Intravenous Therapy in Severe Diphtheria.

by

R. Hardy.

April, 1939.
It is salutary to recall, when recording one's observations on a series of cases of Diphtheria, that it was first defined as a specific throat inflammation by Bretonneau, as long ago as 1828, and named by him Diphtherite. Fifty years and more passed before the causal organism was identified microscopically by Klebs, and in 1884, a year later, Loeffler succeeded in growing it on the solid medium known as Loeffler's serum, which is in habitual use today. He also was able to isolate the organism in pure culture — an important advance. Loeffler cultured virulent bacilli from the throat of one healthy child among twenty children examined. For by this time, the proof had been established of its pathogenicity to, and constant production of specific lesions when injected into animals. Loeffler remained guarded as to the relationship of his bacillus with the disease, although he had succeeded in obtaining Diphtheria toxin in 1887-1888, and had postulated that it was the disease-producing agent. However, on injecting the toxin into animals he had produced local lesions only and a general toxemia ending in death. He was unable to produce Diphtheria paralysis. This astiological uncertainty was finally settled in 1888 by Roux and Yersin, who injected a filtrate from a broth-culture of bacilli into guinea-pigs, and obtained paralysis of hindlegs, as well as local reaction. Thus, one of the chief clinical features of the disease as it occurred in humans, was reproduced in animals. Koch's third postulate was satisfied.

Behring may be said to be the originator of antitoxic serum therapy in Diphtheria. As a result of his researches, he declared in 1890 that the phenomenon of immunity was due to the presence of certain antitoxic substances in the blood which could neutralize toxin. He inoculated guinea-pigs with cultures of K.L.B. subcutaneously, followed by injection of certain amounts of Iodine Trichloride, for three days. Such animals remained well, while controls died in 24 hours. The crucial point was reached, when it was found that these animals exhibited greater powers of resistance to further injections of K.L.B. than controls. They had developed active immunity. He, further, immunized rabbits against Diphtheria, and used their blood with success in immunization and treatment of guinea-pigs. From these foundations, the modern structure of serum therapy in Diphtheria has been built.

The first child was treated with Diphtheria antitoxin in a Berlin Clinic in 1891 — on Christmas night, it is said — and by 1894 the practice was becoming universal.

Ehrlich, in 1897, placed the therapeutic use of D.A.T. on a quantitative basis, by his work on the standardisation of toxin and antitoxin.

In 1908, a memorable year in the history of Diphtheria, Schlick elaborated his well-known test of susceptibility.
When we consider that serum therapy is thus nearly 50 years established, we may well ask if anything remains to be said about it. About some aspects of the subject, I think there remains a good deal to be said. In D.A.T., we have one of the most powerful therapeutic agents known; no orthodox medical opinion, anywhere, denies its extreme value.

In pre-antitoxin days between 1888 and 1894, of 11,598 patients admitted to the M.A.B. Hospitals 30% died, whereas a modern Hospital aims at a case mortality of less than 3%. An interesting glimpse into pre-antitoxin days is given in a paper by K. Koch (1937) in which he has studied the records of 150 children, admitted to the University Children's Clinic at Graz during the period 1890 to 1894, suffering from Diphtheria. In that era, it appears that the active phase of the disease frequently lasted for weeks, whereas now it lasts for days. Laryngeal Diphtheria might develop in a child with purely faucial Diphtheria, which is practically unknown nowadays. In most cases of Laryngeal Diphtheria, there was a relentless progression of membrane into the bronchial tree. However, he makes the interesting observation that toxic Diphtheria, from which 4 children recovered without D.A.T., appeared to behave in much the same way as it does today.

Many factors have contributed undoubtedly, to the reduction in mortality and morbidity of Diphtheria, but to D.A.T. must go most of the credit. We may refine it, and concentrate it, and, in the future, make it in the chemical laboratory, but I am unable to foresee the day when we may give it up.

There still remains, however, considerable diversity with regard to what constitutes a rational dosage, the question of re-dosage, and method and route of administration, especially in the toxic type of Diphtheria, with which this paper is concerned. Even on these questions, there are signs that opinion is, at last, becoming nearly unanimous. It may be relevant, at this stage, to indicate what is the best modern opinion on these problems, and to consider the various schools of thought that have existed in recent years.

RATIONAL DOSAGE.

I intend to confine myself mainly to the upper limits of dosage, since we are not directly concerned with the other end of the scale.

The immediate reduction in case fatality after the introduction of D.A.T. was striking, and yet doses were used which would now be considered quite inadequate. Thus, Schick, early this century adopted the rule of giving 100-500 units of D.A.T., per Kilo of body-weight; which meant that the average child of 5 years received 2,000-10,000 units, depending on the severity of the disease.
Soon, certain clinicians, in an endeavour to reduce mortality further, began to administer higher and higher doses. But the subject was controversial in these days. In 1921, Park of America, suggested 10,000–20,000 units for the severest case, while in the same year, Lie of Copenhagen, advocated enormous doses; viz. 150,000–220,000 units for the severe case.

In 1922, a Ministry of Health Memorandum laid down what they considered to be the minimum therapeutic dose, namely 6,000 units: "it is never safe to rely on less than this" they declared, although it was nearly half what Park advocated for the severest case in 1921.

In 1928, Goodall (1928) stated that "anything higher than 30,000 units was wasted", while Banks (1928) in a series of cases of toxic Diphtheria, gave an initial dose of 70,000–200,000 units, the average total amount of serum given in his series being 102,000 units.

Grundy (1931) compared case-mortality with primary dose at 6 M.A.E. Hospitals, basing his figures on M.A.E. Hospitals Report 1928–29. He found that a relationship did exist, and came to the conclusion that the difference in mortality was probably due to difference in dosage employed; in fact, case-mortality was in inverse ratio to size of initial dose. Here are some of his figures:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Average Initial Dose</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>9,000 Units</td>
<td>7.81</td>
</tr>
<tr>
<td>B.</td>
<td>13,700 &quot;</td>
<td>3.34</td>
</tr>
<tr>
<td>C.</td>
<td>15,000 &quot;</td>
<td>5.43</td>
</tr>
<tr>
<td>D.</td>
<td>16,000 &quot;</td>
<td>4.90</td>
</tr>
<tr>
<td>E.</td>
<td>17,200 &quot;</td>
<td>2.87</td>
</tr>
<tr>
<td>F.</td>
<td>22,000 &quot;</td>
<td>2.66</td>
</tr>
</tbody>
</table>

At Hospital "F", the following dosage had been employed:

<table>
<thead>
<tr>
<th>Clinical type of Diphtheria</th>
<th>Primary Injection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1. Severe.</td>
<td>55,000 Units</td>
<td>145,000 Units</td>
</tr>
<tr>
<td>&quot; 2. Moderate.</td>
<td>25,500 &quot;</td>
<td>40,500 &quot;</td>
</tr>
<tr>
<td>&quot; 3. Mild.</td>
<td>14,500 &quot;</td>
<td>14,500 &quot;</td>
</tr>
</tbody>
</table>

That high initial and total amounts of D.A.T. are being used in severe cases, by clinicians everywhere, is seen from a survey of the recent literature:
<table>
<thead>
<tr>
<th>Name and Year</th>
<th>Initial dose of Antitoxin</th>
<th>Total Amount of Antitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacIntyre, 1926</td>
<td>70,000-100,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Woodcock, 1932</td>
<td>40,000-60,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Benn, 1932</td>
<td>60,000-150,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Banks, 1928</td>
<td>70,000-200,000 Units.</td>
<td>Average.</td>
</tr>
<tr>
<td>Joe, 1935</td>
<td>30,000-60,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Peters, 1935</td>
<td>50,000-120,000 Units.</td>
<td>Average.</td>
</tr>
<tr>
<td>Lyth, 1935</td>
<td>60,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Beggs &amp; Harries, 1935</td>
<td>Up to 180,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Harries, 1935</td>
<td>50-150,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Foisco, 1935</td>
<td>Up to 100,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Menton, 1935</td>
<td>Up to 100,000 Units.</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Carrier, 1936</td>
<td>100,000 Units.</td>
<td>100,000 Units.</td>
</tr>
<tr>
<td>L.C. C. Report, 1936</td>
<td>100,000 Units.</td>
<td>100,000 Units.</td>
</tr>
<tr>
<td>Peters, 1936</td>
<td>46,000 Units.</td>
<td>300,000 Units.</td>
</tr>
<tr>
<td>Bie, 1921</td>
<td>Up to 220,000 Units.</td>
<td>300,000 Units.</td>
</tr>
</tbody>
</table>

It will be seen that massive therapy is favoured: the highest initial dose in this country being 180,000 units, but Bie gives up to 300,000 units in certain cases. Peters, (1935), advocated a large initial dose, but in 1938 had lowered this figure to 46,000 units. Few, however, indicate the total amount of antitoxin they are accustomed to give: the emphasis is, all the time, on the size of the primary dose.

In 1935, a Departmental Committee of the London County Council, was formed to investigate the rational dosage of D.A.T. Their views must necessarily be accepted as being, perhaps, the best modern opinion on the subject, and authoritative to a degree not possible in the recommendations of any individual worker. However, their observations are intended to be a guidance rather than a rigid rule. A Committee contains various shades of opinion; their decisions are reached as a result of compromise and must satisfy as large a body of clinical opinion as possible. Again, one can afford to be dogmatic regarding the dosage of such a substance as Strychnine, especially the upper limits — but not about D.A.T. This Committee agreed that 100,000 units in a severe case of Diphtheria "need hardly ever be exceeded". But they added that cases will occur in which one's clinical judgement will force one to employ more than 100,000 units.

To illustrate the conservative attitude on the subject of dosage, one may draw attention to the work of Zischinsky (1936), who records his observations on 2 groups of children with Diphtheria.

(1) 836 cases where D.A.T. given according to Schick's rule.

(2) 648 cases received 10,000-120,000 units depending on severity.

In both groups case-mortality was the same and the suggestion is that high dosage is not necessary.
In the series with which I am dealing high initial and total dosage with D.A.T. has been employed, as can be seen from the following table:

<table>
<thead>
<tr>
<th></th>
<th>Average Initial Dose</th>
<th>Average Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>152,000 Units</td>
<td>311,000 Units</td>
</tr>
<tr>
<td>Survivals</td>
<td>120,000 &quot;</td>
<td>226,000 &quot;</td>
</tr>
</tbody>
</table>

The highest initial dose was 200,000 units.

The highest total dose was 506,000 units.

The average initial dose is, in fact, higher than that used generally as far as I have been able to discover from a study of the literature. As for the average total amount of serum given in any case, I am unable to compare this with the amounts used by other clinicians, since reference to this point is scanty in the literature. It is certainly much higher than the maximum agreed upon by the L.C.C. Committee. The greater part of the difference is accounted for by the fact that we practised re-injection. Serum was given on successive days up to the 3rd or 4th, thus accounting for the high total dose used in each case. But the initial dose is of the same order as that recommended by the Committee, viz. 100,000 units.

I am not competent to defend high dosage. It was the custom in our Hospital, and, indeed, is almost the universal custom. It is, in all cases, better to give too much than too little — everyone will agree with that. Perhaps the clinical severity of the prevailing type of Diphtheria in London during the period 1936-1938, was a factor: in addition we had many late cases to deal with.

Theoretically, only a small amount of D.A.T. is necessary to neutralize the circulating toxin at any given moment, but I think that it is sometimes forgotten that toxin is being continuously produced at the site of membrane. Until the membrane separates, that well of toxin continues to flow. Has the total amount of toxin produced by a diphtheritic membrane, in a case of severe diphtheria, ever been measured or calculated in terms of lethal doses? How then can one be dogmatic about the limits of antitoxin required. It must depend in the long run on one's clinical judgement.

It is believed that toxin loosely bound to the tissues may also be dissociated and then neutralized by antitoxin. This amount of toxin is also impossible to assess, and hence another cogent reason exists for having an excess of antitoxin available. Toxin firmly bound to the tissues, is not amenable to neutralization by antitoxin.

All things considered then, I think that the dosage of D.A.T. employed in this series of cases, while probably higher than that generally used,
can be amply justified.

ROUTE OF ADMINISTRATION.

There are four possible routes of giving D.A.T., viz. subcutaneous, intramuscular, intraperitoneal and intravenous.

Subcutaneous route is obsolete, on account of the slowness and uncertainty of absorption, and the low concentration that appears in the blood. The maximum concentration is reached in 3 days after injection.

Intramuscular injection is the method of choice in the mild and moderately severe early case. Absorption from it is 3-5 times more rapid than in the case of subcutaneous injection, but the maximum concentration reached in the blood is little higher than that obtainable by the latter route, although it is reached in 48 hours. It may be considered as being slightly more than 3-5 times more effective than subcutaneous injection.

Intraperitoneal therapy is, in my opinion, seldom called for. There is no doubt, however, as to its efficiency. Judged by rapidity of absorption and maximum concentration in the blood, it approximates to the intravenous route rather than to the intramuscular. Maximum concentration of antitoxin in the blood-stream, is reached in about 30 hours, and the level is considerably higher than that reached after subcutaneous or intramuscular injection. But on both issues - rapidity of absorption and level reached in the blood, - it falls much short of the intravenous route.

Clinicians, with few exceptions, agree that for the toxic case of Diphtheria, intravenous therapy is essential. One exception is that of the author of a current text-book of Infectious Diseases, who has declared that, in his experience, no toxic case of Diphtheria ever survived by reason of intravenous therapy that would not have survived if the serum had been given intramuscularly.

Grundy (1931) attempted to show that intravenous therapy was not necessary. He compared the case-mortality rate in Hospital "F", (M.A.B. Report 1928-1929), with that in Bank's series (1928), in which intravenous therapy was employed. Both were approximately similar - 2.6%. Therefore, he claimed that if the same protection is conferred by an early intramuscular injection as in case of Hospital "F", this would seem to be the more reasonable method.

By giving antitoxin intravenously we ensure that it enters the blood at once, or, at any rate, at the end of the period of time occupied by the injection. That is to say, that the maximum concentration in the blood is reached immediately. It is more effective also since this level in the blood is greater, for a given dose, than that
obtained by any other route. Platon (1923) and Platou and Stewart (1928), have dealt fully with the question of antitoxin units in the blood after injection by each of the four routes. Here is a copy of a graph of theirs, which illustrates the concentration reached in the blood after equal amounts of serum have been given by the four routes; it also shows the time factors involved.

There can be no doubt in comparing the relative merits of these routes of administration, about the theoretical superiority of the intravenous.

Toxic Diphtheria should be looked upon as a medical emergency equally worthy of being treated with a minimum loss of time as an acute appendicitis or perforation, in the realm of surgery. Every hour's delay modifies the prognosis as regards life and complications. There is great need, therefore, to choose a route of administering antitoxin whereby there is no delay in bringing it face to face with circulating toxin, and that directly bound to the tissue-cells. Such a route, in my opinion is the intravenous one, and in the series of cases here described, all have been given a large primary dose of antitoxin intravenously.

I have been impressed by the insistence on the part of nearly all those who have written on this subject, that in a proportion of cases, especially very young children, this method is impracticable or even impossible. I think the difficulties have been exaggerated. The very young infant rarely contracts severe Diphtheria. The youngest in our series was a baby 10 months old, who was given 100,000 units of antitoxin through a needle tied into the median basilic vein. Again, the child with toxic Diphtheria is seldom too restless; apathy is the rule. Veins may be collapsed, but it is yet possible to tie a needle or a cannula into a collapsed vein. I have never seen clotting take place inside vein or needle, even when the vein is dissected, and pulled upon as inevitably happens to some degree. These are some of the practical difficulties, but in our series, failure to give antitoxin intravenously either directly or after dissection of a vein was never experienced. The difficulties involved should, at least never deter one from making an attempt at intravenous medication.

It is for these reasons that I think intra-peritoneal injection will seldom be required. On the two occasions on which I have used this route for D.A.T., the children concerned were very young, and both had already had a vein dissected and serum given intravenously. It was necessary to re-inject in 24 hours, and the intra-peritoneal route was chosen, to obviate the need of a second dissection. There was no peritoneal reaction or other obvious harmful result.

The danger of fatal or alarming collapse is also said to limit the general application of this route. It is certainly true that the risk is greater when serum is given intravenously than by any other route, but the risk is exceedingly small. Fatal anaphylaxis, also, is very rare, and has been known to occur even with minute amounts of serum
ANTITOXIN UNITS IN BLOOD AFTER I.V., I.P., I.M., S.C., INJECTION OF EQUAL AMOUNTS OF D. A. T.
given subcutaneously. The L.C.C. Departmental Committee pointed out the extreme rarity of the occurrence of serious shock, and anaphylaxis, and declared that the risk should never deter one from giving the appropriate dose of serum, by whatever route the clinical condition of the patient demands. They indicate the precautions that are to be taken in allergic and sensitized individuals; and these precautions are necessary by whatever route the serum is given. Their advice, we have followed.

I shall discuss the subject of shock and serum phenomena following intravenous injection later in this paper, and describe one case that died while serum was being administered.

SINGLE OR DIVIDED DOSES, AND RE-DOSAGE.

The controversy about the first of these problems is not a new one. Park (1921), said that multiple doses were useless. Friedman (1922), thought that repetition of dosage was an important factor in the treatment of any case, and that re-injection was necessary occasionally, owing to the difficulty in judging the appropriate dose in advance.

The L.C.C. Committee (whom we continue to quote as being the best modern authority), recommend that, if clinical severity has been properly assessed in the first place, and the appropriate dose given by a suitable route, then the concentration of D.A.T. in the blood should be enough to continue having a beneficial action, until the active phase of the disease has passed. They are of opinion too, that a single dose is far more efficacious than the same amount divided. No one will, nowadays, deny the truth of this statement; no later dose can compensate for inadequacy of the first. They continue "if from the course of the disease, it is obvious that the first dose was insufficient, then the severity has not been properly assessed". But this is not always easy. We have all seen the case with tonsillar membrane and moderate toxæmia, get worse in 24 hours, in spite of a dose of antitoxin that would have been adequate in nine out of ten apparently similar cases. However, as the Committee advise, such a case must be re-assessed and a further injection given.

What the Committee make no pronouncement upon is the case, severe from the beginning, where antitoxin does not seem to touch the membrane, nor lessen the toxæmia. These cases were not infrequent in this series. No error was made in assessing their severity - they were obviously hypertoxic when first examined - and as much as 160,000 units of antitoxin were given intravenously. Yet toxæmia was slow to decrease, and membrane to separate. The Committee would have done well to indicate their opinion about re-injection in this type of case. We felt compelled to give more antitoxin on succeeding days, on occasions up to the 4th day. Intramuscular injection was usually the choice, but on two occasions the intravenous route was considered necessary a second time, and in two others, the intra-peritoneal.
It was our opinion, therefore, that in cases of severe Diphtheria, a single massive dose of antitoxin was necessary by the intravenous route; but in many cases (not only in those wrongly assessed in the first instance), re-dosage appeared to be necessary on the second or succeeding days.

"ANTITOXIN-RESISTANCE and MALIGNANT DIPHTHERIA.

I think these two subjects, while separate, should be discussed in the same paragraph.

By "antitoxin-resisting" cases, I mean cases of toxic Diphtheria in which antitoxin seems to be of little benefit, in contrast to cases of toxic Diphtheria which apparently react well to antitoxin at the time, and survive the initial toxæmic phase. Some of this last group die, it is true, as a result of late cardio-vascular failure or paralysis, as, of course, there are other factors involved, such as lateness in undergoing treatment. Many of the fatal cases could, however, be included in the "antitoxin-resisting" group. The reason for this apparent antitoxin-resistance is obscure. I am unable to believe that in our series, the reason was inadequate dosage of antitoxin. Is it due to the failure of ordinary antitoxin to act as a remedy against the "gravis" type of K.L.B., which is associated most frequently with fatal cases? The answer is again no. It is well known that many individual cases, and epidemics too, of "gravis" type respond well to ordinary antitoxin. Animal experiments have shown that it is able to protect animals equally against infection with "gravis" and "mitis" strains.

There is a theory, which has not, however, received much support, that some antitoxins have less "avidity" for toxin than others. While this, if it be proved, might account for some "antitoxin-resistance" I think that the solution of the problem may lie in the question of mixed infection, which is known to occur in certain cases of Diphtheria. Streptococci, pneumococci and other organisms are occasionally found actively associated with K.L.B. in toxic Diphtheria. They - especially the haemolytic streptococcus - sometimes act in symbiosis with K.L.B., and possibly increase the invasiveness of that organism or help the development of its toxin.

Antitoxin is of no avail against these associated organisms, which may, in themselves, decide a fatal termination, in some cases. It is perhaps, in auxiliary measures to overcome these mixed infections that future therapy in malignant Diphtheria lies.

In spite of intensive therapy, case-mortality in severe Diphtheria is still high and in some epidemics, has shown a tendency to rise higher still in recent times.

Since Anderson and his co-workers (1931) described gravis, intermediate and mitis types of the corymbacterium, and postulated that gravis types associated generally with the severest cases, other workers have accepted their findings with reserve.
Robinson and Marshall (1934) enquired into this problem and their findings were in substantial agreement with those of Anderson. They considered that the prevalence of types was changing, and that more gravis and intermediate types were seen in London than in previous years. Begg (1935) working in London, in a series of cases of toxic Diphtheria found that "gravis" and "intermediate" strains were present in 90% of the cases.

On the other hand, there is evidence that this relationship is not constant, and may not hold good permanently or for all geographical areas. For instance, Shapiro at Moscow Clinical Research Station in 1937 found that no close relationship existed between clinical severity and type of bacillus, although gravis occurred more often in fatal cases. He also gained the impression that the majority of cases showing no improvement after antitoxin yielded the mitis type. In London, however, it does seem that mitis causes a milder type of disease and that antitoxin is more effective against this type.

The problem is puzzling, and has not been settled by the isolation of the gravis type. It would appear that factors concerned with individual resistance, immunity, late or inadequate treatment, and mixed infection are still all-important in toxic Diphtheria rather than bacterial type.

OBJECTS OF THESIS.

1. To describe a technique of administering diluted D.A.T. to cases of toxic Diphtheria by means of a modified "intravenous drip".

2. To compare two series of such cases where,
   (a) diluent more than 200 ccs.
   (b) diluent less than 200 ccs.,
   with reference to immediate shock and to serum phenomena.

3. To establish what is optimum dilution of serum.

4. To record my general observations on 130 cases of toxic Diphtheria.

The cases were admitted to the South-Eastern Fever Hospital, London, during the period summer 1936, spring 1938, while I held the position of Assistant Medical Officer; slightly less than 10% of all Diphtheria admissions were in this category. All were verified by culturing K.L.B. from fauces, on admission, and were in addition, so obvious, clinically, as to exclude any possibility of error in diagnosis. In several cases cultures were submitted to typing, and gravis type was reported to be present; no virulence tests were done.

I was personally responsible for the admission and treatment of approximately half the series. With the exception of three cases, all, on admission, were so acutely ill that they were given as soon as possible a large dose of D.A.T. intravenously. The three exceptions were not obviously hypertoxic on admission; however, in 24 hours, the toxæmia had advanced, and the local lesion had spread, so that intravenous therapy was then considered advisable. They illustrate how
difficult it is to assess clinical severity correctly on every occasion.

As criteria of severity, many of the following signs were present in every case:

1. **Local Signs**:

   (a) Extensive pseudo-membrane in fauces or nasopharynx, or on palate; sometimes gelatinous, poorly defined membrane indicative of virulent, spreading infection.

   (b) Oedema and congestion of throat.

   (c) Excoriating, straw-coloured nasal discharge, sometimes epistaxis, or membrane seen through anterior nares.

   (d) Cervical Adenitis and periadenitis.

   (e) Diphtheritic foetor of breath.

2. **Systemic manifestations**:

   (a) Prostration and muscular limpness.

   (b) Pallor and tachycardia.

   (c) Lethargy, drowsiness, stupor, occasionally restlessness.

   (d) Petechial eruption on skin.

   (e) Albuminuria on admission, or within a few days.

All cases were not, however, of the same degree of severity, and I have attempted to classify them using the system of Bie.

Bie (1929), evolved two systems based on:

(i) anatomical extent of membrane,

(ii) an estimate of toxaeaemia.

These two were combined eventually to form a series of groups and sub-groups, into which all cases of Diphtheria might be put. Bie first made an estimate of general toxaeaemia, and each case was placed in one of three classes, A, B, and C, according to clinical severity.

**Class A.** Apathy slight; no albuminuria; tachycardia slight; adenitis and post-nasal catarrh generally slight; heart sounds normal; no foetor.

**Class B.** Muscular prostration; albuminuria considerable; and marked aches and pains on one or both sides. Heart sounds poor; much nasal discharge and foetor.

**Class C.** Is intermediate.

He then sub-divided each class into eight groups, according to extent of membrane. The first five of these groups, we are not concerned with, since all
the cases in our series fell into groups 6, 7, or 8, of severity.

GROUP 6: membrane on whole of tonsils, margins of uvula and soft palate.

GROUP 7: membrane on whole of tonsils, greater part of uvula and soft palate.

GROUP 8: membrane on whole of tonsils and uvula, extending forward on to hard palate as far as molar teeth and backwards on to post-pharyngeal wall.

The method of Bie has been generally adopted and found to serve as a reliable index of severity, in spite of the fact that it leaves out such factors as age of patient, day of disease and toxigenicity of organism, all of which ultimately affect prognosis. Also extent of membrane is not necessarily a guide to severity; some of the severest cases have only tonsillar membrane. The personal element too, in such a classification, is not eliminated, e.g. a case might be placed in B5 by one observer and in B4 by another.

However, on the whole, it serves its purpose.

In this series all cases were in Classes B or C, and in groups 6, 7, or 8.

The numbers in each category were as follows:

<table>
<thead>
<tr>
<th>Bie's Grouping</th>
<th>No. of Cases</th>
<th>% of Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>B 6</td>
<td>32</td>
<td>24.6%</td>
</tr>
<tr>
<td>B 7</td>
<td>15</td>
<td>11.5%</td>
</tr>
<tr>
<td>B 8</td>
<td>1</td>
<td>.8%</td>
</tr>
<tr>
<td>C 6</td>
<td>38</td>
<td>29.2%</td>
</tr>
<tr>
<td>C 7</td>
<td>27</td>
<td>20.8%</td>
</tr>
<tr>
<td>C 8</td>
<td>17</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

Total = 130

There were 48 cases in Class B; 82 in Class C of Bie's grouping. In order of frequency cases fell into C 6, then B 6 and C 7; the incidence in C 8 and B 7 are approximately equal. Only one case was placed in B 8, that of an adult with very extensive membrane in fauces, and yet toxaemia was only moderately severe.

The highest number of cases were in the categories B 6 and C 6, i.e. where anatomical extent of membrane was equal but a slight difference in toxaemia was observed.
Eight cases in the series presented a petechial eruption on the skin; 6 were in C 8; 2 in C 7; and all were fatal.

<table>
<thead>
<tr>
<th>Bie's Grouping.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivals.</td>
</tr>
<tr>
<td>Deaths ...</td>
</tr>
</tbody>
</table>

As one would have expected, all the deaths occurred in Class C, the all-important factor of toxaemia being greater in this Class.

In C6, there were 7 deaths out of 38 cases = 18.4% (mortality).
In C7, there were 8 deaths out of 27 cases = 28.8% (mortality).
In C8, there were 16 deaths out of 17 cases = 91.1% (mortality).

TECHNIQUE OF ADMINISTRATION OF D.A.T.

The direct injection of D.A.T. from a syringe is the customary method of intravenous therapy in Diphtheria. This method, while presenting few problems in adults, can be difficult, or even impracticable, in young children; and it is this group which will predominate in any series of cases of toxic Diphtheria, that we are likely to treat. The difficulties become greater when a large dose of D.A.T. is to be given, since this will entail detaching the syringe from the needle and re-charging the syringe once or oftener, while the size and weight of the syringe are in themselves hindrances.

D.A.T. as used in the L.C.C. Fever Hospital is concentrated and contains 40,000 units in a volume of 20 cc., so that in order to give 120,000 units of antitoxin the syringe will have to be re-charged once if a 40 cc syringe be used. In direct injection, there is also a great temptation to hurry, and this must be avoided, at all costs, if the risk of shock is to be avoided.

Thompson (1936) has described an ingenious method of giving D.A.T. intravenously, making use of a 100cc all glass syringe as a reservoir connected by L.R. tubing to a 1cc syringe whose function is merely to act as a needle holder. He claims that his method is successful, in that a slow rate of injection can be assured, no anxiety need be felt about the needle slipping out of the vein, and that alarming shock was never encountered. By this method he gives D.A.T. and also Glucose-saline, in amounts varying from 50 - 100 ccs.

His method would appear to have many of the disadvantages of the direct method, if it is necessary to inject more than 100 ccs.

The Departmental Committee of the L.C.C. state that serum should be warmed and injected slowly, and in suitable cases be diluted with saline or glucose-
saline in order to minimize reaction. They do not state what constitutes a suitable case, or what is the optimum dilution of serum. Our method has been evolved in an endeavour to put these recommendations into practice. It is a modified "intravenous drip" method and it has the merit of introducing fluid slowly under perfect control and at body-temperature.

**APPARATUS REQUIRED.**

Glass Reservoir graduated in ccs. and of capacity 500 cc. fitted with a cork through which passes a glass funnel. Reservoir can be suspended by a wire ring encircling neck.

6" by 4" I.R. Tubing fitted with an adjustable screw-clamp; tubing connects reservoir to a Laurie glass drip-bulb.

2' - 3' I.R. Tubing to connect drip-bulb to a spiral piece of pyrex glass tubing contained in a vacuum flask.

2' - 3' I.R. Tubing connecting glass spiral to a glass "insert".

6" I.R. Tubing connecting "insert" to a Marie's junction, which in turn connects to needle in vein.

20 ccs. Record Syringe with eccentric nozzle and intravenous needle with short bevel.

Enamelled iron stand 6' high with heavy base; upper part of stand is adjustable to various heights. Stand has hook for reservoir and ring for vacuum-flask.

Those parts of the apparatus which are to contain fluid are sterilized by boiling for 20 minutes. The operator having scrubbed up, dons a sterile gown and fits the apparatus together. The reservoir is hooked on to the stand at a height of 3' above bed. The Marie junction end of the apparatus is allowed to rest in the basin in which apparatus has been boiled, until it is required. It is convenient to have this basin placed on a side table within easy reach. The vacuum flask is previously filled with water at 130°F.

The reservoir is then filled with 5% glucose saline up to the 200 ccs mark, and all air bubbles are expelled from the rest of the apparatus by allowing the "drip" to flow for a few seconds. It is advisable to have the fluid in reservoir previously warmed on a water-bath at 130°F.

The patients arm is then extended and lightly held by an assistant at the wrist and above the elbow, a tourniquet having been applied.

With due aseptic precautions the needle, attached to the syringe, is thrust into one of the antecubital veins, some blood is allowed to flow from vein into syringe, and the tourniquet is released.

The drip is allowed to start flowing, and then the syringe is detached from the needle in the vein,
and the Marie junction is connected up to the needle.

When it is evident that fluid is entering the vein, the needle is strapped to the forearm with thin strips of adhesive plaster.

When everything is going satisfactorily the requisite amount of D.A.T. (and more glucose-saline if necessary) is added to the reservoir which is shaken gently to mix the fluids.

When the reservoir is empty, there still remains a quantity of fluid (approx. 30 cc.) in the I.R. tubing and various parts of the apparatus. It is necessary therefore, to allow the "drip" to flow until the fluid level is observed to reach the glass "insert" near the needle. The "drip" is then stopped by tightening the screw-clamp. Thus the patient gets the full amount of D.A.T.

When for any reason, it was found impossible to get into a vein directly, we dissected one of the antecubital veins and tied in a needle or cannula. On a few occasions the internal saphenous vein behind the internal malleous was dissected.

TECHNIQUE OF ADMINISTRATION BY DISSECTING VEIN.

A 3/4" longitudinal incision is made under local anaesthesia in the skin overlying an antecubital vein. If the vein is not prominent, then the tourniquet is applied, but is released when the skin incision is made.

By blunt dissection the vein is exposed and a piece of fine I.R. Tubing is passed through the space between the vein and the tissues beneath, and serves to make the vein present out of the small wound.

A fine catgut ligature is then tied round the distal ends of the vein presenting, and the ends left long. Another ligature is passed round the proximal end, but is not tied, the ends being clipped together by artery forceps.

The vein is now held up by the long ends of the first ligature and a transverse incision made in its wall by means of scissors, just proximal to distal ligature. The cannula is inserted and the proximal ligature is tied securely around the cannula in the vein. The distal ligature is tied around the body of the cannula and the ends of both ligatures are then cut short and the small piece of I.R. tubing removed.

Previously the cannula has been attached to the drip apparatus as follows:-

A 2" length of fine I.R. Catheter tubing is attached firmly to the Marie Junction and the other end is slipped over the end of the body of the cannula.

The drip is then commenced so that glucose-saline is already dripping from the nozzle of the cannula before it is slipped into the vein.

When the injection is finished the cannula is withdrawn from the vein and the proximal ligature is removed. The distal ligature is left on the vein to prevent bleeding. The skin wound is
closed by one horse-hair suture; iodine, a pad of gauze and bandage are applied to the arm.

The alternative to a cannula was to tie in an intravenous needle. Personally, I found that a cannula of ordinary tapering type was easier and more reliable and gave a water-tight joint, which was difficult for the needle to do.

In this gravity-flow method of injection, one of the problems is to ensure that the solution is being given at body-temperature. The precautions we used were:

1. Glucose-saline warmed on water bath at 130°F. before placing in reservoir.
3. Water in vacuum flask warmed to 130°F. before starting drip.
4. Water in flask changed every 20 minutes by siphoning off cooled water and adding warm water.

However, in spite of precautions some variation in temperature undoubtedly takes place; heat is lost from the fluid as it passes through the tubing and various parts of the apparatus. This heat loss is greater if the injection is a large one and occupies a corresponding longer period of time. Those who have much experience in blood-transfusions and "continuous drip" injections, say that it is sufficient to place a hot water bottle along the course of the vein in the upper arm. We think that it is very important not to overheat D.A.T., since if it becomes cloudy or tends to clot, its therapeutic value may be considerably lessened.

The important factor deciding whether direct "intravenous drip" injection is possible, is age of patient; the younger the patient, the more often will dissection of a vein have to be resorted to.

Other factors are skill and predilection on the part of the operator, for one or other method. I endeavoured myself to attempt the direct method first, in all cases, with the exception of infants. If that failed, - and often, the needle slipped out of the vein after the drip had commenced, - I dissected a vein and tied in a cannula.

I do not think that any patient suffered harm by having a vein dissected; the operation was quite painless and could give rise to little shock. In fact, it is much more painless than a large intramuscular injection.

In a few cases the wound did not heal by first intention. Septic infection of the arm never occurred in our series.

TIME TAKEN BY INTRAVENOUS INJECTION.

This depended on amount of fluid given and rate of flow. As will be seen in next part of paper, our cases were divided into two groups:

A. Where D.A.T. given with more than 200 cc. of fluid, and
B. where D.A.T. given with less than 200 cc of diluent.

In the first group the total amount of fluid given (including D.A.T.) was 250-500 cc., in the second the amount was 150-250 cc.

It has been calculated that a rate of flow of 40 drops a minute is equivalent to a flow of 600 cc in four hours. We adjusted the rate of flow to 50 or 60 drops a minute, and therefore the larger injection occupied on the average two hours, and the smaller injection one hour.

When a vein had to be dissected, generally ½ hour was occupied in making the dissection and closing the wound.

**ADVANTAGES OF METHOD.**

The great advantage over the straight injection from a syringe, is that the injection can be given as slowly as time or convenience permit, and it is agreed that the slower an intravenous injection of serum is given, the less reaction there is likely to be.

Another advantage is that large amounts of D.A.T. can be given, diluted if necessary. By the direct method this would entail frequent recharging of the syringe, in itself, a procedure likely to disturb the needle in the vein, and lead to failure.

That dilution of D.A.T. is beneficial is evident when one compares the incidence of severe shock under the older method. It has been my experience that it is the rule for considerable shock to occur when 40,000 units of antitoxin are given intravenously from a syringe, however slowly one gives the injection. How much more shock, then there would be if 120,000 or 160,000 units were given.

Another feature of the modified continuous drip method is that complete control over the injection is possible; it can be stopped and resumed at will, if the patient's condition warrants.

At various times I have added adrenalin, cortin, or coramine to the reservoir, according to the needs of the patient, thus obviating the need of several injections. Adrenalin is reputed to be dangerous owing to its effect on the heart, when given intravenously. When it is diluted in some hundreds of cc's. of fluid we have never seen any harmful results. Thus subsidiary medication by the intravenous route is easily possible when this method of injection is used.

These are a few of the practical advantages that we claim for this modified "drip" method of administering D.A.T.

In this series it was found possible to administer serum intravenously by one of the methods described, in all 130 cases, 132 drips were performed, and the following table shows number of injections at the various age groups:
No. of Injections (132).

<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>Direct Injection</th>
<th>Vein Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 years</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1-2 &quot;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2-3 &quot;</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3-4 &quot;</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>4-5 &quot;</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>5-6 &quot;</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>6-7 &quot;</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>7-8 &quot;</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>8-9 &quot;</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Over 10</td>
<td>66</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

From the Table it will be seen that:

52 injections were given by dissecting vein = 39.6%
80 " " without " " = 61.4%

Between 0-5 yrs. 20 out of 27 cases were dissected = 74.1%
5-10 " 27 " " 73 " " = 37.0%
Over 10 years 5 " " 32 " " = 16.3%

SERUM REACTIONS.

Concentrated D.A.T., prepared at the L.C.C. Antitoxin establishment (Belmont Laboratories) was used in the treatment of this series, except in 3 cases, where Lederle's concentrated antitoxin was used.

Since concentrated and refined sera began to be generally employed, the incidence of serum reactions has been reduced. Nevertheless, unpleasant reactions still occur, and would appear to be inevitable when a foreign serum is injected.

The worst reactions are seen in hypersensitive patients - those who have become so as a result of a previous injection, and those naturally hypersensitive, e.g. asthmatic and allergic subjects.

It is agreed that, apart from this hypersensitive state in certain individuals, the severest serum reactions are seen when a large dose is given intravenously.

The more common, but less severe, forms of serum sickness are manifested by rashes, urticarial most often, scarlatiniform and morbilliform less frequently; pyrexia, swelling of joints and lymph nodes, and albuminuria may occur.

In patients receiving serum for the first time an urticarial rash appearing in the 2nd week, after injection, is usually the only sign of serum sickness, occasionally accompanied by malaise, headache, pyrexia and a trace of albuminuria; the latter may be associated with slight oedema, which may only be demonstrable by an
increases in weight of the patient. This was a frequent sign of serum sickness in the earlier days of anti-toxin. This ordinary type of serum sickness is never fatal.

In patients who are the subjects of re-injection, serum phenomena are usually more severe, and the latent period is shortened to 2-6 days (accelerated reaction), or to hours or minutes (immediate reaction). Urticaria, headache and malaise, occur as before, and there may be in addition, vomiting, rigors and partial collapse.

Very rare and much more serious, is the other form of serum sickness— anaphylactic shock. It is apt to occur in horse-asthmatic and allergic subjects, and less often, in those who have become sensitized by a previous injection of horse-serum. There is collapse, dyspnoea, bronchospasm, oedema of face, throat or lungs, sometimes vomiting, diarrhoea, or cough. Signs ensue within a few minutes of injection, and in fatal cases, death may take place in 10 minutes or be prolonged.

Acute fatal anaphylaxis is said to occur in 1 in 100,000 cases. During the Great War, there were 60 cases of fatal shock in the British Army and Navy, out of several millions of injections. Eleven followed first injection and were presumably in allergic subjects; 49 were in men who had had a previous serum injection and were examples of true anaphylaxis. A third type of reaction is seen only when serum is given intravenously. It takes the form of immediate shock. The signs are pallor, poor pulse and collapse in varying degree, during or soon after, the injection.

Thermal reaction characterised by a rigor 1-2 hour after injection may also occur.

Rigors and immediate shock are not considered to be true serum reactions, since they may happen during injections of non-protein substances by the same route.

In our series collapse of some degree was seen in 49% of the series, during or shortly after the injection. I think it is due to a direct toxic effect of the foreign material injected into the blood.

Rigors were less common and were only observed in 8.5% of cases; they were often associated with a sharp rise of Temperature to 103-105°. Minor chills were fairly frequent. Rigors occurred in the 3 cases in which Lederle's serum was used.

The relationship between shock during I.V. injection of antitoxin, and serum sickness and anaphylaxis is doubtful. In some respects it resembles the "immediate" serum reaction, but it occurs in others, besides those who have been sensitized by a previous injection, and therefore, would appear to be distinct.

Anaphylaxis is the result of an antigen-antibody combination which has selective action on cells of unstripped muscle and capillary endothelium. This combination acts as a trauma to the cells, and histamine which is normally present in body-cells is liberated. There is considerable resemblance between histamine shock and anaphylaxis. Is it not possible that the relationship between shock during I.V. injection and anaphylaxis may be closer than one suspects? Histamine production may be the uniting link; in the first case histamine
formed by injury to cells as a result of the "foreignness" or toxicity of the injection, and in the second, histamine liberated as a result of antigen-antibody combination.

Rigors and pyrexial reactions are probably due to the foreign proteins in the serum injected. It is true that they may follow I.V. injection of non-protein substances such as glucose or arsenicals. But in these cases it is possible that bacteria, alive or killed, may have gained entrance into the solution and act as a foreign protein in the patient's circulation. It is well known that solutions prepared with tap-water that has been boiled are extremely likely to produce pyrexia and rigors on I.V. injection. The bacteria though killed by boiling, act as a foreign protein.

I have never seen rigors after I.V. injections of glucose-saline, when these solutions are made with sterilized water and stored in screw-capped bottles until required.

Rigors and immediate shock may be followed by exanthematous type of serum sickness, after the usual latent period.

Neurological complications of serum treatment are very rare. Allen (1931), reported that in 40 years of serum therapy, only 50 cases were known, and only 1 in this country. A radiculitis is the commonest form of nervous complication, involving upper roots of brachial plexus on one or both sides. The clinical signs are those of motor and sensory loss, confined to upper part of limb; pronounced muscular wasting is a feature.

Less rarely cortical irritation - twitchings, convulsive movements - ending in a fatal coma, are seen. In our series there were no neurological complications of serum sickness.

Other atypical accompaniments of serum sickness are known, orchitis, acute articular rheumatism, acute suprarenal insufficiency. Rashes may assume an unusual form - multiform erythema, circinate urticaria, which is usually a late rash, and recurrent rashes.

Prior to giving serum intravenously (or by any route) it is advisable to enquire regarding a history of asthmas, or of previous serum administration. We did this in every case; asthma was not a factor in this series. 19 patients had a history of previous serum, or a history of having been in hospital with measles, in which case passive immunization with D.A.T. or Sc.F. A.T. was presumed. This figure is probably not accurate as histories of previous illness and serum administration could not be relied upon; in measles cases we had to rely upon circumstantial evidence in regard to previous serum.

All cases in our series were given 2,000 units of antitoxin on admission. A few minims were injected intradermally, and subcutaneously, and the needle was pushed on into muscle and the remainder given intramuscularly.

If a patient had a Positive skin test, he was given 64,000 units intramuscularly in one hour, and the intravenous injection was proceeded with in 2 hours. If the
A skin test was Negative in 1 hour, the intravenous injection was begun as soon as possible thereafter.

We considered that any more elaborate method of testing sensitivity and of desensitization was unnecessary. Skin sensitivity does not always mean general sensitivity. On the contrary, serious reactions can occur, following subsequent therapeutic injection when the skin test has been Negative. Desensitization, too, cannot be relied upon, and some go so far as to say that complete desensitization is impossible. It is imperative, however, to attempt to do this in the case of a known allergic subject.

Table showing examples of reactions in sensitized individuals:

<table>
<thead>
<tr>
<th>CASE</th>
<th>Reactions to Injections in Sensitized Patients.</th>
<th>Later Serum Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1435</td>
<td>Neg.</td>
<td>-</td>
</tr>
<tr>
<td>2167</td>
<td>Neg.</td>
<td>-</td>
</tr>
<tr>
<td>2578</td>
<td>Pos.</td>
<td>No reaction.</td>
</tr>
<tr>
<td>2354</td>
<td>Neg.</td>
<td>-</td>
</tr>
</tbody>
</table>

It will be seen that in sensitized individuals:

1. Intradermal injection gave Negative skin test in some cases.
2. Intramuscular injection usually Negative.
3. Intravenous injection gave rise to immediate serum reactions in some cases.
4. Later serum reactions usually accelerated.
5. No later serum phenomena in 2 cases that died.

**Analysis of Serum Phenomena.**

71 cases showed evidence of serum reaction = 55%
59 " no " " " = 45%

69 cases showed urticarial type of serum reaction,
 of which
64 cases showed general urticaria after usual latent period.
2 cases showed local urticaria only after usual latent period.
3 cases showed serum rash during I.V.
 injection only.

2 cases showed albuminuria during period of potential
 serum sickness, and no other signs.

Table showing day on which rash appeared:-

<table>
<thead>
<tr>
<th>Days after Injection</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>Over</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>12</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>13</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

It will be seen that serum rashes occurred most often in our series on the 8th day. This is earlier than usual but may be accounted for by the massive dosage employed. In 12 cases urticaria was seen during injection of serum; excluding these, the average day on which a rash appeared 8.3 days.

No. of cases showing immediate serum reaction = 12
No. of cases showing accelerated serum reaction = 19
No. of cases showing I and A serum reaction = 5
No. of cases showing I and Late serum reaction = 4
No. of cases showing Immediate and no other serum reaction = 3

Recurrent serum rashes occurred 1.4 times. 9 had rash during injection, followed by rash after latent period. 4 had rash after usual latent period, followed by recurrence of rash in about a week. 1 case showed an urticarial rash on 4 separate occasions, viz. during injection, 6th, 9th and 30th days.

**Serum Disease in 31 Fatal Cases.**

23 showed no serum sickness at any period.

1 case only, had a local rash during injection and an evanescent rash on 10th day - 2 days before death.

7 cases exhibited varying combinations of oedema of face, tongue or larynx during administration.
I think it is remarkable that only 3% of fatal cases showed a serum rash either at once or after a latent period, whereas 70% of survivals had a serum rash at some period.

This absence of rashes may be accounted for partly by the fact that 11 patients died during first week when serum rashes not likely. Some of these, however, might have been expected to produce an accelerated rash.

Is it because fatal cases have such an overwhelming toxaemia that the cellular mechanism of producing urticaria is put out of action? Or due to failure of peripheral cardio-vascular system, and comparable to the poorly developed rashes of malignant exanthematous infections?

Some writers mention the "cachectic" rash, but I have seen nothing in the literature regarding this infrequency of serum phenomena in fatal Diphtheria.

**OCCURRENCE OF OEDEMA DURING INJECTION.**

31 cases showed oedema during I.V. injection and it happened equally in fatal cases and survivals.

- Oedema of tongue occurred 20 times.
- Oedema of face occurred - 16 times.
- Oedema of larynx occurred 7 times.
- Oedema of neck occurred - 3 times.

Usually some combination of above was observed, e.g. oedema of tongue and face.

Is this oedema to be considered a serum reaction? If it is, then it should have been present only in the 19 cases that were sensitized by previous serum injection. The 12 cases showing immediate serum reaction in the form of urticaria, were all in this sensitized group. However, oedema occurred indiscriminately whether the patient was previously sensitized or not. Thus, 24% of all cases in the series had oedema during I.V. injection, whereas only 15% of all cases had been sensitized.

Against it being a serum phenomena, too, is the fact that in 4 cases only, rash and oedema occurred together; the other 8 cases that exhibited a rash during I.V. injection had no oedema.

Adrenalin had a beneficial effect on the various forms of oedema, and this certainly indicates that it is due to an allergic response.

If oedema, as it occurred in our series, can be looked upon as a true serum phenomena, then the mechanism must be distinct from that of the "Immediate reaction".

The incidence of oedema was slightly greater when D.A.T. was diluted with the smaller amount of diluent: 19.6% of cases treated with large volume of diluent, showed oedema of tongue, face or larynx, or combinations of these; the incidence in the other group was 26%. Thus it seems that oedema was unrelated to the volume and saline content of the fluid injected, which we feared was the case at one period.
It is probable that this is an allergic phenomena in individuals who are naturally sensitive to horse-serum.

**OTHER MANIFESTATIONS OF SERUM SICKNESS.**

Joint pains occurred in 6 cases; most often in females. The signs were arthralgia, slight synovial swelling, & stiffness accompanied by general urticaria after the usual latent period. Joint pains were not seen in the accelerated type of reaction.

Vomiting was seen only in 4 cases and was associated with the more intense urticaria and general symptoms of the accelerated reaction.

**Albuninuria** is the rule in severe Diphtheria so that any resulting from serum disease is likely to be masked. However, in 2 cases there was albuninuria due probably to serum disease. The first had albuninuria and oedema of face from 11th - 26th days, the second had albuninuria from 11th - 14th days, i.e. both commenced having albumen during the period of potential serum sickness, whereas up to that time, the urine had been clear.

Oedema as a late serum phenomenon occurred on 3 occasions, and in each case the face was the only region affected. In 2 cases the oedema of face was probably due to confluent urticaria, since a heavy serum rash was present on the trunk and limbs. The other case had oedema of face and albuminuria from 11th - 26th days, with no accompanying rash.

Slight thermal reactions were common during the period of serum sickness, but no rigors occurred. Conjunctival injection was a frequent occurrence and in 2 cases was severe.

**SHOCK DURING I.V. INJECTION OF DILUTED D.A.T.**

<table>
<thead>
<tr>
<th>TYPE of REACTION</th>
<th>D.A.T. diluted with large volume - (&gt;200 cc.)</th>
<th>D.A.T. diluted with small volume - (&lt;200 cc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>%</td>
</tr>
<tr>
<td>Severe Shock</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Moderate &quot;</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Slight &quot;</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>No &quot;</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>Required Adrenalin ..</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>Required No Adrenalin .</td>
<td>20</td>
<td>36</td>
</tr>
</tbody>
</table>

It is evident from above Table that there are differences in incidence of shock during I.V. injection.
when -

(A) D.A.T. diluted with > 200 cc.
(B) D.A.T. diluted with < 200 cc.

In all cases an estimate of shock was made clinically during, and at the end of, administration and shock was classified as severe, moderate, slight or absent.

In group A, shock was less severe and less frequent than in group B. Thus in the first, shock of some degree occurred in 36% of cases, whereas in the second it was seen in 59% of cases.

I think we are entitled to compare the 2 groups in this respect, since as regards age-groups, day of disease, there was no essential difference between them. Group A contained 58% of class C of Die's classification, and group B, 67%; but I do not think that this accounts for the difference in shock between the 2 groups.

That the incidence and severity of shock is less in group A is corroborated by the number of times that injection of Adrenalin was necessary in the 2 groups, viz. in 6% of group A, 7% of group B.

Other manifestations during I.V. injection were noticed — rigors, restlessness, nausea, retching and vomiting, incontinence of bowels and bladder, drowsiness and subjective sensations such as throbbing in head, constriction of throat. In almost every respect group A was favoured. Thus vomiting occurred in 51% of group A and in 49% of group B, restlessness in 16% of A and 23% of B. The presumption is that dilution of D.A.T. with a comparatively large amount of fluid was the cause of the lessened incidence and severity of shock in group A. Another factor was that the injection in this group occupied a longer time than in group B.

I have already discussed oedema in various situations, arising through injection of serum.

Another interesting feature was a definite increase in adenopathy and nasal discharge in some cases, during the injection. This was observed in 8 patients in group B, and 2 in group A. Thus, (together with oedema, as we have seen), this phenomenon was more frequent when the diluent was less than 200 cc. Perhaps it is due to a local toxin-antitoxin reaction, or is merely another manifestation of allergic reaction.

A comparison between case-mortality in group A and group B.

Group A. — 8 deaths in 55 cases = 14.5% mortality.

Group B. — 23 deaths in 75 cases = 30.7% mortality.

The difference is striking but these rates are not comparable. They refer to patients admitted during different epidemics, and group B contained more very severe cases, as we have seen.
Table showing day on which death occurred after treatment in the 2 groups A. and B. :-

<table>
<thead>
<tr>
<th>Day of Death from onset of Treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 Over.</td>
</tr>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Group B</td>
</tr>
</tbody>
</table>

i.e. 4 out of 8 cases treated with large dilution died in 1st week .......................................................... = 50%

11 out of 23 cases treated with small dilution died in 1st week .......................................................... = 48%

2 out of 8 cases treated with large dilution died in 2nd week .......................................................... = 25%

10 out of 23 cases treated with small dilution died in 2nd week .......................................................... = 43.5%

2 out of 8 cases treated with large dilution died after 2nd week .......................................................... = 25%

2 out of 23 cases treated with small dilution died after 2nd week .......................................................... = 8.5%

The following inferences may be drawn :-

1. Approximately 50% of both groups died during 1st week, i.e. cases in both groups had equal chance of survival into 2nd week after treatment began.

2. That cases in group A. had a better chance of survival into the 3rd and later weeks.

3. That the greater shock which we have seen to occur in group B. did not have prejudicial effect on immediate mortality.

It is now time to consider what is the optimum dilution of D.A.T. when it is given I.V. and what is the best diluent.

**OPTIMUM DILUTION.**

I think this lies between the quantities used in our 2 Groups.

It is probable that when D.A.T. is well diluted there is less immediate shock and less risk of oedema and increased adenopathy. If this oedema occurs in the glottis it may be serious. On the other hand we have to consider the age and size of the patient. Thus 500 cc. injected I.V. into an adult is equivalent to 25 cc. in case of an infant. A 5 year old child has a blood volume of 1000-1500 cc. and an injection of 250 cc. will raise this temporarily by 20-25%. By using well diluted antitoxin we may overload a heart which is suffering in the general toxemia if it is not already failing. This danger may be present as early as the 3rd day, later, of course, the risk is greater.
These considerations lead us to adopt a compromise between the 2 methods, and I would suggest the following dilutions of antitoxin as being the optimum:

Under 5 years total injection should not exceed 100 cc.

5 - 10 years of age total injection should not exceed .......................... 150 cc.

10 - 15 years of age total injection should not exceed .......................... 200 cc.

Over 15 years of age total injection should not exceed .......................... 300 cc.

Allowing that 100,000 units B.A.T. = 50 cc.

The Best Diluent.

Coller (1936) has shown that, in case of continuous drip therapy in other conditions and diseases it is undesirable to give much saline, unless chloride is being lost in abundance by vomiting or sweating, on account of danger of producing oedema. Isotonic glucose solution (5%) is preferable as it does not tend to produce oedema.

In toxic Diphtheria, there must be no chloride lost in the early stages at least, and I think that 5% glucose solution is probably the best diluent for antitoxin. 5-10% glucose in saline as used in our series is hypertonic, and may have been a factor in producing the oedema which we have noticed to occur. Too massive injection of isotonic solutions may have the same effect.

If a hypertonic salt solution is injected into a vein, the osmotic pressure of the blood is raised, and the first effect is to attract fluid from the tissue spaces, and so further dilute the blood — a condition of hydramic plethora. This is transient, since the consequent rise in venous and capillary pressure soon increases the filtering processes in the capillaries, and tends to drive fluid out of the vessels into the tissue spaces.

The rise in osmotic pressure in the blood, too, is coincident with a rise in osmotic pressure in the cells. Since cell membranes are impermeable to Na ions, the osmotic pressure in the cells can only rise by water permeating from them. Thus the end result of giving hypertonic solution is increased fluid in the tissue spaces.

The immediate effect of injection of isotonic solutions into the blood, is to raise the blood volume. Appreciable elevations are maintained up to 2 hours after the injection. This results in a dilution of the plasma proteins, the osmotic pressure they exert is reduced, and therefore exudation occurs as the power of blood to retain fluid is lowered.

It can be argued that in both cases — hypertonic and large isotonic injections — there is a tendency to upset the delicate balance between extra and intracellular fluids with oedema as a result.

Glucose in Treatment.

On admission all patients received 5-10% glucose
saline along with D.A.T. intravenously.

Table showing amounts of Glucose-saline given and number of cases in each group:

<table>
<thead>
<tr>
<th>Volume of Glucose-saline.</th>
<th>No. of Cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 cc. and Over.</td>
<td>16</td>
</tr>
<tr>
<td>400 - 499 cc.</td>
<td>10</td>
</tr>
<tr>
<td>300 - 399 cc.</td>
<td>5</td>
</tr>
<tr>
<td>200 - 299 cc.</td>
<td>24</td>
</tr>
<tr>
<td>150 - 199 cc.</td>
<td>15</td>
</tr>
<tr>
<td>100 - 149 cc.</td>
<td>24</td>
</tr>
<tr>
<td>50 - 99 cc.</td>
<td>36</td>
</tr>
<tr>
<td>Total = 55</td>
<td></td>
</tr>
<tr>
<td>Total = 75</td>
<td></td>
</tr>
</tbody>
</table>

103 cases received Glucose-saline I.V. on admission only.
27 cases Glucose-saline was repeated once or oftener.
Highest number of Glucose-saline injections in 1 case = 7.
19 patients received 2 intravenous injections of glucose.
4 patients received 3 intravenous injections of glucose.
3 patients received 4 intravenous injections of glucose.
1 patient received 7 intravenous injections of glucose.

It was considered essential to administer Glucose intravenously at the onset of cardiac vomiting. Nausea, precordial or abdominal pain of cardiac origin were often the first indications for glucose therapy.

Insulin was given 35 times out of 172 injections of glucose, 1 unit for every 1-2 gm. Glucose.

RATIONALE OF Glucose THERAPY.

Schwandt and Noel (1929, 1930), were first to study carbohydrate metabolism in Diphtheria. Here is a summary of their conclusions:

1. Hyperglycemia is present in severe Diphtheria after 3rd day.
2. Progressive inability to assimilate glucose from blood.
3. Reduction in stored glycogen in heart-muscle, liver, etc., during toxaemia, leading to an increased vulnerability to toxins.
4. Prelethal hypoglycaemia in severe Diphtheria.
5. In view of above an effort should be made to stabilize carbohydrate metabolism by insulin and glucose.

E. C. Benn et al (1932) found that in Diphtheria the sugar tolerance curve after administration of glucose, was of the diabetic type. They considered that the initial B.S. curve was a valuable guide to prognosis, and that the greater the toxæmia, the greater lag in return of curve to normal. This lag type of B.S. curve lasted for a period of 3 weeks, on average from onset of illness.

They treated a series of cases with insulin and glucose as an adjuvant to D.I.T. and succeeded in reducing the case-mortality from 35.9% to 22.5%. They found that the effect of insulin was to give a B.S. curve approximating to the normal.

Begg and Harries (1935) treated an accurately controlled series with glucose and insulin. Their conclusions were:

1. Insulin and glucose therapy did not reduce mortality or incidence of paralysis.
2. Insulin had variable effect on B.S. curves, some improved, some no change, others got worse.
3. Altered carbohydrate metabolism is not a result of metabolic abnormality controllable by insulin.

Harries recalled the work of Esther Harding on the blood in Diphtheria. She found a polycythaemia and increased specific gravity of the blood. Harries suggested that the concentration of blood sugar runs parallel with this concentration of the blood.

Cross and Holmes (1937) as a result of their work on carbohydrate metabolism in livers of animals suffering from Diphtheria toxæmia, put forward the following theory:

Diphtheria toxæmia leads to an increase of those factors which tend to prevent deposition of glycogen in liver - increased Adrenalin may be one. Such a reaction leading to an increased amount of carbohydrate in the blood may be a defensive reaction. Toxæmia causes increased metabolism and more rapid oxidative processes in tissues. An increased carbohydrate supply in blood will presumably supply tissues with a readily oxidizable substance - glucose. If oxidative processes are ultrarapid then hypoglycaemia may result.

The metabolism of carbohydrate is a complex process depending on many factors; liver, anterior pituitary, thyroid, adrenals, insulin, all play their part. Diphtheria upsets the balance of these endocrine factors, and I think that an attempt to restore that balance by insulin alone, is not likely to meet with complete success.

Glucose has a protective effect on the vital organs. Cross and Holmes found that if concentration of glucose in the blood is kept high, the liver no longer fails to store glycogen. Here is one indication
for glucose therapy; surely. Glucose is also indicated when the toxaemia is severe enough to cause a hypoglycaemia. Both sets of workers indicate that this occurs at a certain stage of the toxaemia.

Peters (1930) suggested that Glucose had a de-toxicating effect. Glucose, it is claimed in high concentration overcomes colloid flocculation in the blood, which is believed to take place as the result of the action of Diphtheria toxin.

To these protective and de-toxicating actions of glucose must be added its specific effect on cardiac failure and vomiting. Other cardiac drugs are of little or no use.

In our series 10 - 40% glucose in saline was given I.V. at the onset of cardiac failure; or in anticipation of it, in the hypotonic cases. 42 such injections were given, of which half were more than 200 cc. in volume and half were less than 200 cc. Most of the injections were by the drip method already described. In a few cases 40 cc. x 50% glucose were given I.V. direct from a syringe.

It was our practice to give children under 10 years, less than 100 cc. I.V. in order not to overload the circulation, since the heart-muscle is already failing, and there is diminished urinary output at this stage. Large I.V. injections are of no avail and are actually dangerous when given late in the disease.

Insulin was only given if glycosuria was marked in the hours following the injection. We considered that it was safer to omit routine administration of insulin, since if it is uncontrolled by blood sugar estimations, it may lead to hypoglycaemia.

In several instances spontaneous glycosuria was seen, during the acute stage of the illness, apart from I.V. administration of glucose.

Account of a case that died during I.V. Injection

D.A.T.

Case No. 193, Male, 6½ years, no history of asthma or previous serum administration.
Admitted 17. 1.1937. Died same day; ill for 3 days.


2,000 units D.A.T. statim. No reaction.

6-7.30 p.m. Upper part of chest oedematous.
160,000 units D.A.T. + 350 cc. 5% glucose, intravenously; vein dissected.

Half way through "drip" became restless, blue and had a moderate degree of asphyxia: tongue swollen. Injection stopped. Adrenalin given.
In five minutes colour returned and breathing normal. Injection continued slowly for ½ hour, when there was sudden onset of acute asphyxia, and in a few minutes patient was cyanosed and in great distress with obstructed breathing. He was placed on Tracheotomy table which had been prepared ½ hour previously, and tracheotomy performed but with no relief. Patient died.

A post-mortem examination revealed severe faucial Diphtheria, but no involvement of larynx. There was marked glandular swelling and quantities of free fluid in tissue spaces of neck. Cause of death: Oedema of glottis and toxaemia due to malignant Diphtheria.

This case was remarkable for the degree of periglandular oedema. In fact all the soft tissues of the neck and upper part of chest were involved. I do not think that it was true anaphylaxis that caused death. But perhaps the large I.V. injection - 300 cc. had been given before death - tipped the scale, by causing an increase in the oedema which was then sufficient to obstruct the larynx.

From that time onwards we limited the amount of glucose saline injected to less than 200 cc. per patient.

In December 1937, a tracheotomy was performed on a patient 3 hours after I.V. serum and glucose saline, on account of progressively severe laryngeal obstruction, which had commenced during the injection. This patient, a very severe case of nasopharyngeal Diphtheria, had, however, aphonia and a croupy cough on admission, and obviously had laryngeal involvement. The tracheotomy was successful, but she died next day. I do not think this death could be attributed to serum.

Two other patients died on day of admission from cardiac failure, without rallying from the primary intravenous injection. They were late and hypertoxic cases, and serum was not a factor in their deaths.
GENERAL OBSERVATIONS ON THE SERIES.

Table showing No. of Deaths and Survivals at the various age and sex groups:

<table>
<thead>
<tr>
<th>AGE GROUPS</th>
<th>DEATHS</th>
<th>SURVIVALS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>0 - 1 yr.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1 - 2 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2 - 3 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3 - 4 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4 - 5 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5 - 6 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6 - 7 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7 - 8 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8 - 9 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9 - 10 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10 - 11 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11 - 12 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12 - 13 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>13 - 14 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>14 - 15 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15 - 16 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16 - 17 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>17 - 18 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18 - 19 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>19 - 20 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20 - 21 yrs.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Over 21</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTALS</td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>

From the Table it will be noted that:

31 Deaths out of 130 in whole series = case mortality 23.8%
Male mortality rate .......... 21.8%
Female mortality rate .......... 25.3%
Excluding 4 cases who died within 24 hours, case mortality = 21.4%
Between 0-5 years, 9 out of 26 died = mortality 34.6%
" 5-15 " 21 " " 93 " = " 22.6%
Over 15 " 1 " " 11 " = " 9.1%
Range, 10 months to 33 years.

It will be noticed that the maximum mortality falls upon those of pre-school age; while in the age group 5-10 years, there occurs 71 cases, i.e. 55% of the whole series. The sex incidence was higher in females and also the case mortality.

Average day of disease before treatment begun:

Deaths .... = 4.1 days.
Survivals .... = 3.7 days.
Table illustrating importance of early treatment.

<table>
<thead>
<tr>
<th>Day of Disease on which treatment began.</th>
<th>2nd.</th>
<th>3rd.</th>
<th>4th.</th>
<th>5th.</th>
<th>6th.</th>
<th>7th &amp; Over.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases:</td>
<td>Deaths:</td>
<td>Cases:</td>
<td>Deaths:</td>
<td>Cases:</td>
<td>Deaths:</td>
<td>Cases:</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>42</td>
<td>12</td>
<td>35</td>
<td>7</td>
<td>22</td>
</tr>
</tbody>
</table>

% Mortality: 10.0 | 28.5 | 20.0 | 31.8 | 16.7 | 40.0

If treatment was commenced on the second day of disease, mortality rate was 10%, whereas on the 5th day mortality rate was 31.8%, and on the 7th day or over, 40%.

I am unable to explain why those treated on the 4th day, in our series, appeared to do better than those treated on the 3rd day: probably there was a greater incidence of very severe cases in those undergoing treatment on the 3rd day.

Observations on the Heart in Fatal Cases and Survivals.

Schwentkr and Noel (1929), on a pathological basis divided cardiovascular failure in Diphtheria into two groups, which are to be distinguished from the clinical classification where "early" and "late" merely indicate time of onset.

"Early" c.v. failure is due to degenerative changes in the heart muscle and is essentially part of the Diphtheritic toxaemia; while "late" c.v. failure can be looked upon as a complication of the disease due to degenerative changes in the heart muscle and inflammatory reactions incident to repair.

Just as pathologically these 2 groups must merge into each other, so clinically it is not easy to differentiate them. From the practical point of view, no differentiation of any kind is necessary for the treatment of both is identical.

About half the deaths in Diphtheria occur at the height of the disease, from 2 to 9 days. The other half die from the 9th day onwards. In our series the latest day of death from cardiovascular failure was 20th day. Deaths from the early type of c.v. failure may occur as late as 9th day, while the onset of late c.v. failure may be as early as 8th day.

Between the 2 groups, certain differences can be seen in the clinical picture.

In the "early" group, there is a progressive deterioration in the cardiovascular system as the toxaemia advances. The temperature of the body is usually raised. There is pallor and cyanosis, small thready pulse, signs resembling shock rather than heart failure. An enlarged
liver is present often; vomiting and abdominal pain are rare. The first cardiac sound is always muffled, and there is often a systolic murmur along left border of sternum. Clinical cardiac enlargement is seldom to be made out. As toxemia progresses there may be present a gallop-rhythm of the heart, and in the last stages a total arrhythmia. Blood-pressure usually remains normal until just before death.

In the "late" group; the onset of c.v. failure is usually sudden, and is ushered in by restlessness, abdominal pain and vomiting. Enlargement of the liver is frequent. Temperature is usually normal and may be subnormal. Clinical cardiac enlargement is frequent; both cardiac sounds are blurred, and B.P. becomes progressively lower from time of onset. Tachycardia or Bradycardia and irregularity of the heart are very common.

The manner of death in early and late c.v. failure is usually different. In the first, death is quiet and preceded by a period of unconsciousness; sometimes a convulsion ends the scene. In late failure, pain resembling that of coronary thrombosis in severity, is a feature; patient is usually restless and fully conscious until fatal syncope supervenes.

Begg (1937) in an electrocardiographic study of the heart in severe Diphtheria, found that an abnormality was present in 82% of cases. But he found that in the first few days of the disease electrocardiographic changes were not conspicuous. After that stage, such changes were more striking and signs of myocarditis were often overshadowed by evidence of conductive lesions.

Thus 2 groups "early" and "late" appear to be differentiated by the electrocardiograph, as well as on clinical and pathological grounds.

Table showing day of death from onset of disease.

<table>
<thead>
<tr>
<th>Day of death from onset of Disease.</th>
<th>No. of Cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 Over.</td>
<td></td>
</tr>
<tr>
<td>28 cases died from c.v. failure.</td>
<td></td>
</tr>
<tr>
<td>2 &quot; &quot; &quot; paralysis.</td>
<td></td>
</tr>
<tr>
<td>1 case died during administration of serum.</td>
<td></td>
</tr>
<tr>
<td><strong>CARDIO-VASCULAR FAILURE.</strong></td>
<td></td>
</tr>
</tbody>
</table>

Average day from onset of disease, on which death occurred .................................. = 10·5

Earliest day from onset of disease, on which death occurred ................................. = 3rd.

Latest day from onset of disease, on which death occurred ................................. = 20th.
In the series 13 out of 28 cardiovascular deaths occurred in the first 9 days = 46%  
In the series 15 out of 28 cardiovascular deaths occurred after 9 days = 54%  
No. of cases dying from early c.v. failure .... = 10  
No. of cases dying from late c.v. failure ..... = 18  

On clinical grounds, I have placed 10 deaths in the group of early c.v. failure; all occurred in first 7 days of disease and 5 of them exhibited petechial eruption of the skin. They all showed a rapid and progressive deterioration from the time of admission, and failed to survive the initial toxemic phase. Six died before membranes had disappeared from the throat.

Table showing Heart signs and symptoms in survivals and 28 cases dying from c.v. failure:

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Incidence of Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivals = 99</td>
</tr>
<tr>
<td>Liver enlarged .....</td>
<td>5 cases = 5%</td>
</tr>
<tr>
<td>Vomiting ............</td>
<td>12 &quot; = 12%</td>
</tr>
<tr>
<td>Extra-systoles - (1st 14 days)</td>
<td>12 &quot; = 12%</td>
</tr>
<tr>
<td>Extra-systoles - (In convalescence)</td>
<td>20 &quot; = 20%</td>
</tr>
<tr>
<td>Arrhythmia - (1st 14 days) ....</td>
<td>3 &quot; = 3%</td>
</tr>
<tr>
<td>Arrhythmia - (in convalescence)</td>
<td>5 &quot; = 5%</td>
</tr>
<tr>
<td>Tachycardia ............</td>
<td>12 &quot; = 12%</td>
</tr>
<tr>
<td>Tachycardia - (persistent)</td>
<td>11 &quot; = 11%</td>
</tr>
<tr>
<td>Reduplication of heart sounds ......</td>
<td>6 &quot; = 6%</td>
</tr>
<tr>
<td>Systolic Murmurs ..</td>
<td>10 &quot; = 10%</td>
</tr>
<tr>
<td>Clinical Cardiac enlargement ....</td>
<td>12 &quot; = 12%</td>
</tr>
<tr>
<td>Syncope (non fatal) ..</td>
<td>2 &quot; = 2%</td>
</tr>
<tr>
<td>Cardiac Oedema and general anasarca ..</td>
<td>- -</td>
</tr>
</tbody>
</table>

14 out of 19 patients showing enlargement of liver died.

The grave prognosis of cardiac vomiting is indicated by deaths of 21 out of 33 patients who had this symptom.
Extrasystoles and arrhythmia occurring in 1st 14 days, were seen in 15% of the survivors; in fatal cases they occurred in 39%. It will be noticed that these signs were common in convalescence (25%).

Bradycardia in the survivals usually happened after the acute stage of the disease; in 2 cases it was seen as early as the 6th day, the pulse rates being 44 and 58 per minute respectively. 3 cases only, of late c.v. failure, showed bradycardia, of 30, 50 and 60 per minute respectively, and all were fatal. One was undoubtedly complete A.V. block. Begg (1937) found that complete heart block may be missed clinically, if concurrently there is an increased ventricular rate.

Systolic murmurs appeared in 10% of all cases at some period of the illness. Osier (1926) stated that 94% of cases of Diphtheria presented this sign, at some time, usually at end of first week and lasting several days or months. In our series the incidence was strikingly lower than this.

Clinical cardiac enlargement occurred in 25% of the fatal cases, but in "early" cardiac failure the heart was seldom enlarged clinically. In the whole series 12 out of 19 patients with this sign recovered.

One case that died of "late" cardiac failure, exhibited dyspnoea and cyanosis, dilation of veins of neck, ascites, hydrothorax and general oedema. Three other fatal cases had pitting oedema of lower extremities of cardiac origin.

54 out of 99 survivals showed one or more of above signs; 45 showed no definite clinical signs of cardiovascular involvement. Over whole series 34 cases (65%) showed some clinical evidence of this.

Table showing incidence of heart involvement in -

<table>
<thead>
<tr>
<th>Class B. and Class C. of Bie's Grouping.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. (48 cases).</td>
</tr>
<tr>
<td>23 cases = 48%</td>
</tr>
<tr>
<td>25 cases = 52%</td>
</tr>
<tr>
<td>C. (61 cases).</td>
</tr>
<tr>
<td>61 cases = 75%</td>
</tr>
<tr>
<td>20 cases = 25%</td>
</tr>
</tbody>
</table>

(1 case that died during I.V. injection has been excluded).

Cardiovascular disturbance is therefore 1½ times more frequent in Class C. than Class B.

Deaths from other causes than cardiovascular.

1 case died during I.V. injection of D.A.T. and has already been discussed.
There were 2 deaths from respiratory paralysis; one died on 29th day, the other on 39th day from onset of disease.

Observations on Paralysis in the Series.

Table showing incidence of various forms of paralysis:

<table>
<thead>
<tr>
<th>Type of Paralysis</th>
<th>No. of Cases</th>
<th>% of whole Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palatal</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>Peripheral Neuritis</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>Strabismus</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Facial</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Giliary</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Pharyngeal</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Sternomastoids</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Ptosis</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Muscles of Extremities</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Deltoids</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Trunk Muscles</td>
<td>2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

67 cases out of 130 in series had one or more forms of paralysis .............................................. = 52%

63 cases out of 130 in series had no paralysis ........................................................... = 48%

59 cases out of 99 survivals had one or more forms of paralysis ............................................. = 60%

40 cases out of 99 survivals had no paralysis ................................................................. = 40%

6 cases out of 31 fatal cases had one or more forms of paralysis ........................................ = 26%

23 cases out of 31 fatal cases had no paralysis ......................................................... = 74%

Palatal paralysis was very common, in 56 cases it occurred at the usual period, 2 - 4 weeks, but on 11 occasions it was precocious, i.e. it happened in the first 2 weeks from onset of illness. The earliest day on which it developed was the 4th, but it was most frequent between the 6th and 10th days. Out of 11 patients with early palatal paralysis, 5 died and therefore the prognosis is grave in those who develop it.

Peripheral neuritis was also observed in a high proportion of the series, and no doubt it was even commoner as many cases must have been missed. It was not possible to carry out a full neurological investigation in each case. It affected almost exclusively motor
Fibres and also involved chiefly the lower limbs. Flaccid paresis and loss of tendon jerks were the usual signs, but in 2 adult cases it was associated with anaesthesia of "stocking and glove" distribution. Knee jerks were lost more frequently than ankle jerks and the time of onset was usually about 5th week. Two cases, however, presented signs in the 2nd week of the disease and both were fatal. Rolleston (1935) found Babinski's sign present in 20% of cases during the acute stage, which indicated pyramidal tract involvement in the toxemia. We found that few patients presented this sign.

Abdominal reflexes were lost in severe cases of multiple paresis. Return of tendon jerks was gradual and loss sometimes persisted for weeks into convalescence, together with the "stepping" gait.

Two adults showed severe peripheral neuritis: Case No. 20842, M. 33 years who had paralysis of palate, ciliary muscles and paresis of trunk muscles and muscles of fore-arms, developed peripheral neuritis in arms and legs on 57th day of disease. He had loss of arm and leg jerks, abdominal reflexes, and sensory loss up to mid-thigh on both sides, and of fore-arms. He was able to support himself and walk at the beginning of the 4th month. On his discharge in the 5th month, he still complained of numbness of fingers and toes.

Case No. 12392, P. 19 years, had ciliary paralysis on 32nd day and on 62nd day complained of numbness and pins and needles in fingers and toes. All forms of superficial sensation were diminished up to calf of legs, and pain diminished on dorsum and tips of fingers. Arm and leg jerks were absent.

Strabismus was bilateral in 7 cases and involved the 6th nerve; on 12 occasions it was unilateral. There were 2 cases of precocious squint on 9th and 10th days respectively. Both were fatal.

Facial paralysis occurred in 13% of the series. By far the commonest expression of it was a weakness of the lower face on one side. Precocious facial paralysis occurred on the 11th day of disease in one fatal case, which had precocious palatal paralysis on 10th day; paralysis of whole of Right side of face on the 11th day, pharyngeal palsy on 32nd day and respiratory paralysis on 36th day.

Ciliary paralysis was probably more frequent than was evident in our series. It is not always easy to detect in young children. It was always bilateral.

Paralysis of sternomastoid, deltoide, muscles of extremities and trunk muscles, occurred in 11.5% of the cases; it is probable that some cases escaped detection. General motor weakness of the lower limbs was associated, too, with peripheral neuritis, the more distal part of the limb being chiefly affected.

Pharyngeal paralysis was recovered from 5 times in the series, and it is obvious that some cases are of a milder type, or perhaps only a segment of the pharynx is involved. Four fatal cases had this form of paralysis; 2 of these had precocious type on 10th and 12th days respectively. The other 2 cases began to show paralytic signs on the 22nd and 33rd days,
which was followed by fatal respiratory paralysis in a few days.

Ptosis was bilateral in 4 cases; unilateral in 2.

Only 2 cases of respiratory paralysis were seen. Both were very severe cases of diphtheria, who had survived grave cardiac failure, only to develop diaphragmatic paralysis, one on the 27th day, the other on the 36th day, from which they died.

Nine patients exhibited multiple paralyses, i.e. occurring in 5, 6, or 7, different situations. Three had paralysis involving 7 different groups of muscles:

Case No. 2630: Palatal, L. ptosis, R. facial, R. sternocostoid, R. deltoid, pharyngeal and peripheral neuritis.

Case No. 1555: Palatal, L. 6th Nerve, double ptosis, R. facial, R. sternocostoid, pharyngeal and peripheral neuritis.

Case No. 1114: Palatal, ciliary, double ptosis, R. 6th Nerve, R. facial, both sternocostoids and peripheral neuritis.

The pathogenesis of paralysis in diphtheria is still subjudice. Broadly there are 2 conceptions:

(i) that paralysis is an ascending neural intoxication from focus of infection,

(ii) that it is due to blood borne infection of the peripheral nerves, or C.N.S.

If we hold the latter view then we have to explain why there should be an orderly sequence of paralysis. If there is a haematogenous spread to C.N.S. or peripheral nerves, then one would expect that the various paralysis would occur synchronously, i.e. after a latent period that was similar for all the nerves involved.

In our series, a feature is the occurrence of precocious paralysis, only in the severest cases with nasopharyngeal membrane. I have used this term to describe those occurring after a latent period shorter than is usual. Thus we have seen palatal paralysis as early as the 4th day of the disease, strabismus on 9th day, pharyngeal on the 10th day and facial on the 11th day. In all, 16 cases of precocious paralysis were observed.

It would appear, therefore, that the rapidity of onset of these paralyses is directly related to extent of membrane, which presumably facilitates the passage of more toxin into the C.N.S. It is tempting to suppose that this transportation is via nerve fibres or perineural lymphatics to the cranial nuclei themselves. Those nuclei nearest the entry of toxin are involved earliest and there is a spread to neighbouring nuclei with a quick succession of paralyses.

Obvious peripheral lesions as in neuritis affecting the lower limbs are accepted as being due to blood-borne intoxication.

However, there is no unanimity as yet, about the pathology of paralysis in diphtheria.
Table showing incidence of paralysis in Bie's Groups:

- **107 Cases** -

<table>
<thead>
<tr>
<th>Bie's Groups</th>
<th>With Paralysis</th>
<th>Without Paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. (48 cases)</td>
<td>19 cases = 39%</td>
<td>29 cases = 61%</td>
</tr>
<tr>
<td>C. (59 cases)</td>
<td>48 cases = 81%</td>
<td>11 cases = 19%</td>
</tr>
</tbody>
</table>

(23 fatal cases have been excluded as they died before paralysis was likely to occur.)

The incidence of paralysis in Class C. is more than double that in Class B.

Observations on Albuminuria in the Series:

In whole series incidence of albuminuria was 76.5%.

70 of survivals had albuminuria ...... = 71%  
29 of survivals had no albuminuria ... = 29%

Of 31 fatal cases, 27 had a cloud of albumin in the urine throughout the illness. Three patients died before specimen of urine was available. Case, No. 7, who died on 36th day, had albuminuria for first 20 days.

9 survivals had albuminuria up to 1 week after treatment began.

21 survivals had albuminuria up to 2 weeks after treatment began.

16 survivals had albuminuria up to 3 weeks after treatment began.

9 survivals had albuminuria up to 4 weeks after treatment began.

15 survivals had albuminuria over 4 weeks after treatment began.

Range 3 - 56 days.

In 2 cases Haematuria accompanied albuminuria, but as there was no oedema or rise in B.P., they were probably cases of acute focal glomerulo-nephritis.
Table showing incidence of albuminuria in Bie's groups:

<table>
<thead>
<tr>
<th>Bie's Groups</th>
<th>With Albumin</th>
<th>Without Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. (48 cases)</td>
<td>27 cases = 56%</td>
<td>21 cases = 44%</td>
</tr>
<tr>
<td>C. (79 cases)</td>
<td>75 cases = 95%</td>
<td>4 cases = 5%</td>
</tr>
</tbody>
</table>

(Three cases were excluded since they died before sample of urine available.)

Thus albuminuria was nearly twice as frequent in Class C. as Class B.

It is interesting to compare the incidence of paralysis, cardiovascular involvement and albuminuria as found in the whole series:

- Incidence of Paralysis .......... = 52%
- Incidence of c.v. involvement .... = 65%
- Incidence of albuminuria ........ = 77%

Other Complications in the Series:

Seven cases developed otorhhea (3.4%) from which K.L.B. was cultured in a few only. H. streptococci were present in the majority of ear discharges.

One case developed a cervical abscess which was incised on the 12th day of disease. H. streptococci were cultured.

One case of septic parotitis (R) occurred on 17th day of disease.

There were two cases of clinical melena, one of frank haematemesis, and two of "coffee ground" vomit, all occurring in fatal cases.

Intercurrent diseases were 3 cases of Scarlet Fever, 2 of Chicken Pox, and 1 of erysipelas of trunk, which developed 3 days before death in one of the fatal cases. One case developed B. Coli pyelitis on the 45th day and there were 3 cases of furunculosis all occurring during the convalescent period.

Scarlet Fever Antitoxin in Diphtheria.

This was given with benefit to certain of the severest cases in which there was much periglandular oedema and congestion of the throat, as it is recognised that H. streptococci is commonly associated with K.L.B. in the throat in this type of case.
Vitamin B1 and Diphtheria.

In recent years the antismittic vitamin has been used empirically in the treatment of post-diphtheritic paralysis, but the results have not been striking. Peters (1937) reported that it was without benefit. In Germany it is apparently more favoured, and there are many accounts of its use in Diphtheria, almost invariably, however, in individual cases of paralysis. Newman (1935) and Knapp (1937) have reported cases successfully treated with Betaxan and Reich (1938) gives an account of personal experience of the use of Vitamin B1, when he, himself, was the subject of severe diphtheritic paralysis.

The Vitamin was being used in our Hospital before this series began, and 26 patients at the beginning of the series were given 1,000 International units of B1, intramuscularly, daily for 3 weeks. Treatment was commenced soon after admission, but in no case were there any signs of benefit, either to existing paralysis, or in preventing the onset of paralysis. The treatment was abandoned.

Cortin in Diphtheria.

The rationale of the use of the cortical hormones of the adrenal in Diphtheria is logical. The adrenals in fatal cases show marked pathological changes of which the predominant is a haemorrhagic necrosis of the cortex. In Addison’s disease which is due to a destructive lesion of the adrenal cortex, the essential symptoms are due to a deficient secretion of cortin and substitution therapy is life-saving. It has been thought that cortin, therefore, might be useful in Diphtheria.

Clinically, asthenia, hypotension and subnormal temperature in Diphtheria, resemble Addison’s disease and lowered serum sodium chloride is common to the 2 diseases. Cortin therapy restores normal metabolism to normal in the adrenalecortized animal. Bernhardt (1936) and Bamberger (1935) have found cortin and Vitamin C. of value in severe Diphtheria, but other clinicians have found cortin alone useless.

Throughout this series we administered cortin to 58 patients in doses of 5 cc. intramuscularly for periods up to 3 weeks from day of admission.

It is notoriously difficult to assess the value of any non-specific therapeutic measure in Diphtheria where there are so many variable factors. In addition, our experiment was not controlled, as only the worst cases received cortin. If any benefit was to be obtained from cortin, we did not feel justified in withholding it from this type of case.

Our clinical impressions were that in some cases a slight but definite improvement in the asthenia and general condition resulted; that it did not prevent the onset of cardiovascular failure, but in the “late” type it seemed at times to postpone, and occasionally prevent, a fatal termination. In the worst cases with “early” heart failure, it was of no avail. Blood pressure readings were taken many times during cortin treatment, but the drug had no direct effect on B.P.
within a period of hours.

We continued to give cortin throughout the series, which is the best indication, perhaps, of our opinion as to its merits. MacLean (1936) has produced evidence that Na Cl. alone is beneficial in Diphtheria; we did not administer extra Na Cl. along with cortin.

Vitamin C. and Diphtheria.

Much research has been done recently into the state of Vitamin C. nutrition of the body in disease, and in many pathological conditions a state of sub-nutrition has been found.

In infections and toxanemia, there is an increased "usage" of Vitamin C. in the body, and the infected patients are in a condition of relative "unsaturation" with respect to the Vitamin. Perhaps an undue significance has been attributed to these findings, with the consequence that there are not many diseases in which Vitamin C. has not been used therapeutically, in some cases with extravagant claims as to the results.

Amongst other workers, Bamberger (1935) and Degwitz (1937) have reported favourably on the use of synthetic Vitamin C. in the treatment of Diphtheria gravis, as an adjuvant to specific therapy. There are destructive lesions in the adrenal cortex in Diphtheria, and since this is a particularly rich storage depot for Vitamin C. in the body, the rationale is perhaps more obvious for this form of therapy in Diphtheria than in some other diseases.

Using the titration technique of Harris (1935), I have studied the urinary excretion of Vitamin C. in 60 cases of Diphtheria in the acute stage, during a control period of 2 days and in the 24 hours following a test dose of Vitamin C.

It is fairly well established that in addition to his usual output, a healthy person will excrete 20-50% of a test dose of Vitamin C. within 24 hours. The test doses I used, varied from 300-500 mg. of Vitamin C. according to age, since weighing the patient was not practicable.

Briefly here are my results :-

1. In age group 5-6 years (15 cases), 87% excreted less than 20% of test dose during next 24 hours.
2. In age group 6-7 years (16 cases), 80% excreted less than 20% of test dose during next 24 hours.
3. In age group 8-10 years (15 cases), 67% excreted less than 20% of test dose during next 24 hours.
4. In age group 10-15 years (11 cases), 72% excreted less than 20% of test dose during next 24 hours.
5. Over 15 years (3 cases), 67% excreted less than 20% of test dose during next 24 hours.
6. In 20 cases of toxic Diphtheria, average of test dose excreted = 8.5% 
   In 19 cases of severe Diphtheria, average of test dose excreted = 12.9% 
   In 21 cases of mild Diphtheria, average of test dose excreted = 17.5% 

7. "Resting-level" of Vitamin C. in 24 hours urine, during 2 days of control period was not lowered, according to accepted standards.

8. Seven patients who gave poor response to first test dose, excreted >20% of a second test dose given next day. One patient only failed to do this.

These results show that in Diphtheria there is retention of Vitamin C. in the body following a large test dose, and that this retention is in proportion to the severity of the disease. On the other hand there is no gross retention which would indicate a state of extreme "unsaturation" since 7 out of 8 patients appeared to react normally to the second test dose, i.e. they were "saturated" after a dose of 500-1000 mg. of ascorbic acid.

Redoxon Vitamin C. was given in doses of 150-300 mg. daily, to a few cases that exhibited petechiae and a haemorrhagic tendency, but no beneficial results were observed. It was not considered necessary to administer Vitamin C. in other cases. The drug produced a moderate diuresis - the only clinical evidence of its administration.
SUMMARY.

After a brief survey of the history of Diphtheria, culminating in the discovery of antitoxin, an attempt has been made to review the changing customs as regards dosage and methods of administration of the latter, and the trend of modern opinion has been indicated.

A series of 130 cases of toxic Diphtheria has been treated, and a method described, by which large doses of antitoxin, diluted if necessary, can be given intravenously.

Consideration has been given to the questions of the optimum dilution, and what is the best diluent of antitoxin.

An analysis has been made of the complications of Diphtheria and of the serum phenomena occurring in the series.

Observations have been recorded on Vitamin C. metabolism, in Diphtheria, and on adjuvant therapy with Vitamin Bl., Cortin, Glucose, and streptococcal antitoxin.
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