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Introduction

Diphtheria's effects are caused by a toxin produced by the bacterium *Corynebacterium diphtheriae*. This toxin produces not only diphtheria's effects in the upper respiratory tract, but also later complications, including myocarditis and peripheral neuropathy. These complications, and superinfection with other bacterial pathogens (streptococci, in particular), contribute to the serious morbidity and mortality associated with the disease.

In the early 1890s, in Berlin, Emil von Behring and Shibasabura Kitasato developed a serum from a hyper-immune horse, which seemed to confer passive immunity on patients with diphtheria. Experience with this serum was first reported in a paper published in 1893.[1] The following year, Emile Roux, Louis Martin and Auguste Chaillou reported detailed information on 448 children admitted to the diphtheria service of the Hôpital des Enfants-Malades in Paris. One hundred and nine of the 448 children admitted died – a fatality of 24.5%. This compared very favourably not only with a rate of about 50% in the same hospital during the four years 1891 to 1893, but also with a fatality of 60% in the Hôpital Trousseau, where serum had not been used.[2,3]

The evidence from Paris and other evidence using historical controls did not convince everyone of the value of anti-diphtheritic serum, however. The debate was complicated both because the disease was undergoing spontaneous fluctuations with decreasing virulence and by claims that the success of serum treatment showed that laboratory research was a more promising approach to tackling diseases associated with poverty than the social reforms for which Virchow and others had been calling.[4] Furthermore, deaths had been attributed to the antitoxin, some of which attracted wide publicity.[4–6]

Søren Thorvald Sørensen's studies in Copenhagen

Copenhagen was one of the places where doubts about the claims made for serum therapy remained. Sceptics emphasized the unpleasant effects of serum therapy, and these meant that even doctors who were themselves ill with diphtheria rejected the therapy.[7] Søren Thorvald Sørensen, professor at the Blegdamshospitalet, conducted numerous investigations and remained unconvinced of the serum's assumed benefit and concerned about its adverse effects.[8–18]

Sørensen conducted studies of anti-diphtheritic serum at the Blegdamshospitalet, first using German serum from October 1894 to February 1895,[8–11,18] then French serum and Danish serum from presumably March 1895 to March 1896.[13–17] These studies attempted to evaluate the effects of serum by selecting hospital patients who were as comparable as possible with respect to age and symptoms but who had or had not been treated with serum.[7,8–18] The results of these comparisons using observational data failed to identify convincing beneficial effects of serum, possibly because sicker patients had been selected for serum therapy.

Sørensen reported that 17 of 51 patients (33.3%) treated with German serum had died compared to 15 of 46 patients (32.6%) receiving no serum during the same period. Of patients who had received French or Danish serum nine of 36 (23.8%) had died compared to five of 19 patients (26.3%) who had not received serum during the same period.

In both periods the decision to treat or not was by choice, albeit trying to divide the patients to serum or no serum 'as equally as possible'.[16] Sørensen made clear that the slightly lower estimate of mortality compared to untreated controls in patients who had received French or Danish serum should not be ascribed to the serum used, but rather to the changing character of the epidemic. He appears to have been fully aware of the fallacies of studies based on such observational data for assessing the effects of interventions, mentioning allocation biases and fluctuations in disease severity. Accordingly, he went on to alternate patients to receive or not receive serum[16]:

> *During the last months of the experimental phase [with French and Danish serum, likely November 1895 to March 1896] we also tried to select every second severe case for serum, but under the available circumstances this method seemed less successful. On the one hand, the method was difficult to carry out, and a subjective factor could not be excluded; on the other hand, we obtained only a few usable cases for our statistics, and the cases seemed far more biased than the ones arbitrarily [Danish: vilkårlige] selected.*

Because of these problems Sørensen abandoned his attempt to do a controlled trial and did not report separately the number of patients allocated by alternation, nor their clinical results.[16,18] Fibiger later referred to these problems as 'practical difficulties'.[7]

Sørensen's conclusions after these studies were clear and balanced. Although they provided no evidence that serum therapy had had a beneficial effect on either the course of the disease or the risk of death, this absence of evidence could not be taken as evidence that there was no beneficial effect: the experiments had been too few in number; most patients had been selected for serum treatment or no serum treatment using subjective clinical assessment; and the number of deaths had been too few to provide reliable statistics.[7,17,18]

Johannes Fibiger's controlled trial of serum treatment

These uncertainties prompted Johannes Fibiger, professor Sørensen's junior colleague, to propose that further, more rigorously controlled research was needed.[7] Professor Sørensen consented to Fibiger's plan, as long as Fibiger himself carried out the experiment.[7] We have reported elsewhere what ensued.[19]

The introduction to Fibiger's report explains why he had remained unconvinced by the evidence provided by Emile Roux and his colleagues.[7] Fibiger acknowledges that the comparison of serum-treated patients to concurrent patients not so treated provided the basis for a potentially dependable verdict on the effects of serum. However, he was concerned that the introduction of serum treatment at the Hôpital des Enfants-Malades had coincided with improvements in isolation routines and hygiene, so that 'the evidential weight of the experiments was lost'. (Considering that Roux and his colleagues had obtained their non-serum treated controls from another hospital [the Hôpital Trousseau], Fibiger might also have drawn attention to the fact that the Hôpital Trousseau was located in a working-class area of Paris; but he did not.)

Fibiger summarized a number of reports from the USA, Germany, Norway, and Denmark suggesting that diphtheria had become less aggressive at the end of the 19th century, as well as referring to Sørensen's unconvincing results.[7] He concluded that 'a new series of experiments had to be planned, and planned in such a way that the result would be absolutely conclusive'.[7]

Fibiger's introduction sets out the rationale for the methodological features of his trial:

> *Even with minimal knowledge of diphtheria epidemics, one will recognise that it is necessary to have (1) large numbers, and (2) a long study period.*
>
> *To compensate for the large seasonal variation in mortality, the study should last at least one year.*
>
> *Truly, the control cases in the earlier studies were selected to be as similar as possible to the ones treated with serum, but to eliminate completely the play of chance and the influence of subjective judgement, one had to use a different procedure. The only method that could be used rationally was to treat every other patient with serum and every other patient in the usual way.*
>
> *In many cases a trustworthy verdict can only be reached when a large number of randomly*

[Danish: tilfældig] *selected patients are treated with the new remedy and, at the same time, an equally large number of randomly* [Danish: tilfældig] *selected patients are treated as usual.*

The choice of Fibiger's allocation method probably reflects Sørensen's[13] earlier decision to abandon a trial in which he had planned to allocate patients alternately to receive or not to receive serum. Whatever the nature of the 'practical reasons' may have been for abandoning this plan (see above), Fibiger proposed and Sørensen accepted that all admitted patients would be treated with serum on one day, but none on the following day.[7] As noted by Hróbjartsson and his colleagues,[19] this arrangement left open the possibility of allocation bias, since physicians could favour the admission of the most severely affected patients on the days that serum was being used. Because Fibiger was also aware of the possibility of observer bias in this unblinded trial, he tried to minimize inter-observer variation by using 'concordant observations' by the consultant and himself.

Between 13 May 1896 and 13 May 1897, 1004 patients were admitted to the Blegdamshospitalet with presumed diphtheria. Fibiger excluded 520 of these patients from the analysis, and gives a full account of the reasons. Exclusions were mainly made because the diagnosis had not been confirmed bacteriologically (493 patients), but other patients were excluded because they were moribund on admission or had additional serious infections. The remaining 484 patients – all with bacteriologically confirmed diphtheria and croup – were included in Fibiger's analysis.

These arrangements led to a comparison of well-matched groups of 239 patients who received serum with 245 patients who did not. There were eight deaths in the serum group (3.3%) and 30 deaths in the control group (12.2%).[7,19] Using terminology which antedates its more specific meaning today, Fibiger concluded that 'no objection can be raised against the statistical significance of the numbers', which were deemed correct by an inspector from the Sick Benefit Association.[7,19] However, this beneficial effect came at a cost: at least 145 out of the 239 patients (60.7%) who had been treated with serum developed serum sickness.

Comment

Sørensen's and Fibiger's studies were conducted in the setting of scepticism surrounding the use of serum. Such scepticism also led to a similar trial being carried out in America during the latter half of the 1890s.[20,21] Further important evaluative research on serum therapy was reported by Bingel in Germany,[22,23] and controlled trials were done in France[24,25] and the Netherlands[26] assessing the effects of calcium chloride in preventing the sometime very unpleasant side-effects of serum treatment. In brief, the history of the evolution and evaluation of treatments for diphtheria was a truly international endeavour.[27]

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