Thesis
for the
Degree of
M.D.

"Serum Therapeutics in Diphtheria"

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Historical Retrospect.

Bacteriologists have long been aware of the fact that many species of these organisms introduced into the circulation of living animals, ultimately appear from it, but can then be found in the affected tissue or a dermalised condition. To account for this loss of power, it is evident, that they must have been subject to some depressing influence, during their re-entry within the circulation.

Such a condition of affairs although inadequate was generally recognised, too long as being satisfactorily explained; for it was not until 1887 that Joffe demonstrated the fact that freshly drawn blood had decided germicidal properties. Properties which although marked at first, gradually diminished so that blood stood for any time, or was kept above a temperature of 40°C, after which it became a certain medium for the growth of organisms. This germicidal property it was observed was present to a greater or lesser degree in all cases, but was always most strikingly manifested by the blood of those animals, which were succoured by the action of certain bacteria as was shown by Betsch and Niessen. These observations also prove that the blood of a susceptible animal...
Then added to that of one which was inoculated, the culture of naturally or artificially so, was greatly increased in its germicidal power, even although the properties of the culture were no greater than 1 to 8.

From these results it might have been assumed that this action was chemical rather than biological in character, and could not have been due to the influence of the amoeboid cells or phagocytes as maintained by Katschukoff.

This latter theory has gained no material support by the elucidation of the fact that the phagocytic action of these cells is not due to any special property inherent within themselves, but rather depends upon the vitality of the organisms against which they act.

It remained for Biedermann to show that the germicidal power of blood depended not upon its cells, but upon its serum. This he found to be true. Most markedly, when the albumen of the serum was contaminated with the PII, or as he termed it, "in an active state," and although lost after heating or standing, it did not in any way influence the blood.

As the result of these and other experiments Biedermann came to the conclusion that the germicidal power
was due to some albuminous body present in
the serum - a substance Ogata was able to isolate.
In addition to this, Ogata in Japan in 1850
found that the blood of animals inoculated by the
sera contained not only the geruncidal element,
but others of an autotoxic nature. These protected
them against a further attack. In proof of this
they found that their inoculated with virulent
autotoxins to their bodies are peculiarly susceptible,
did not account if they received at the same
time a drop of blood from an inoculated ani-
mal. Moreover they showed that if they were al-
ready infected, the onset of the disease was cut
short, provided that a test to appreciate prior
had elapsed between the onset of the attack and
the time of inoculation - thirty days. The autotoxic
as well as the geruncidal elements, of the serum.
In the autumn of 1871, Behring publicly announced
that the serum of animals artificially inoculated
against diptheria, protects and cures completely ani-
mal inoculated with the Bacilli or the toxic product
of the Bacilli of this disease.
One may therefore reasonably assume as Behring did
that if this serum, with its protective ingredients.
to transferred to the tissues of a human subject out perly from an attack of the same disease, a deadly mean, so at hand by which that disease might be held in check, provides that it is administered in sufficient quantities and at a sufficiently early date.

This assumption Behring immediately put into practice, so that it is not unjustified to point at the present time by the satisfactory results that have followed its application to the treatment of diphtheria. In the end of 1891, a trial was made of the protective serum, or Antitoxin, as it was called, on the patients in the Clinic of von Bergman at Berlin, but the results it would appear were far from reassuring. A condition of affairs probably due to the weakness of the serum and the insufficiency of the dose. This was the first trial of its effect on human diphtheria. Behring thereafter set himself to intensify this Antitoxin or Curative property of the serum, until he produced that he termed a "normal serum", the result obtained, which he published in 1893 showing a material improvement on those of previous years.
From this time onward particular attention was paid to the protective power or strength of the antitoxin. Since it was found dependent for its intensity upon the degree of artificial immunity produced by the animal furnishing it. Recognizing this, Schieck & Kasserman in 1893, were able to produce a serum which had 20 times the strength of Behr's, & their gauze inoculated rats that they were enabled to publish a series of cases (972) or treated with a death rate of 23.6%, only, a decided improvement on that of the previous seven years where it had averaged 55.

Excellent as the results of these observations were, it would seem, that they were looked upon, with more or less skepticism, by the majority of competent authorities, who doubted their accuracy. This impression remained until some month later. (Sept. 24) Thee Rome by his clear and convincing address, read upon the Congress of Hygiene and Demography at Buda-Pesth, cleared all doubts on the subject, from the minds of those present.

He demonstrated the failure of toxic therapy.
Diphtheria as well as prompt and speedy of the support of all those who desire the alleviation of the suffering and distress caused by this terrible disease.

In the following month it was introduced into the Country for the first time, and tried in a series of 72 cases at one of the Metropolitan Asylums Board as an Hospital in London. To me these produced an appreciable fall in the frequency of death.

A few months later, viz., in November 1894, it came into general use in the other hospitals of the Metropolitan Asylums Board, and has continued to up till the present time, with very satisfactory results.

The medical superintendents of the general hospital have just written a joint report in which they point out this disease as being a therapeutical and in the treatment of diphtheria, more valuable than any yet known.
Before discussing the mode of action of anthrax
it will be as well to consider briefly,
the Pathology of Diptheria.

There seems now to be a very general consensus
of opinion, that the local lesion in Diptheria
results from the presence or growth of a Bacillus
at that point, as described by Klebs and Löffler.
The general symptoms produced being emergent
upon the toxic products of the Bacilli generated,
gaining admission into the Circulation.

That this is so, has been proved Connolly by
demonstration, for if certain animal substances are
inoculated with these Bacilli, not only are the
local symptoms reproduced, but also subsequently
more general toxamic effects, so characteristic
of the later stage of the disease.

Further, it is interesting to note, that the injection
of these toxic products cutaneously, reproduces
the exact Counterpart of the general symptoms first
described.

At this point it may be mentioned that certain
authorities do not admit that the local manifestation
of Diptheria can be produced experimentally by
inoculation of the latter animals, as maintained by
Höfler asserts his effects produced are unlike those of human diptheria, but this is partially so, to no doubt true, but it must be borne in mind that many of the lower animals are more or less susceptible to the disease and therefore the symptoms they exhibit after inoculation, must necessarily be modified in proportion to their degree of susceptibility.

The experiments of Höfler have, however, been further confirmed by Mora of Rome. Garcia, Illeni and Welch, who have been able to produce characteristic pseudo-membranes on injured, mucous surfaces, their presence afterwards followed by well-marked toxic symptoms.

As to the nature of Diptheria genus nothing very definite is known, but certain authorities, chief amongst them are Harms, believe them to belong to the class of ferment or Enzymes. These reaching on the tissues form Albuminuric. These are again capable of breaking up into simpler bodies, or compounds. Both retain the virulent and poisonous properties of Diptheria, but if anything the albuminuric seems to be the more virulent.
In the opinion of many observers the severity of the local lesions is of the greatest significance, as having a more or less direct relation to the amount of locoecia absorbed, and the degree of paralysis to be afterwards produced. It is a most fortunate circumstance that the presence of the Diphteria Bacillus in the human body is manifested locally by the production of a necrotic or necrotizing inflammation, a condition no treatment, as to which one to begin treatment at the very outset of the disease, either simultaneity with or shortly after the entrance of the locoecia into the system. If this was a point of importance in the best treatise hitherto pursued, it will I think, that the action of Antitoxin is understood, be fully recognized as of new greater value now.
Note of a Chol.

The question how arises. In that way does the Cares and serum or Antitoxin act. Then injected into the tissues of persons or animals suffering from Puerperal fever.

It was at first generally held that it acted in virtue of its bactericidal properties, but recent work in this direction has proved such an assumption to be practically groundless. For it has been shown experimentally that no such effect is produced by Antitoxin on the Bacilli, although it is admitted that it arrests the spread of the local inflammation if administered early enough.

From this one might assume that it acts either by the neutralizing of toxins, as it's name implies. This view is now well supported by Tabers, although no certain knowledge is possessed, as to the actual process by which such a neutralizing is brought about. In Replacment of the there are two main theories.

I. The Chemocid or Direct Theory.
(2) The Vital or Ferment Theory

The Chemical Theory is based on the assumption that Autotoxin as soon as injected, neutralizes the poisons in the system, rendering them inert. The action of certain well known therapeutic agents, their act similarly on one another undoubtedly supports such a view. But it must appear, that such a simple theory, hardly explains the action of Autotoxin, for it would necessarily follow there were such the case, that equal quantities of Autotoxin and Toxemis injected simultaneously would produce no effect. A suppression theory is briefly disproved by the experiments of Bouchet and Rome on animals, in which the susceptibility was artificially increased.

On behalf of the Vital or Ferment Theory, numerous and most earnest arguments have been brought forward.

The supporters of this theory claim that Autotoxin acts through the cells of the body. In order to understand how it does so, it will be almost to consider the action of those cells towards...
The toxin of Diptheria.

It must be remembered that the essential factor in preventing the growth and multiplication of the Diptheria Bacillus is the immuno-reactive action of the antibodies in the lymph and blood. Should these bodies be absent or present only in small quantity in the system, the tissues are unable to resist the attack of the bacilli; in other words, they are susceptible. The toxin then is free to produce their specific symptoms, in virtue of their action on the various cells or tissues of the body. Should recovery take place, it will be found that there is a true, immunocompetency to a further attack, a condition of affairs which is probably consequent upon some profound change that has been produced in them, by the action of the antibodies. The result of this change being, it is maintained, that these cells which were previously so easily sensitive to the action of these toxins, are now no longer so influenced by them. This it is supposed, is brought about by these cells having shown into the circulation some protective agent or antibody which counteracts the action of the bacilli and their products, thus rendering them harmless.
On this theory the action of Antitoxin is explained by supposing that it stimulates the cells to produce more of these aleurines, and so a kind of temporary and artificial immunity is conferred.

A more reasonable theory, I think, is the idea that the beneficial effects produced by Antitoxin serum, as due to the presence in it of aleurines.

Clinical Effects:

Henry traced the gradual development of serum—
Hereinbefore and expounded the theories as to the nature of Antitoxin, and its mode of action. I propose now to consider the clinical effects of the drug beneficial or otherwise when injected into the bodies of patients suffering from Diptheria.

For this purpose I shall take all the cases of Diptheria which were admitted into this hospital (the South Western Fever Hospital, London), during the year 1895. A large number of which were under my own immediate care and observation. For purposes of comparison, I shall narrate the Diptheria Cases of 1894, with the exception of those admitted during December of that year, that being the month when the use of Antitoxic serum was commenced.

I shall first of all discuss the good effects of Antitoxin, and then those which seem to be of a harmful nature.

Beneficial Effects.

Amongst the good effects, the most striking feature to the doctor in the morbidity of the disease. In 1894, 546 patients were admitted suffering from Diptheria. Of these 156 died, a mortality of 28.5%.

During 1895, 467 cases were admitted, 316 of
such were comedians severe enough to experi-
the rate of autotomic, of near 200 cases, 99
died, a mortality of 21% being at least 7.
4% lower than that of 1894, in which the
death rate then was below that of any
year previously recorded.
This fact one may safely attribute 6 to
the rate of autotomic, as the treatment during
the two years was otherwise identical.
Good as this result is, it is really tell
than the figures would seem to show.
For, in the first place, the reduction is
that marked with there it was most
needed and also most difficult to
obtain. viz., in cases under 5 years of
age.
During 1894, 1897 children of this age were ad-
mitted, of these 96 died, a mortality of 50
under 51%.
Whilst last year 182 children, under the age
of five were admitted, of these 60 died, a
mortality of five under 33%.
It is here therefore a difference in favor of
autotomic, of no less than 18%.
In the second place, all Diphtheria Cases admitted during 1895 were entrusted to a bacteriological examination at the hands of Dr. Louis Morehead. This necessary meant that the number of Cases, though certified as Diphtheria, would be largely increased. In 1894 when the clinical diagnosis was not subject to bacteriological control, the number of such Cases, mainly Tomelius's, was 8. Last year the number recoiled to 80. This necessarily meant that many Cases of mild throat affection which had in previous years diluted the statistics, and lowered the mortality, were struck out of the Diphtheria returns. This strongly tended to make more difficult for Autitoxin to produce a diminution in the mortality.

Thirdly, there was a certaininite of Cases which were clinically Diphtheria but in which repeated bacteriological examination failed to demonstrate the presence of the specific bacillus. Here in the interests of Autitoxin might have been omitted, so the death rate in this group was high, much higher than that of the general Diphtheria mortality. But as they were clinically Diphtheria of that disease, it seemed the right thing to
inclusion. In attempting to appreciate at its proper value, the action of Antitoxin in reducing the mortality, it is well to remember to take into consideration a most important factor, viz., the date at which the patient came under treatment. For it has been emphatically stated by certain leading German authorities that little can be hoped from Antitoxin, if injected later than the third day, of the disease.

Of the 99 deaths thus occurred during the Antitoxic year of 1895, no less than 78 came in or on or after the third day of disease. That is to say, too late for Antitoxin to have much chance of success was especially if the case is a severe one. Mild cases, of course, do not require this treatment. This point lends emphasis in view of the attitudes assumed by the opponents of Antitoxin. They ask, "How is it that there are still so many deaths, if this be such a wonderful remedy, as thought to one was to die of diphtheria, even being injected with antitoxin." Clearly it is hopeless to expect Antitoxin to save life in those cases which come under treatment at a later date.
The toxins of the disease here had time to act and do severe damage. Structural changes in the system which ultimately led the illness to a fatal termination. One might well as well say that no case of poisoning by a drug, for there is no such doctor, ought to be treated.

It is too good a practice to administer an antidote to one who is already moribund. To give Diphtheria, too often the poison has infected a fatal wound on the Constitution of the Child, before the Antitoxin has a chance. Indeed, could there be a certainty of bringing all cases of Diphtheria under treatment on the first day of disease, there would still be a mortality. For in some instances the poison seems to be so virulent that there would be nothing the patient's system death alone can put an end to its sufferings.

Besides this, one can say that quantity of poison is already circulatie in the tissues of the patient or that harm may not have done by the time the first symptoms of the illness show themselves. It is only fair to acknowledge that these facts should be taken into consideration in formulating its value, as a life-saving remedy in the
treatment of Diptheria.

Faucial Cases.

When treating faucial diptheria, we have the great advantage of being able to see the local lesion and therefore of obviating the effects of anthrax when upon it.

If the drug has the power of inhibiting the activity of the bacilli, it should in a very short time check the formation of membrane. Similarly, it should cut short the inflammatory process in the parts about the back of the throat.

Clinical experience shows that the timely administration of anthrax in faucial cases is followed by beneficial results in both these directions. The inflammatory nature of the local process is cut short, and this is so in cases which are severe as well as those which are mild.

The most striking effect produced is the limitation of the membrane. The spreading margin of that becomes abrupt and sharply demarcated from the surrounding mucous surface.
In practically all cases, there is but slight detumescence after injection, although there may appear a thin film of sero-dermatitis round the margins which is partly due to the tissues being still invaded and the bleak edges are not yet rendered harmless producing some slight irritation at that point. This however rapidly disappears.

Moreover the membrane itself is changed in appearance. Whereas it was more or less polished looking tipsy it is now roughened or granulated on the surface, from superficial disintegration, a process that gradually spreads through its thickness and ultimately leaves the underlying mucous surface bare. This separation of the membrane takes place much more rapidly than was formerly the case. In 1894 the average duration of membrane, from the commencement of treatment was 4·6 days, but in 1895 it was only 2·8 days, a reduction of 1·8 days.

The importance of this will be for reasons stated on a previous page, only too apparent.

Another important effect of Antitoxin is to diminish the farcical excoriation and discharge which in former cases are often present to such a degree as to
Make examination of the throat practically impossible as well as cause great difficulty in swallowing. But after Antitoxin the rapidly outside. The pain and distress they produce gradually disappear, thus adding materially to the general comfort of the patient.

In addition to this, the tenderness and swelling of the glands at the angle of the jaw is characteristic of all bad cases, likewise as rapidly diminishes.

**Nasal Cases.**

As a rule, in all acute febrile attacks the inflammation spreads to the nose, setting up there a prolific and irritating alkaline discharge. If this is any one symptom which adds to the distress of the patient more than another, it is the Rhinorrhea, not only does it cause reddness and congestion of the skin round the anterior nares, but there occurs in such quantity as to block up the nasal passages. Hence great difficulty is experienced in breathing, which takes place through the swollen and inflamed throat. The effect of Antitoxin in such cases is most startling, and shows itself within a few hours of its administration. The
inflammation is checked. The rhinorrhea rapidly ceases, with the result that within 48 hours the condition of the patient is changed from one of intense discomfort and unrest to one of comparative ease. The gain this is to the patient must be very considerable.

Should incontinence be present in the nasal passages, as well, it undergoes disintegration and removal similar to that occurs in that of the fauces.

**Laryngeal Cases.**

A very severe test of Autistocin is its effect in patients suffering from laryngeal aspirations. The great desideratum in these cases is:

1. To obtain the necessity for tracheotomy.
2. Should this operation be performed, to increase the number of recoveries.

Now this is to point that Autistocin does not only does it lessen the proportion of laryngeal cases that come to tracheotomy, but it also increases the number of recoveries from this operation, as the following figures show. In 1895 the proporion of laryngeal cases requiring tracheotomy was 80% whereas in 1896 it was no less than 68.1%.
difference of over 20% in favour of antibiotics.
In 1893 the mortality of tracheotomy cases was
52.0%, whereas in 1894 it was 76.5%, a differ-
ence of over 24% in favour of antibiotics also.
This favourable result in the former cases of
Cases is probably largely due to a CAST down-
of the laryngeal cartilages, and also to that other
occurs in the Case of the Nose and Throat.
But obscured a recurrence he actually present it is
times more difficult to ward off the necessity
for operation.
The increase in the number of the recoveries after
tracheotomy is probably due to the more rapid
recovery of the membrane and hence a diminished
risk of it extending downwards into the trachea
and bronchi. Another fact that is how consist-
in the recovery of such cases is a Considerable
shortening of the period during which the larynx
has to remain in the trachea. In 1893 the
average number of days, during which the larynx
was born was 6.2 whereas in 1895 it was
reduced to 3.1 days so nearly the half.
For this reason there will be less likelihood
of an unhealthy respiratory condition of the wound.
and hence less tendency to Broucho pneumonia. A much higher mortality necessarily occurs in cases which have largegul symptoms, than in those which have not. This relation holds good in the Autocruc year of 1893, but the disparity between the death rate in the two sets of cases is greatly diminished, as is shown by the following figures.

In 1892 the mortality amongst largegul cases was 52.1% as opposed to that of 26.1% in small cases. Whereas in 1893 the mortality of largegul cases was 26.2%, which is far below the rate of small cases of 26.3%. These figures are most instructive and show that underin the general condition in which the general mortality is far above as to a Considerate extent by diminishing the death rate in largegul cases.

Effect on Temperature.

Most continental observers maintain that the ad

ministration of Autocruc is followed by a more

or less sudden fall of temperature.

It is believed difficult to say whether this is so
or not, the frequency of delirium being very variable, and not always present, even in severe attacks. No doubt there is a fall of temperature after the injection, but it is questionable whether this takes place more rapidly or early than in pre-antitoxin case.

In comparing a series of cases in 1874 and 1875, I find that the average length of time before the temperature takes to fall is almost identical in both. It appears however that there is less often a secondary rise after it has reached normal, with antitoxin, than without. This is probably due to the fact that short of the local inflammatory process, rather than any direct action on the temperature itself.

Some observers believe that there is a temporary rise of temperature immediately after the injection. This is certainly contrary to my experience.

**Effect on Pulse.**

No direct effect on the pulse can I think be attributed to antitoxin. Some observers however claim that there is an improvement both
as to its tension and frequency. But this is probably due to the fall in the temperature it seems to occur coincidently with it, in both toxin + non-toxin cases alike. This effect therefore is an indirect one, unless one can assume that the injection of a quantity of serum into the circulation acts mechanically in raising the blood pressure and so stimulating the heart's action.

The next point to be considered is the influence of antitoxin upon the complications of diphtheria. Ought we to reflect a diminution in the frequency of their appearance?

Paralysis of various kinds. There are known to be experimental evidence are the result of a nerve degeneration which is produced by the toxin of the disease. This degeneration P. Meyer has shown to be in existence as early as the 3rd day of illness. The exact date of its commencement must clearly vary with the severity of the case. Now antitoxin can only diminish the number of paralyses by inhibiting the action of the toxin.
before they have had time to inflict any damage upon the nervous system.

no one pretends or believes that it possesses
the power of effecting a regular and so preventing
the occurrence of symptoms. Then once again we
have considered. Of the Cases treated by Anti-
toxin in 1895, in less than 66% came in on,
or after the 14th day of illness. As their Case
were all of a more or less severe type, we
may fairly assume that by that time the toxin
had initiated degenerative Changes in the nervous
system. From these it follows that Antitoxin
had but a poor chance of diminishing the
percentage incidence of paralysis in 1895.

Albunemia, There is at present considerable
doubt as to the exact pathology of this compli-
ation. That it is but very seldom due to a
true leukocytosis I am quite convinced, by
experience, both in the hands of the first worker,
room enough justify this statement.
In the former I have very rarely seen a Case
of diphteria presenting any of the clinical
features of Bright's disease, with the exception
of albuminuria; in the latter, there were nothing
more than slight microscopic changes in the
kidney structure. It seems to me that the simple
declaration of albuminuria in dipstick, so,
if we regard it as a functional disturbance of
the kidneys, caused by the passage through the
organ of the bodies, since in process of elimina-
tion. If this be the case it can hardly be
that anthracin to diminish albuminuria, since
this must be in every case, bodies in the
system, which can be got rid of and which
may therefore give rise to the presence of albumi-
na in the urine.

repirents. It necessarily follows from what I
have just said that if the bodies of hepatitis
do produce repirents, the serum treatment can
be no specific influence in preventing it.

Harmful Effects
Eruptions.
One of the most interesting features connected with
anthracin is the occurrence of certain skin
Eruptions which appear at more or less definite intervals after it is injected.

These rashes are of various forms, sometimes heretical or purple looking at other times resembling a measles or scarlet fever eruption. The two forms are about the same common.

Of the total number of cases treated with autogenous last year, rashes appeared in 54.7%. As a rule, they were observed about the 7th or 8th day after the first injection of serum. It being very exceptional for them to appear earlier. In many cases however, they were present at late dates, up to the end of the 3rd week. A peculiarity of these rashes was, that they made in a considerable number of cases in the area of skin immediately surrounding the spot of injection, from which they spread over the body generally. In some cases the eruption was patchy in its distribution.

Almost invariably the first eruption to appear was an eczema. This persisted for about 48 hours and as a rule was unaccompanied by any temperature. After an interval of 2 to 3 days it was succeeded by another rash which lasted
for as long as 4 or 5 days and in a majority of cases was accompanied by fever and some general constitutional disturbance. This second eruption was of the nature of a Peculiar erythema.

The varicella and morbilliform eruptions were relatively brief and were usually temporary. They were not so invariably followed by a second eruption as in the case of the virchowian. There was usually a good deal of itching during the presence of the eruption, more especially in the case of the virchowian which caused considerable annoyance to the patient. This rapidly disappeared as the rash faded.

Rinderpest desquamation frequently followed the virchowian.

In no case have I seen any serious symptoms accompanying morbilliform eruptions.

I ought also to state that these complications of antitoxin are much less frequent now than they were in 1895. Moreover there is usually only one eruption most often of a virchowian type appearing about a week after inoculation. This
improvement is almost certainly due to the better quality of the serum.

Arthritis.

This is a small percentage of cases was coincident with the appearance of the first of the two symptoms just mentioned. In rare cases it occurred as late as the 14th week. The hips or spine were the joints most commonly affected, there being considerable pain but only slight effusion.

This complication was present in 7.6% of the cases, and was one only in the joint affected generally. In this case the temporal, brachial, and some of the vertebral joints were implicated, the latter being aggravated by the patient Catharina Chile. The onset of arthritis was usually sudden or by a rapid rise in temperature to 102° or 103° 7. With pain heat and some slight fulness of the affected joints. This state of affairs lasted about 48 hours. By this time the temperature began to fall and the pain to diminish. By the 4th day the temperature was normal and the joints had assumed their ordinary appearance.
The condition readily yielded in all cases to treatment, and in no case has I seen it followed by any permanent injury to the joints.

Abscess at Seat of Injection.

This is the complication of which we are told, that much has been laid by the opponents of this method of treatment.

It is certainly a most regrettable result, and the fact that we have striven to prevent by every means in our power.

The back of each patient is always prepared for injection by a thorough cleansing with soap and water, followed by the application of an antiseptic compress. The eponge is carefully sterilized by boiling each time it is used. Notwithstanding this precaution 6 or 7% of the patients treated with serum, developed these abscesses.

One reason for this high percentage, so I think, is as follows.

The serum made last year was sent out in bottles each containing 30 or 40. When opened it was sometimes found to be quite sterile. But on more than one occasion
Staphylococci were grown from the contents of a half-emptied bottle. Now a new phenomenon had occurred. When the bottle was 20 e. c. to 30 c. c. not very much avoid leaching from the half-emptied bottle, the contents if kept at one of the best day or kept at one or two days, did not furnish prevent the development of germs. Then once or twice been exposed to the air.

Another reason for the large number of abscesses at this hospital is that large doses were given and repeated frequently.

Thus if giving each patient more serum than was usually administered, the risk of abscess forming was increased.

In some cases the parts injected became inflamed almost immediately after the operation, thus showing a special susceptibility on the part of the individual.

Now that antitoxin is prepared in much more concentrated form, it is gratifying to add that abscesses are of much less frequent occurrence.
An increase in the number of complications.

The complications I am referring to are albuminuria and the various forms of paralysis, since these are by far the most frequent and important.

Of late, there has been a larger number recorded in 1896 than in 1894. This at first sight seems to be a decided point against antitoxin. Yet if we put them down to the direct action of the drug, we must admit that we have been injecting something more than antitoxin, or something very like the toxin of the disease. This hardly agrees with the diminished mortality.

The following points seem to me to afford a more satisfactory explanation:

1. A large number of severe cases have recovered. Those cured by antitoxin are naturally the very cases that we should expect to develop albuminuria and paralysis. Thanks to the various methods of treatment they have survived, and it is no fair test that the complications they almost necessarily accompanying death remains, if life short.
be put to the debit account of antitoxin.

(2) From careful observation,
the great interest which has been taken in the serum treatment of diphtheria, must have led to a more careful noting of the clinical symptoms of the disease.

Hence, many cases of slight albuminuria and paralysis were recorded which in previous years would not have been noted.

These two considerations, I think, in a great degree, account for the increase in the number of complications during 1893.

But on, however, these two complications, or even whether the increase in either or both can be logically put down to the use of antitoxin.

Paralysis.

If antitoxin ever leads to the production of renal degeneration, it shows in some cases, at any rate, produce this condition in the terminal fities of the body, and thus give rise to fatal complications, paralysis of the heart. This is the cause of death in the great majority.
If the fatal Cases of diptheria, so that if autotomus nerve affects the lungs it must raise instead of lowering the death rate, since the opposite is the Case, we may fairly assume that it is never responsible for the onset of Case failure.
If it were affects the lungs, it is probably partly hemorrhage in respect of degenerative change in this disease.

Albuminuria
If autotomus gives rise to Albuminuria in patients suffering from diptheria, it could also give rise to it. There injected into patients who are clinically but not bacteriologically susceptible of this disease. Such commer, so hot it is.
This is a strong argument against认为 the increased frequency of albuminuria to be charge of the serum treatment, unless we suppose that the kidneys of patients suffering from diptheria are in a peculiarly vulnerable condition, that autotomus is thereby enabled to take care with their proper working.
It may be that the injection of large quantities of serum albumen into the biceps, accounts for
its elimination in the urine. This would only
replace those cases of albuminuria that occurred
at the same time as, or shortly after, the in-
fection were given
rephritis.
I can already state that, in my opinion, Anti-
toxicin is in no way responsible for the occurrence
of nephritis. It is of such utter rarity in diptheria, that the number of cases in any
one year are too few for the purpose of drawing
conclusions.
Acure.
There are some who attribute the occurrence of the
condition to acetocain. To deny one of these
with the Clinical aspect of diptheria, this
statement is obviously unfair.
Acure has always been a recognized factor of the very severe forms of this disease.
It did not appear more frequently in '93 than
in '94.

Dosage
I feel that I ought to say a few words with regard
to the quantity of acetocain that was given to the cases
on which my conclusions are based.

At the commencement of last year comparatively
small doses were given, averaging about 20 c.c.
6 each patient.

After the first four months this amount was very
largely increased, a bad case having 20 c.c
every 6 hours for the first two days, and a similar
dose over a day afterwards until the facial
or neural symptoms began to subside. This change
was instituted in order to see whether, large quan-
tities of serum exerted a more markedly antitoxic
effect than small. The results were not suffi-
ciently striking to enable one to say that much
was the case.

At present we are administering very much smaller
doses, with very better results than those obtained
in 1906, but these we have a much stronger serum
now.

Last year 1000 Bechamp immunization units were
contained in 20 c.c. of serum, whereas now they
are 30 c.c. and mixture in 6 c.c.

The injections are always given under the skin of
the back. The operation being less painful here
than when performed on the chest or abdomen.
In conclusion I should like to mention briefly the arguments for and against Antitoxin.

In the first place, the evidence in its favour, has been furnished by experimental pathology is very strong.

To compare it, as so many have done with Koch's tuberculin treatment is unfortunate, since the two remedies bear really very little in common.

The good effects produced by Antitoxin at the Hospital in '96 were:

1. A reduction in mortality of 7.44%, as compared with the previous year.

2. A reduction of 2.6% in the number of croupous cases which needed tracheotomy.

3. A reduction of 24.53% in the mortality after tracheotomy.

4. A more rapid separation of membranes, and excretion of nasal discharges.

5. A prolongation of life in fatal cases.

These are surely very material advantages against them or her to put.

1. The frequent appearance of a rash causing a certain amount of irritation and constitutional disturbance.
(2) The occasional formation of an abscess at the root of injection.
(3) The presence of joint pain in a small pro.
portion of cases.

Can any unbiased observer say that these have
in conveniences, for they are nothing more, in any
way, than the effects obtained by the use of Antitoxin.
Are we to be deterred from earning life because
the remedy there is, or dare to employ Carri,
t and in the probable risk of some buphig stimul,
Rah, let no perseverre in the hope that im-
proved methods of preparation will give us a drug
that is devoid of these drawbacks. Even indeed,
look to a certain extent already the case. The com-
pliation directly due to Anthitoxin having been
very much less frequent during the last three
months than in '95, while the good effects are
more marked.

Thus, with increased knowledge of this disease,
a more powerful arm was to be used. The experi-
ence of the future, judging certain
that, although some must die, our strongest
and most reliable weapon in fighting again.
Ophthalmia vs Acute Conjunctivitis

May 6th 96