, the organisms show its normal reaction for the basic stain. Mononuclear leucocytes also have a very distinct affinity for diphtheria bacilli and take up a good number of them, but the organisms taken up by the mononuclears show fewer color changes than those taken up by the polynuclears."

Bordet observed similar phenomena in vivo, after injecting the diphtheria bacillus into two guinea-pigs. (page 37. Bordet's studies). One of the guinea-pigs receiving the day before 3 c.c. of bouillon in the peritoneal cavity; the other 3 c.c. of anti-diphtheria serum. He writes—
"The injection of bouillon produced a rich leucocytic exudate composed largely of polynuclears, but also containing a few mononuclears.
In the animal injected with preventive serum, the exudate contained many polynuclears, but, in addition, a number of mononuclears (macrophages).
In both animals phagocytosis is noted after injection of the culture, and, as is usual, the polynuclears seem to take the greater part in it. In the case of the guinea-pig vaccinated with serum, however, the macrophages are found to have taken up considerable numbers of organisms.

After an hour there are numerous intraphagocytic bacilli staining red both in the animals that had

"received bouillon and in the one immunized with serum.

Although the taking up and destruction of the organisms appears to go on without any difficulty, there remain certain resistant bacteria, so that positive cultures were obtained from the exudates of both animals 18 hours after injection."

There can be little doubt but that the leucocytes play a very important part, and that this theory of phagocytosis contains a large proportion of the truth; but in man, at all events, this phagocytic action is not the sole factor in the struggle with the bacillus diphtheriae.

I am more and more confirmed in this view, however, that many gaps in our knowledge have yet to be bridged over before we can possibly expect a clearly intelligible understanding of this difficult problem.

It remains yet to be discovered whether it is the leucocytes that in a particular manner contain the bactericidal substances, and if so, whether the elaboration of these substances is a special characteristic of their protective activity, and whether this activity is brought about by an adaptation that occurs in them in consequence of serum treatment.

Pfeiffer and others incline to the view that phagocytosis is only a secondary function, and that the destruction of bacteria in immune animals is

primarily due to the activity of the body fluids apart from cellular activity.

Our definite knowledge of antitoxines is even smaller than our knowledge of toxines. We know that diphtheria toxine produces in the body the corresponding antidote, which is a normal but complementary product of the tissues. According to Ehrlich's theory, the broken-off receptors which are secreted under the stimulus of the haptophore group.

They are substances with only one haptophore group, which coincides with the corresponding group of the toxine.

They possess so far as we know little physiological or chemical activity. They can only combine. They ward off the toxophore group from the unaltered cell.

Such benign characteristics do not apply, however, to the serums in which the antitoxine is present, for we know that albuminous substances foreign to the body are in a certain sense invariably poisons. They give rise to protective substances.

It is evident, therefore, that unlimited quantities of horse-serum cannot be ingested into man without producing reaction. Disturbances due to this cause have often been observed in the therapeutic use of diphtheria serums. In such cases the ill effects must be attributed to the serums rather than to the antitoxine.

Antitoxine disappears rapidly from the blood after subcutaneous injection. It is not well known what becomes of it. Certainly after the first few days it cannot with certainty be demonstrated in the tissues.

The relation between diphtheria toxine and antitoxine can only be experimentally determined.

It is to the brilliant and unwearying researches of Ehrlich that we owe so much. According to his "side-chain" hypothesis the only poisons that can act as true toxines are those possessing a specific affinity for the definite cells. Ehrlich assumes that both the toxine and the attacked cell have in their protoplasm an atomic group which reciprocally coincide and thus enter into combination, bringing the toxine within the immediate reach of the cells.

The cell is now through this concentration brought within the sphere of action of the toxine and then, of course, follows the specific action of the poison upon the cell.

The toxine, according to Ehrlich, consists both of a destructive substance and a uniting substance joined together in one molecule — the toxophorous and the haptophorous atomic groups.

Such combined toxic molecules seize appropriate "side-chains" — If many of these take up poisonous groups the cell itself dies — If on the other hand only a few of the "side-chains" are fixed upon — these simply die, and are dropped off — the cell itself escaping.

As frequently happens in organisms, the reparative process goes beyond the original supply, and thus the cell comes to possess an increasing number of side-chains capable of fixing the particular toxine. Ultimately many of these are cast off by the cell into the surrounding lymph, and appear in the blood as free "side-chains", which constitute the Specific Antitoxine.

It is supposed that myriads of these free side-chains are capable of uniting with the molecules of the Specific toxine before it can reach the cells themselves; and in this way preventing any poisonous action.

Further, if serum containing these free side-chains be injected into another animal, they will continue to perform the same function in their new environment, and will confer on the animal so treated the same immunity as was possessed by the first immunized one. I should think that a difference would exist only in degree, according to the amount of free "side-chains" injected.

In diphtheria of two or three days' duration, in which the Bacilli have already gained a firm footing in the patient, and are pouring forth a continuous stream of toxine, the injection of an ordinary dose neutralizes the poison; but it is necessary to administer very large doses to counteract the continuous inflow of the toxine.

As a prophylactic however, small quantities are

only required – the free side-chains only being needed to be lying in wait for any poisons that may be formed.

It is claimed for antitoxins that it only neutralizes the free toxins present.

I think, however, that there is also a very important indirect action. – It is acknowledged that bacilli diphtheriae conduct their conflict with the body cells by means of their poisons depressing the cells and so preventing them forming their antibacterial bodies. The neutralization of the existing poisons by the antitoxine is a factor enabling the cells to gain time to form their defensive secretion, whatever the precise nature of such may be.

It has been pointed out that so long as the "side-chains" continue attached to their parent cells they are a source of weakness and danger as the toxine is thus enabled to attack and destroy them. The side-chains cast off into the blood stream, however, become a source of protection.

From a clinical point of view it is extremely important to recognise that toxine already in combination with the tissue cells, or may be "side-chains", is practically beyond the reach of antitoxine. In diphtheria, however, I believe it is possible by administering large doses of the antidiphtheritic serum, to withdraw the toxine from its combination with the cells – some sort of mass action having taken place. I consider that I have had such cases.

The Clinical point, however, is that we must never allow such a combination if possible - but to administer diphtheria antitoxine speedily - without delay on the earliest appearance of the disease & but of this again.

Theoretically, all this is fairly intelligible. But when one comes to consider the chemical processes which must occur in living protoplasm - the continual series of changes between a mass of protoplasm and its surrounding lymph - the fermentative effect of a principle in the toxine, itself unknown, - the vastly complex nature of a molecule of living matter - to say nothing of the immense complexity of the Serum itself - it must be brought home to one how really little we know yet of the true nature of very much of all this.

Ehrlich's very ingenious hypothesis of immunity must appeal to all. It has influenced many minds, and has given order at least to what was formerly confusion. It has become pretty generally accepted as a workable hypothesis - and it has the world-renowned reputation of its author behind it.

One would have wished indeed that there could have been less assertion of undemonstrated facts. Professor Jules Bordet in his "Studies in immunity" page 497 writes — for example

"My own impression of the theory has not been

"favourable, and it has seemed my duty to combat it. The principal fault to my thinking is that it is not, strictly speaking, a theory, but rather an assertion of a certain number of un-demonstrated facts. According to Ehrlich, antibodies are produced as follows: in the first place the antigen when introduced into the animal body meets with a substance with which it unites. So far we all agree. It is quite certain that foreign substances which lead to the formation of antibodies are taken up by the tissues and produce a reaction with certain substances in the body to which, for convenience, the name of receptors may be given. The body restores these destroyed receptors by producing new ones identical with the original. But, according to Ehrlich, these new receptors are over-produced to such an extent that they flow over into the fluid of the body, retain their essential property of uniting with the antigen, and are then to be designated as the antibodies of the serum. In short, the antibody is identical with the receptor affected by the antigen. To draw such a conclusion is, however, to affirm a fact that has never been demonstrated."

Much might be written regarding the manifold characteristics of immune serum - not only in its relation to the antitoxic substances (capable of neutralising the poisons of bacteria) - and the antibacterial substances (which are fitted to destroy the organisms); but also of such substances as agglutinate the bacilli (agglutinins), and those which precipitate the albumens of the serum (precipitins), - even those which destroy the living cells (cytolysins).

It would appear that in the conflict with bacteria each destructive substance is met with its corresponding antibody e.g. toxines being met with antitoxines, bacteriolysin with antibacteriolysin, and so forth.

To all who have given attention to this subject, - the immense capacity possessed by animal bodies of protecting themselves against attack is only yet revealing itself. We know only but a small part of this also.

With regard to the action of diphtheria antitoxine on toxine, the facts are clearer, though even in this, much diversity of opinion exists.

Direct relationship between toxine & antitoxine having been established, it has been proved that the action does not depend upon any direct destruction of the poison by the antidote - the facts indicating

that there is a form of simple combination between these two constituents. In many neutral mixtures of toxine and antitoxine, it is possible to break up the combination in such a way by heating, that the original toxic activity can be restored, especially when the combination has only been formed for a short-time. This would seem to give strong support to the theory that the combination between toxine & antitoxine is of a loose nature.

In diphtheria toxine and antitoxine which have been neutralised - the combination does not so respond, however. The toxine being the more destructible element, becomes transformed by the heating process into toxoids - and the combination not being broken up, no free anti-toxine can be detected. (quoted by Carl Oppenheimer, page 32).

The combination of diphtheria toxine and antitoxine, therefore, is of a much more stable nature. This was shown by Ehrlich.

We are justified in assuming on practical and theoretical grounds that the action of an antitoxine upon a toxine consists essentially of a reciprocal combination of two groups endowed with specific affinity. The conception that antitoxine not only modifies toxine but unites with it is in perfect harmony with much we know regarding them.

Does antitoxine unite with toxine in definite proportion? – in which case the neutralised product would have a fixed and invariable composition –

Or does one of the substances unite with the other in varying amounts? – in which case the combination will not be endowed with the same characteristics.

Ehrlich thinks that a union in definite proportions is true within certain limits – certain very curious phenomena being observable – indicating that the combination is not one of simple chemical type. Like the simple action of a monobasic salt with an alkali. He proves this simply — after standardising his toxine & antitoxine in the usual way. Ehrlich takes as his neutral mixture,

100 m. l. d. of toxine = 1 unit of antitoxine.

By adding to this neutralised mixture, one extra minimal lethal dose, he does not, however, find that this additional toxine has its usual effect of killing a guinea-pig of 250 grms in 4 days.

On the contrary the animal recovers from the injection with some oedema at the point of entrance.

Indeed he found that it was necessary to add large numbers of toxic units before a point was reached at which the guinea-pig was killed by the injection in four days. This additional quantity of

toxine is called by Ehrlich the L + dose.

He tested the combination in different ways; and the explanation arrived at was that, the culture medium in which the bacteria had grown contains several different substances, all of which have the power of combining with antitoxine - these substances differing in degree of affinity. —

The substance "prototoxoid" having the greatest affinity
" " "toxone" " " least "
" main toxine intermediate between these.

The first addition, therefore, of antitoxine to such a mixture, does not reduce the toxicity of the mixed poisons, because it only neutralises the prototoxoid, which is inert. A further addition neutralises the "main toxine", with its highly toxic characteristics, while a still further addition of antitoxine prevents the topical effects of the toxone.

In short, in adding antitoxine to diphtheria poison, the prototoxoids must be completely saturated before any of the main toxine is neutralised.

There are phenomena exhibited in the behaviour of these substances with antitoxine most difficult to explain on the basis of a simple chemical combination e.g. if the mixture be heated to 100°C. the antitoxine is destroyed & the toxine remains unneutralised. — or if the mixture be passed

through a Chamberland filter, the toxine passes but the antitoxine remains behind.

Jules Bordet draws from his many interesting Experiments, the deduction that toxine + antitoxine may combine in different proportions to form a series of Compounds eg. TA^1, TA^2, TA^3, TA^4, TA^5 – at the Extreme end of which we have "toxone" which is really nothing more than a molecule of toxine incompletely saturated with antitoxine. These mixtures TA^1, TA^2 &c being more or less toxic according to the amount of anti-toxin present. "The first TA^1 would be rather poisonous although less so than pure toxin; the following TA^2, and TA^3 would be successively less toxic; TA^4 & TA^5 may be supposed to have no toxic effect, & so forth". (page 265 Bordet & Gay "Studies in immunity".)

According to Bordet, the simplest explanation of "Ehrlich's phenomenon" is the one in which the antagonistic substances (toxin and antitoxin) combine in variable proportions.

Bordet writing on this subject, (page 267 "Studies in immunity" – concludes in these words. "As a matter of fact we have simplified this Explanation considerably, for Ehrlich has attributed an extraordinarily complicated composition to the toxic bouillon in order to make his theory

"agree fully with experiment. The explanation is unquestionably ingenious but the existence of certain of the substances, particularly of "toxons", is purely hypothetical. The question then is still an open one."

Roux and Büchner maintain that antitoxine does not act directly on toxine at all, but does so indirectly through the medium of the living cell. The cell being stimulated to resist the poison.

In the combination of Tetanus toxine & antitoxine Behring is of opinion that a third body, which he calls the "conductor", is necessary; This body acting in a similar manner to the copula in haemolysis. Bordet and Gay propound a similar view in relation to diphtheria. (Ann. de l'Inst: Pasteur, 1906 xx, 467.)

I conclude this part of my thesis in the words of Prof: Jules Bordet, words used by him at the beginning of his concluding article on "A general résumé of immunity" - page 496.

"I should have been pleased to conclude this volume with a synthetic view of the entire subject,

or a general theory capable of coordinating the many facts that have been acquired. But in spite of the results that have been obtained by an army of investigators for many years, I must admit that such an attempt seems to me at the present day both rash and of questionable value. It is rash on account of the great gaps that still exist in our knowledge of immunity. In spite of the numerous data which we possess, it is as yet impossible to offer a coherent whole or an harmonious and complete system; many of the facts which we have, cannot, as yet, be classed according either to relations or consequences.

Anyone who should attempt at the present day to penetrate the mystery which shrouds the numerous problems of immunity by reason alone would be sure to fall into error." ----------

"It is better, then, to seek for the truth without wishing to define it before we have found it."

Concluding his résumé (pages 528 & 529) — he writes thus of phagocytosis —

"Although I have discussed in some detail the properties of sera, I have not taken up at all the essential topic of phagocytosis.

"The importance of this phenomenon in the defence

of the animal body, which was so much com-
-batted fifteen years ago, has no need, at the
present-day, of emphasis. We have long since
passed the time when the exact observations and
the decisive experiments of my former master and
present-friend, Elie Metchnikoff, met with warm
but also superficial opposition from those scientists
who were too exclusively preoccupied by the
antibacterial properties of the body fluids.

"Many facts which have been long known, but-
the significance of which has not been appreciated,
have been confirmed and re-studied now that there
is a generalizing acceptance of the value of phago-
-cytic defense. And this is particularly the case
with the numerous facts which we owe to Metchnikoff.

"Such is the case also with certain of the facts that-
have been mentioned in various articles of this volume,
particularly as regards negative chemiotaxis, the phenomena
of adaptation which bacteria employ to protect themselves
against phagocytosis, and the visible index of which
consists in the appearance of a capsule, the manner
in which leucocytes act with certain poisons, toxins,
or alkaloids like quinine, and the like.

"The fundamental importance of phagocytosis
is today universally admitted and is moreover

"Evidenced by the large number of articles which deal with means of computing the intensity of this phenomenon in normal, infected, or immunized animals".

The infinitely greater success that has attended the serum treatment of diphtheria, as compared with some of the other specific sera, is, I think, in no small measure due to the fact that diphtheria can with certainty be diagnosed at an early stage in its development — certainly before any profound intoxication of the system can take place.

With such a determining factor, therefore, and with our present practical knowledge of serum-therapy, there can be little wonder that year by year additional experience shows that Antitoxine treatment is not only safe, but is in the highest degree efficacious.

It is misleading, however, to judge of this efficacy with any approach to accuracy in individual cases, the variations natural to this disease being even more marked than in many other affections.

Dealing statistically with this disease also, account must be taken of a number of what might be misleading data, such as fluctuations in virulence of epidemics when viewed over considerable periods — the attendant mortality rising and falling in accordance with obscure

periodic laws — making it possible at such times to have a low mortality, or the reverse, apart from the effect of any new remedy.

Also we must take into account all that stands for enlightenment in methods of improved hygiene and strict aseptic cleanliness.

Moreover, I believe that the disease, known to the bacteriologists as diphtheria from its etiological criterion, has become more common in recent years — the type at the same time less virulent. There is an increasing tendency also to class as diphtheria those milder cases of exudative throat affection, in which the specific bacillus is found — such mild types, from a statistical point of view, swelling the numbers in diphtheria returns — without adding correspondingly to the mortality.

Taking all these, and other contingencies into account, however, in forming a scientific judgment on the interpretation of available statistics, we are bound to recognise the great value to mankind of this treatment in diphtheria.

Since the use of diphtheritic antitoxine became general, carefully compiled statistics show that almost everywhere throughout the world, the mortality from diphtheria has fallen in a very marked way.

Such a simultaneous effect, relating to as

particular disease, can in no sense be regarded as a coincidence.

I need scarcely at this time of day append any actual statistics in support of these statements – already a very huge mass of such are available.

To show, however, that the fall in diphtheria-mortality has been very general throughout the world, it may be worth while briefly to quote from one or two widely-apart sources —

In New York, the mortality fell from

36.7 % in 1891, to 19.1% in 1895. (year of the introduction of Antitoxine treatment.)

in 1896, the mortality per cent fell to 15.4

1897, " " " 14.6

1898, " " " 12.2

1899, " " " 13.1

(New York Med: Jour: 17th Feb: 1900 – Billings).

In Vienna, Siegert states that

from 1892-4, 4894 cases, 2000 deaths, mortality 50% –

" 1895-7, 4143 " 817 " " 25% –

(Jahrbuch f. Kinderheilk, Jan. 1902).

In Mülhausen, Jaeger states that

the death rate was 32% – 55% in ordinary cases } in
65% – 68% " laryngeal " }

pre-Antitoxine days.

But fell to 16% - 20% in ordinary cases
20% - 25% " Laryngeal " } after the use of diphtheria Antitoxine became General.
(Deutsch: Arch: f. Klin: Med: LXXIII.)

In Berlin, the mortality per 100.000 of population was 90.6 — in pre-antitoxine days.
It fell to 38.5 during the five following years.

In Paris,
The fall was from 62.2 to 13.3: and so forth —

In 1899, Goodall published in the Brit: Med: Jour: some very interesting matter, regarding his experience in Laryngeal cases — (v. page 197) —

Before the introduction of Antitoxine —
3275 cases Laryngeal Diph: 1267 deaths - mortality 66.2% -
After Antitoxine treatment became General —
3486 Laryngeal cases, 964 deaths = mortality 27.7% -

Cases requiring tracheotomy —
Percentage of recovery under 30%, in pre-Antitoxine days.
" " " 63.4%, after Serum treatment:

Goodall concludes "Whereas in pre-antitoxine days, of 100 tracheotomies you could not expect to save more than 29, - you can now expect to save no fewer than 53.
"I think I am fully justified in claiming for Antitoxine the Great reduction in mortality among cases of Laryngeal diphtheria that these figures reveal."

The statistics of the comparative rates of mortality in diphtheria are even more conclusive. Cases in which the Antitoxine is administered early in the disease, and those in which some days have been allowed to elapse. These possess, moreover, a very special interest to all interested in this subject. & to my thinking, they are of paramount importance in relation to the early Serum treatment of cases.

The records of the Brook Hospital, under the Metropolitan Asylums Board (M.A.B. Rep: 1907 - page 165). Thus in the years 1897 - 1907 (inclusive) —

250 cases treated on 1st day of the disease — mortality = nil.
1513 " " 2nd " " mortality - 4·29%.
1690 " " 3rd " " " 11·24%.
1338 " " 4th " " " 16·89%.
1765 " " 5th & subsequent days - " 18·58%.

For eleven years, therefore, not a single death occurred at this hospital amongst the first-day cases.

Very similar statistical records were published both by the New York Board of Health and also the Chicago Health Board, and others - all bearing most strikingly on the immense advantage to be gained in early treatment.

The universal testimony of Clinicians also being that there is invariably a progressive increase in the mortality as the Antitoxine is given later and later in the

course of the disease.

No stronger evidence could be found in favour of the use of antitoxine in diphtheria.

It is unnecessary for me to go into the subject of the most approved method of production of diphtheria serum, such being given in much detail in many books. Special care must be taken that such sera do not contain either living bacteria or their toxines.

To obviate the former, a portion must be mixed with culture medium and incubated.

To make absolutely certain that such antitoxic serum contains no toxine - a guinea-pig must be used on a list guinea-pig.

Recognising that ill-effects appear to be associated with the quantity of serum used for the injection - efforts are being more and more directed towards the preparation of sera of increasing antitoxic activity, so as to obviate the necessity of giving large quantities of horse-serum.

Diphtheria antitoxine has already been prepared up to 1500 units to the cubic centimetre.

Attempts have been made to separate the antitoxine from the rest of the serum by precipitating the globulin, and using this for injection.

Ehrlich inaugurated our present standard of toxine and antitoxine —

A unit of toxine being the amount which will kill a guinea-pig weighing 250 grammes in four days.

A unit of antitoxine, on the other hand, being the smallest quantity which being mixed with 100 minimum lethal doses of toxine, and injected into a guinea-pig prevents the appearance of any toxic symptoms.

A standard antitoxine can now be procured from the "Serumprufungs Institut" at Frankfort-on-Maine.

This is everywhere used as a standard.

The most important diphtheria antitoxine sera in use in this country are —

1. Allen & Hanbury's Ltd (Agents for): London.
   (Agents for the Lister Institute of Preventive Med.).
2. Anglo-American Pharmaceutical Co: —
   (Agents for the Lyons Pasteur Institute).
3. Burroughs, Wellcome & Co: London.
4. Meister Lucius and Brüning. London.
5. E. Merck: London.
6. Parke, Davis & Co: London.
7. Rebman Ltd: London: —
   (Agents for the Berne Serum Institute).

The exhibition of diphtheria antitoxine serum by the mouth is, I think, of questionable value, and may be dismissed at least as unscientific.

The rule is to administer it subcutaneously. In very serious cases, especially those in which the disease has been allowed to develop unchecked for 3 or 4 days, the intravenous method may be had recourse to.

Subcutaneously administered, the diphtheritic serum acts well - and there are few disadvantages to this method. The site of the injection is immaterial, almost invariably I have used the loose cellular tissue between the shoulder-blades for my primary injection, and on no occasion have I observed any sign of local mischief at the seat of puncture. What does materially matter, is the strict observance of antiseptic precautions in this operation. After thoroughly washing the part, I use solution of Lysol - and sterilize the glass antitoxine syringe by boiling. After the injection, I seal up the puncture with a "scale" of collodion, under which is corrosive sublimate wool - and apply a bandage-support over all. In repeating injections I make use of the cellular tissue in abdominal flanks - sometimes over front of abdomen.

I have formerly made use of one or other of the serums mentioned on page 59.; lately I have stuck very constantly to the diphtheria antitoxine serum prepared by B. W. & Co.:

This serum of Burroughs Wellcome & Co:'s, I believe to be a thoroughly reliable product. On repeating injections of it, I have never experienced either disagreeable constitutional symptoms, or observed that any patient exhibited any symptom pointing to that peculiar hypersensibility - known under anaphylaxis. I conclude, therefore, that I am justified in my adherence to B. W. & Co's serum.

Since bacilli diphtheriae, in any case of diphtheria, are continuously pouring out a constant stream of toxine which is continually uniting with the receptors of the cells, it is, therefore, of the greatest importance to introduce the diphtheria antitoxic serum at the earliest possible moment, before any irreparable mischief is done to the cells. All experience points to this. Statistics show conclusively that the power of the remedy over the disease varies directly with the promptitude of its administration.
The first great principle, then, is the prompt administration of the serum. Give it in some form. Administer freshly prepared serum if possible. If such is not available, or only obtainable after delay - better to use an older brand than none at all.

Evidence shows that diphtheria antitoxic serum tends to deteriorate with time; but specimens have been known to retain their antitoxic power for 18 months & even longer.

The second principle, I think, is the administration of a large initial dose. We have no power, or method of judging the amount of toxine to be counteracted, and besides, the supply of the latter is constantly increasing. I consider also that we ought not to hesitate to repeat the dose if necessary. It is better to err on the side of giving too much, rather than too little.

Moreover, there is also the possibility that the presence of a large quantity of the antitoxine may tend to withdraw from the cells any poison that has already united with them.

As a prophylactic, I think that it has been found beyond reasonable doubt, that the administration of a comparatively small dose of antitoxine will produce immunity for a certain period. Such immunity is said not to begin for about 18 or 20 hours, and to pass off in about 3 weeks.

My own cases of prophylatic treatment are too small in numbers to admit of forming any decided opinions thereon. Formerly, I used to give as much as 1000 and even 2000 units as a prophylatic dose. This I now consider was excessive. I now regard anything between 300 and 500 units as sufficient. And considering the transient nature of the immunity so induced, I would have no hesitation, if circumstances demanded it, to repeat the dose and so renew protection.

American writers strongly favour the prophylactic use of antitoxine. Park (Jour: of the Amer: Med: Assoc: 1900, I. page 902) records 6506 cases of immunisation amongst which 28 developed the disease within 24 hours (which was before the protection was effective), while only 27 were seized after the 1st day.

I do consider that there is a real risk in administering the antitoxine. It may be small, three now & again we meet with peculiarly susceptible subjects, and may in consequence have deaths even — directly attributable to the action of the serum. Most of the fatal cases recorded have of a sudden character, occurring quite early after the injection. More frequently, however, the alarming symptoms take the form of dyspnoea which appears some time after, due perhaps to the direct action of the toxine itself on the cardiac muscle, rather than to the serum.

The fatal complication may now in great measure be lessened. Since a concentration of the prophylactic dose has been arrived at — 500 units in ½ a cubic centimetre of serum. Such must reduce the disturbing effect of horse-serum to a minimum.

On the whole, therefore, if contacts can be kept under strict observation, and apart from others, I consider that prophylactic measures need not be unduly insisted on,

as the prompt serum treatment on the first local suspect, gives such uniformly good results.

In the management of epidemics, the most efficient method is undoubtedly that which includes the examination of swabbings from the entire community, segregation of all carriers, and the prophylactic injection of antitoxic serum into all contacts.

An immediate diagnosis without cultures is sometimes possible by making a smear preparation of the exudate from the throat. The Klebs-Loeffler bacilli if present in sufficient numbers may be quite characteristic enough to justify a diagnosis.

When a bacteriological examination cannot be made, the physician must regard as suspicious all forms of throat affection in children, and carry out measures of isolation and disinfection. In this way alone can serious errors be avoided.

In the actual treatment of diphtheria very much larger doses of antitoxic serum are required. Tilly (Med. Chronic: 1900 II - Page 241) recommends 2000 units in cases of moderate severity + repeated in 12 hours. In severe cases, 8000 - 12000 units as the initial dose - followed by injections of 2000 - 6000 units in 12 hours.

Dr. J. H. McCollum, of the Boston City Hospital — a physician of exceptionally wide experience in diphtheria in all its phases, gave in one severe case, an initial dose of 8000 units, following it up with 4000 units some hours afterwards, and repeating this last dose every four or six hours until 92,000 units were given. This case recovered.

Mc Collum insists that the guiding principle in the use of antitoxine is to give it until the characteristic effects are produced, whether 4000 or 70,000 units are required. He judiciously remarks that there is no way of estimating the quantity of toxin generated by the membrane, and, therefore, one must administer the antitoxine until the characteristic effects are produced, namely — "the shriveling of the membrane, the diminution of the nasal discharge, the correction of the foetid odour, and a general improvement in the condition of the patient."

No case, he says, should be considered hopeless in the acute stage of the disease. The following are Dr. McCollum's written words (extracted from Professor Wm. Osler's Practice of Medicine page 156.), — "when one sees a patient with membrane covering the tonsils and uvula, profuse sanious discharge from the nose, spots of ecchymosis on the body and extremities, cold, clammy hands and feet, a

"feeble pulse, and the nauseous odor of diphtheria, and finds that after the administration of 10,000 units of antitoxin in two doses the condition of the patient improves slightly; that after 10,000 units more have been given there is a marked abatement in the severity of the symptoms; that when an additional 10,000 units have been given the patient is apparently out of danger, and eventually recovers — one must believe in the curative power of antitoxine.

"When one sees a patient in whom the intubation tube has been repeatedly clogged, when the hopeless condition of the patient changes for the better after the administration of 50,000 units, one can not help but be convinced of the importance of giving large doses of antitoxine in the very severe and apparently hopeless cases.

"In the majority of instances these large doses are not required, particularly if the patients are seen early in the attack - 4,000 to 6,000 units being enough to produce the characteristic effect on the membrane."

Rolleston, (Practitioner 1904 LXXIII, page 615 & following) found goes further than Mc Collum, in advocating large doses of diphtheria antitoxic serum in malignant cases —

in mild cases he advocates the injection of 3000 — 12,000 units

" average " " 12,000 to 18000 units

" severe " " 18,000 — 24,000 " (repeated).

Cairns (Lancet, 20th Dec. 1902) puts the doses for subcutaneous injection at 4000 to 20,000 units, while intravenously he gives from 20,000 to 35,000 units. He maintains that an initial dose of 20,000 units is not an excessive one in severe cases.

Other authorities recommend small doses for treatment, and do not advise the use of prophylactic injections at all, on account of the bad effects occasionally met with.

For my part, I have never had occasion to use antitoxic serum in anything like the quantities used by McCollum, Rolleston, or Cairns. Do extremely, however, I would have no hesitation in following out a treatment on similar lines.

With experience of many isolated cases in the country, and of two really severe epidemics in Eyemouth, the former of which in conjunction with my father, (the late St. James Forsyth, Medical Officer for that Burgh), the latter one in 1906 - alone, in which good results may be claimed - I have come to the following conclusions as to the amount of antitoxic serum required in various Groupings of cases —

I. For Children, 7 years and under.

(a) In cases seen very early, or in those of mild type,

Initial dose 1000 to 2000 units according to age,

(Thus in children of 3 years and under, = 1000 units
" " Between 3 years & 5 years, = 1500 "
" " 5 years and upwards, = 2000 ")

in each case 1000 units to be repeated in 12 or 24 hours if necessary. This repetition of dose I have frequently found to be unnecessary in mild cases, especially in those cases where initial dose was administered very early in the course of the disease.

(b) In severe types, or in cases seen about the 4th or 5th day of the disease, also in nasal diphtheria, Initial dose 2000 units, irrespective of age, to be followed in 12 to 24 hours, according to severity, by 2000 units, this again to be repeated in 24 hours.

My Experience has been that children stand antitoxic serum remarkably well.

II. In adults: —

(a). In mild type, seen early.

Initial dose 2000 units, to be followed in 12 hours by 2000 units more, this to be repeated in 12 to 24 hours, according to results.

(b). In cases of moderate severity, and in those seen about the 3rd or 4th day of the disease, —

Initial dose 4000 units, and subsequent doses of 2000 units at intervals of 12 hours - until shrivelling of the membrane, diminution of discharge &c - are effected.

(c). the foul-smelling, sloughing anginas, and in the malignant forms seen first in an advanced stage — Initial dose 4000 units, to be followed in 6 to 12 hours by another 4000 units, this dose to be repeated again in 12 hours. Doses of 2000 units to be repeated only if necessary. A careful look-out to be kept on the condition of the membrane, nasal discharge, foetid odour, and the general condition of the patient.

I have never made any distinction in my cases seen for the first time after the 5th day, as regards the administration of antitoxine. The view expressed by certain authorities that the administration of antitoxic serum after the 5th day is ineffectual or even harmful, I have totally disregarded. Such a view being contrary to the accepted theory of the nature of the disease. I think that serum ought to be given even in cases in which there is relapse.

I believe moreover in the restraining power of antitoxic serum as with regard to the production of subsequent paralysis. I should most certainly think that according to the accepted theory of the disease, that so far from having any part in the production of post-diphtheritic paralysis, antitoxic serum has a definite power in restraining it, especially when early administered.

Comby (Lancet 1906 II 54, 243.) actually advocates the use of antitoxic serum in the treatment of post-diphtheritic paralysis.

Personally, I have a record of some 48 cases of diphtheria in Dunmore and district. Besides some isolated cases in Tralee district and elsewhere. Amongst these I find quite a number of representative types. My cases though ranging very much in intensity of type, and in attendant sequelae; afforded uniform testimony to the value of, and the immense advantage resulting from prompt initial treatment. I had full opportunity afforded me of judging regarding this. The people of Dunmore, aware of my views in this matter, had no early to me suspected cases in the great majority of instances.

It was principally amongst the early cases in both epidemics that I was called in late, and therefore the fatal results.

Although, amongst those 48 cases, I had six deaths. These, with one exception, being in cases first seen late in the development of the disease.

The nature of these fatal cases were briefly as follows —

1. Child - 18 months - pronounced extensive laryngeal type - seen only in closing stages - mother an ignorant irish woman - looking upon the condition as "simply cold". This child succumbed to obstructive symptoms shortly after my visit - died during the night.

2. Girl - 3 years - marked pharyngeal & nasal diphtheria - Copious rhinorrhoea, Died in my presence during my first visit.

3. Girl - 3½ years - Extensive faucial membrane - haemorrhagic form - collapsed - seen very late. 2000 units of Antitoxic Serum were promptly administered, but this little patient died shortly after administration of second injection in 12 hours.

4. Robust boy - 4 years - previous good health - Case one of severe and extensive faucial type - tonsils uvula & pharynx involved. Seen late. Given 2000 unit doses of antitoxine were given. Throat was completely clear on the 3rd day - leaving this little fellow extremely debilitated. Despite the strictest vigilance and minute precautions about keeping him rigidly on his back, he suddenly expired two days later from heart failure.

5. Young man (23 years) - the imbecile son of a farmer, with large tonsils. This case was one of extremely foul gangrenous invasion of both tonsils with free extension to mucous membrane of nares - two or three deep punched-out-like grey spots on soft & hard palates. This case seen also late. Treatment appeared to be of no avail, he died shortly among my hands.

6. Girl - 4 years - Extremely mild type - seen quite early. No antitoxine. Throat absolutely clear of every sign of membrane within 24 hours. This girl did not spend the customary period in the recumbent posture. She suddenly collapsed during the 5th week of disease - heart failure. There were marked post-diphtheritic paralytic symptoms.

I had singularly happy results in all my this cases - many of which were quite as severe in type as any of those in which I have noted a fatal issue. Such good results, I attribute very largely to the promptness of early treatment.

Writing of my conclusions, in regard to the quantities of antitoxic serum usually necessary in the serum treatment of different cases - I took occasion to enumerate various groupings. In specifying such, I am conscious that my quantities of serum in the more severe cases at least, leaned on the side of leniency - In the years 1905 and 1906, I had not the decided views I now hold regarding the initial large dose - this those quantities used.

Allow me, however, very briefly to illustrate such from a few of my own cases. —

I. (a). Infant (Nicol), 11 months, infected from elder child (one of my fatal cases).
Slight exudation limited to one tonsil.
No severe constitutional symptoms.
Seen almost at commencement of attack.
Only one injection of Antitoxic Serum given, 1000 units.
Throat completely cleared within 24 hours.
Recovery — no sequelae.

(b). Sophia Scott - Armbank - 5 years.
previously robust and in good health.
Returned from School with sickness & pain in throat.
Examined her within 2 hours from outbreak.
Appearances - Tonsils both injected, slight focus on Right tonsil. Diagnosis uncertain - I at first thought it might be case of follicular tonsillitis.
Kept her in isolation with antiseptic applications.
Next morning a fairly extensive pellicular exudation over right tonsil - Temp very slightly to temp 101°F.
Diagnosis certain.
Administered 2000 units at once.
On the evening Exudate had advanced - membr. thicker.
Administered 3rd 2000 units. The following morning membrane recognised to be disintegrating, being decidedly shreddy. On the 3rd day throat absolutely clear.
Result. recovery - 2½ months & subsequently debilely?

On this case I noticed the extreme weakness in lower extremities, which is sometimes observable, apart from any condition of actual paralysis. This little girl walked much better at the end of first month, than she did at the expiry of second.

Ultimately she made an excellent recovery.

(b) Maud Gibson - Springbank - 6 years.

Seen early. Extensive creamy exudate over both tonsils - uvula free - glandular tenderness. Temp. 102.2°F.

Condition appeared to be rapidly spreading.

I administered 2000 units at once, followed it in 12 hours with this 2000, and 1000 in twelve hours after second. Swallings with 1 in 2000 Sublimate.

On the 2nd day edges of exudation hanging into pharynx, spread of process arrested. By the end of 3rd day throat nearly clear.

On 4th day no vestige of membrane could be found. This girl did not show any great weakness. She was kept in bed for a month, liberally fed, and never exhibited any bad symptoms of any kind.

I carefully kept watch over her during the 2nd month, and I failed to observe any post-diphtheritic phenomena of any kind.

(b) Ernest Chalmers (4 yrs) – School House –
a very robust little lad – previous history good.
Case one of severe and extensive faucial type, seen first on 3rd day of disease.
Four 2000 unit doses were given at intervals of 12 hrs.
Throat clear on 5th day. Extreme debility followed.
Tempre on 6th & 7th slightly subnormal, pulse 70-76.
He was having small doses of Tinct. Strophanthus and ℞ nucis vomicae – and taking plenty of strong beef and chicken soups – with Brand's Essence of beef. Yet despite that he suddenly expired on the 7th day. Heart failure.

(b). Janet Young: Free Mason's Hmse 6 years.
anaemic, dry-haired underfed growing girl.
Thick creamy exudate completely covering both tonsils, and uvula – also extending around pharynx.
Seen first on 3rd day. Swabbings with perchloride of Hg:
2000 units B.W. & Co's antitoxic serum at once,
Then 2000 in 12 hours, a 3rd dose at the expiry of 24 hrs after 1st injectn – a fourth in 24 hrs.
At beginning of 5th day exudation appeared quite loose & hanging in detached portions. On 6th day throat almost clear – characteristic raw surface showing itself where membrane had recently separated.

Temp. 98° F. pulse 104. a trace of albuminuria.
Quantity of urine fairly good.
Antiseptics were continued locally, along with Syrup Ferri Phos: Comp: & Cod liver oil Emulsion.
This girl, despite her former anaemic condition, never showed a bad symptom in her convalescence.
Recovery was complete. No Sequelae.

II. (a) Daisy Sinclair (14yrs): Post-office
Healthy girl - Seen quite early.
Thick creamy white exudate over right tonsil, which rapidly spread to left, & slightly over pharynx.
No severe constitutional symptoms. temp. 101° F.
I administered 2000 units of B. M. & Co's Serum at once and 2000 more in 6 hours.
She was then removed to Millerston Hospital where she did exceedingly well.
She was discharged from that institution well. And never afterwards exhibited any post-diphtheritic phenomena. I paid attention for another month but nothing that manifested itself.

(b) Maggie Johnston (21 years), Church Street;
Seen by me at very commencement.
Case, abundant thick & creamy tonsillar deposit

which rapidly advanced over both sides of throat
ending in gangrenous formation - at first the
membrane appear grey, and ultimately black.
Temp^{re} 102°F. pulse 96 - Marked toxic symptoms.
4000 units of Wellcome's serum were given at once,
and the 4000 in 12 hours, and afterwards two more
doses of 2000 each at intervals of 12 hours.
The tonsils, which were rather large completely
sloughed off, leaving a deep angry surface.
abominable foetor - temp^{re} on 3rd day 97.6°F.
pulse 69. She was stimulated freely and kept
rigidly on her back - under care of a friendly
trained diphtheria nurse.
This gangrenous action gave place on the fourth
day to reaction - and by 7th day throat
was absolutely clear of membrane but very
red looking - and difficulty in swallowing.
Gloabbings throughout were of $Hg Cl_2$ Sol: (1 in 2000).
This young lady was afterwards freely nourished.
was confined to bed for 5 weeks under care
of trained nurse. I visiting her once or 2ce daily.
She certainly remained anaemic and weakly
and recourse was had to iron tonics & Strychnine.
I kept her under observation until nearly the 3rd month.
But she never manifested a single post-diphtheritic
symptom. Ultimately she entirely regained her former strength.

61. Mary Conor (20yrs) : Albert Road :

A rather stout ruddy complexioned robust woman. Marked thick pultaceous tonsillar deposit over both tonsils & uvula when I first saw her (on 2nd day). The poison seemed of exceptionally virulent type, not only rapidly encroaching on adjacent structures, but manifesting a marked tendency to deeper invasion of tissues with gangrenous formation. Manifest toxic symptoms. This patient was very ill. I used strong swabbings of perchloride of mercury &c. I gave her immediately 4000 units of B. N. T.'s serum, and this 2000 in 12 hours, & 2000 in 12 hours after. The local condition certainly showed abatement but never completely disappeared as in my this cases. I had at a late stage to give another 4000 units before the process was thoroughly mastered.

I certainly think my dose in this case was too small. I should now be disposed under similar circumstances to give a much larger initial dose 6000 or even 8000 units : and doses of 4000 afterwards.

However, this case completely cleared up locally. but it was actually over the 9 months before she felt at all strong. She had never any actual paralysis : but developed that peculiarly characteristic weakness in lower extremities.

She remained for months anaemic & breathless on the

slightest exertion. She had abundance of every kind of nourishing food and iron tonics &c: still her convalescence was unduly protracted. She ultimately became quite strong, & married and had afterwards healthy children.

(c). David Kinloch Brown (23) Highlands.

Imbecile son of farmer.

Malignant rapidly-spreading dangerous form, both pharyngeal and nasal. Seen very late. Frightful factor. & General depression. Large multiple doses of Antitoxine absolutely useless against this condition.

This young man died in my presence the following day. - partly induced by severe toxaemia, and partly by obstruction.

This case produced a strong impression upon me, and often have repelled with horror given much larger quantities of Antitoxine.

It is just in such cases that heroic doses - at least what I formerly so regarded - would be of avail.

Treatment such as that laid down by J. St. Mc Collum - in the case already mentioned (pages 65 and 66) —

I might run over so a great many of my cases but let these examples suffice. I had a lot of very bad cases; but I think with the opportunity afforded me of being on the spot, and seeing them early, - and administering the doses I considered efficient, in keeping with safety - I was enabled in great measure to obtain the results I did.

I think now however that my doses were on the small size. Under similar conditions I would most certainly administer much larger doses in bad types.

I consider also that my results bear out the diminished frequency of post-diphtheritic symptoms, in cases where the antitoxic serum was given early.

I had only one typical post-diphtheritic paralysis case, and three of pronounced weakness in lower limbs.

In short, the more I come into contact with diphtheria, the more I am convinced of the value of a large initial dose of antitoxic serum, given at the earliest possible moment.

I recognise however the value of local treatment - formerly I used Tolisol Comp: said at that time to be active. I found this preparation too much an irritant, producing in several of my cases a oedema of an alarming nature. I discontinued the use of Tolisol.

Throughout my last epidemic in Plymouth in 1906. I almost invariably make use of cotton-wool swabs saturated in (1 to 2000) Corrosive Sublimate - the swabs squeezed fairly dry, used to swab nose every hour at first - in a bad case.

Lately however, I have considered such treatment to be a source of much unrest - and have recently been using with excellent results Tablets of "Formamint" - of Duncan Flockhart & Co's "Aldoform" - According to Seifert "Formamint" is a chemical combination of formic aldehyde with milk sugar. Each tablet contains so much of this new chemical combination that, when the tablet dissolves in the saliva, ·01 of formic aldehyde is set free, and, in its status nascendi, exercises a strong disinfectant action.

Seifert made experimental investigations with diphtheria Bacilli. He found that a solution of one tablet in 10 c.c. of water destroyed the germs in from 5 to 10 minutes.

Such an antiseptic (1% free formaldehyde), I consider is an extremely useful addition to our armamentarium against the Bacillus diphtheriae. It being pleasantly acidulated is an agreeable ingredient with children.

It is a proved antiseptic & bactericide,

It is non-toxic & very efficient, especially in those class cases in which rest is a consideration.

My cases treated so however are too limited in numbers to warrant my saying more of the Tablets.

Summary:

That the toxaemia of diphtheria is due to the absorption of soluble complex poisons, produced at the seat of the membranous formation, and that the etiological criterion is the Klebs-Löffler bacillus, is universally acknowledged.

It is likewise no longer doubted that diphtheria antitoxine is a specific antidote for free-uncombined diphtheria toxine. But whether these antagonistic substances combine in variable proportions (Border and Theis); or whether antitoxine combines with toxine in fixed definite proportions - the culture-medium containing several different substances having different degrees of affinity for antitoxine (Ehrlich) - it is difficult to say.

As to the curative properties possessed by Antitoxic Serum - I firmly believe in phagocytic intervention. The bactericidal properties possessed by the Blood-Serum being derived from the Leucocytes - the opsonins formed from the Leucocytes in response to the stimulus of the specific poison - the action of opsonins facilitating Chemiostaxis.

I consider that the elaboration of these substances is a special characteristic of their protective activity: this being largely brought about by an adaptation that occurs in them in consequence of serum treatment.

Regarding my conclusions on diphtheria antitoxic serum treatment — I think that given in doses of from 300 — 500 units as a prophylactic, it exhibits a definite power of preventing the onset of diphtheria.

In actual treatment — The curative effects of the serum are thoroughly established. In my experience it is simply a question of seeing the case in its earliest stages, and immediately administering the efficient quantity of serum.

In my cases, I never had the least doubt of result when I had them very early.

Therefore, if the clinical appearances are those of diphtheria I administer antitoxine without waiting for the bacteriological report.

In children under 7 years seen early —
1000 — 2000 units I think is sufficient for initial dose & to be repeated in 12 hours if necessary.
In severe types, or when seen late —
2000 units repeated in 12 hours again if necessary.

In adults —
Mild type - seen early — 2000 units repeated in 12 hours - a third dose only if necessary.
Moderate type — and in those ordinary cases seen late in the course of disease — initial dose 4000 and subsequent doses of 2000 units at intervals of 12 hours.

In severer cases I think very much larger doses may be given than 4000 for initial dose. In malignant types I would advise 6000 or 8000 units for an initial dose, and doses of 4000 units at intervals of 6, 8, or 12 hours, according to the severity of the type. — a careful look-out to be kept on the condition of the membrane, the nasal discharge, the foetid odour, and the general condition of the patient.