French 19th century contributions to the development of treatments for diphtheria

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Tracheotomy and tracheal intubation

Diphtheria most often leads to death if left untreated because of obstruction of the upper airways by an adherent membrane. Pierre-Fidèle Bretonneau – who introduced the term diphtheria in 1817 – is usually credited with having documented the first successful use of tracheotomy to relieve laryngeal obstruction caused by the disease. After two unsuccessful operations in 1818 and 1820, his third (done in 1825) was successful.[1] Bretonneau's pupil, Emile Trousseau, also had two failed operations (in 1826 and 1828) before succeeding in 1831.[2,3] In 1855, Trousseau reported on the fate of 216 children in whom he had used tracheotomy at the Hôpital des Enfants-Malades in Paris.[4] Forty-seven children (22%) had survived, a result that he rated as remarkable given the dire natural history of laryngeal obstruction caused by diphtheria:

> *This result is considerable if one thinks about the social conditions of the children brought here, about the deplorable treatment given by the midwives (…), if one thinks about the disastrous conditions of the hospital itself, where children are placed in the middle of the most serious and most different contagions: so that very often, at a time when everything seems to work well after tracheotomy, scarlet fever, measles, cowpox, or whooping-cough introduce formidable complications.*[4]

Tracheal intubation, an alternative to tracheotomy but an ancient and forgotten practice, was revived in France in 1855 by a surgeon in Lyon, J-F Reybard (1795–1863), who specialized in urethral cannulation and used silver cannulae to perforate the diphtheritic membrane. Although passing references to Reybard's use of tracheal intubation were made frequently, no published report is mentioned in the list of Reybard's publications published by Dechambre.[5] To the satisfaction of opponents of tracheotomy, Reybard's method of tracheal intubation was presented to the Academy of Medicine as a substitute for tracheotomy. Intubation was later presented to academicians in greater detail by Eugene Bouchut (1818–1891) as a method to replace tracheotomy, provided a new type of cannula was used:[6,7]

> *On pouvait remplacer la trachéotomie, opération difficile et dangereuse, qui donne une mortalité de 80 à 90% et quelques fois d'avantage, par une opération nouvelle, non sanglante, exempte de tout danger, aussi facile à concevoir que facile à accomplir: c'est le tubage de la glotte.*[6]
>
> *[One can replace tracheotomy, a difficult and dangerous operation with a mortality of 80 to 90%, and sometimes with advantage, with a new operation, without bleeding, free of danger, which is as easy to conceive as it is to accomplish: namely, intubation of the glottis.]*

Bouchut's report was discussed in November 1858 at the Academy of Medicine and Trousseau was asked to examine and report on the method. Because tracheal intubation challenged tracheotomy,[3] Trousseau's long report dismissed the former and promoted the latter, drawing attention to the insufficient number of cases (only seven) treated by intubation.[8] Despite continued criticism of tracheotomy – prompting a Danish physician to propose that it be assessed in a controlled trial[9] – the operation remained dominant, although tracheal intubation remained on the list of hospital practices. When Bouchut was appointed chief

physician at the Hôpital des Enfants-Malades in Paris, he placed intubation on the top of his list of treatments for diphtheria, followed by tonsillectomy (which he described in great detail). Tracheotomy was relegated to be used only after other techniques had failed.[10]

In 1887, an American paediatrician, Joseph O'Dwyer, using an improved technique of tracheal intubation, published a detailed account of 50 patients with croup treated by intubation, 12 (24%) of whom survived.[11] Tracheal intubation was widely accepted in the United States and rapidly superseded tracheotomy as a standard procedure. Although guidelines for performing intubation were widely publicized in France,[3,12,13] however, the procedure was not readily accepted in Europe, both because of the influence of prominent physicians, but also because of the perceived risks associated with intubation through inflamed tissues. Intubation became a common practice in Europe only after serum therapy had been introduced, with consequent reduction of local inflammation and the risks associated with it.[3]

In attempts to kill the bacteria, measures used in the late 19th century included disinfection of the upper respiratory tract with glycerine and salicylic acid, and washing with calomel, or with boric and phenolic acid added to water.[14–16] However, the purported effects of these interventions were not quantified, but supported with statements such as 'the membranes were more easily dislodged after such washings'.[13]

Use of historical and concurrent controls to assess the effects of measures to prevent cross-infection with diphtheria and other organisms in hospital

Although tracheotomy and intubation could be lifesaving, the patient fatality rate remained high throughout the 19th century. At the end of the century, about half of the children admitted to hospital with diphtheria died,[17] the most seriously affected patients often being infected with streptococci or staphylococci as well.[15] Joseph Grancher (1843–1907), one of the physicians in charge of the Infectious Diseases Service at the Hôpital des Enfants-Malades, had established that diphtheria was not transmitted by circulating air but rather through person-to-person contacts, or contacts with the personal belongings of diphtheria patients. To reduce such super-infection of diphtheria patients with other micro-organisms, as well as to reduce the spread of diphtheritic infection to uninfected children in the hospital, Grancher established a set of guidelines based on the principles of asepsis and isolation techniques that had been adopted in departments of surgery and obstetrics.[18] Rather than proposing a specialist diphtheria hospital, therefore, Grancher's report to the executive ministry responsible for public health (report read and approved at the *Comité consultatif d'hygiène de France* on November 10, 1890) recommended the implementation of rigorous hygiene and asepsis in existing hospitals, as well as measures to limit cross-infection during the transport of patients by the recently established ambulance service.[19]

Accordingly, Grancher reorganised the wards for which he was responsible by surrounding each bed with a 1.2 metre high wire gauze screen to minimize movement between beds, and by providing each semi-isolated 'cubicle' thus created with individual equipment, sterilized every other day, for food and care. The staff were required to obey very strict asepsis rules when moving from one cubicle to another, washing their hands with mercury sublimate, and changing their overalls. Bed clothes were sterilized after each patient had been discharged from hospital.

Grancher claimed that improvements were evident as soon as these new measures had been introduced.[19] In his wards there had been 19–35 patients with diphtheritic cross-infections out of an average of 500–600 patients per year in the years before the cubicles had been introduced (about 3–6%) compared with only one patient (with a dubious diagnosis) out of 575 patients the year following the introduction of the new procedures. Furthermore, in other wards (for measles, surgery and internal medicine) in the Hôpital des Enfants-Malades which had not been equipped with cubicles, there had been a total of 153 patients of diphtheritic cross-infections (about 3%) of about 4000–5000 patients (an estimate based on the average number of patients in those wards in 1887 and 1888). Grancher gives as an example of the frequency of cross-infections the fact that there had been three diphtheritic

cross-infections (6%) during the first 6 months of 1889 out of a total of 47 patients admitted to Husson ward (for patients with chronic diseases), which had not been equipped with cubicles. By contrast with the reduction in diphtheritic cross-infections, no decrease in the spread of measles within Grancher's wards was observed, circulation of air being incriminated.

Serum therapy for diphtheria

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.[20] They presented their results cautiously, emphasising that all 30 children treated with serum had had diphtheria confirmed bacteriologically, and their promising results called for replication on a large scale.

Grancher's infectious disease department at the Hôpital des Enfants-Malades in Paris was the site of the first controlled evaluation of the effects of serum treatment for diphtheria.[17] Between 1 February and 24 July 1894 (thus including winter and summer months), Emile Roux, Louis Martin and Auguste Chaillou collected detailed information on 448 children admitted to the diphtheria service. In addition to information about the diphtheritic infection itself, such as duration of the illness, data were collected on age, pulse, breathing rhythm, and albuminuria, and information on any complications – from measles, bronchopneumonia, scarlet fever or other co-morbidities. Twenty children died soon after admission to hospital, but 428 received hyper-immune horse serum in doses ranging from 20 cubic centimetres to 125 cubic centimetres, depending on the severity of the illness and the presence of associated pathologies.

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.

Roux, Martin and Chaillou distinguished diphtheritic sore throat (*angine diphtérique*) from laryngeal diphtheria (croup), the latter being defined by whether or not tracheotomy had been used. They also stressed the different degrees of seriousness, depending on whether the diphtheritic croups were pure or associated with other conditions (in cases associated with staphylococcal and streptococcal infections fatality reached 63% and 80%, respectively). Further analyses of their crude statistics showed that, when consideration was restricted to patients with diphtheritic sore throat, more dramatic differences in favour of serum emerged – 12% died compared to an average of 34% over previous years, and 32% at the Hôpital Trousseau. Figures were also presented for the patients in which tracheotomy had been used, among whom 49% had died compared to an average of 73% during previous years, and 86% at the Hôpital Trousseau.

Roux, Martin and Chaillou further refined their analyses of the 448 children in two ways. First, they identified and removed from their analysis the 128 children in whom there was no bacteriological confirmation of infection with the diphtheria bacillus. Second, they excluded the 20 children who had died soon after arriving at the hospital, and who had not received serum. This left 300 patients with bacteriologically confirmed diphtheria who had received serum. These patients experienced a case fatality of 26% compared to about 50% among similar patients in the same hospital over previous years.

Finally, they compared the mortality among 120 children with 'pure' laryngeal diphtheria who had received serum to the mortality among 96 similar children admitted in 1891 and 1892. The case fatality rates were 7.5% and 41%, respectively, and the authors provided plausible reasons for the deaths of the nine infants who had died in spite of receiving serum. Serum treatment had also been associated with a reduced use of tracheotomy.

Unsurprisingly, Emil Roux and his colleagues concluded that this evidence supported their belief that, as serum was the only new element

that had been introduced at the Hôpital des Enfants-Malades, the beneficial changes had to be attributed to the treatment.[17] It is worth noting that Roux and his colleagues used the word *'statistiques'*, albeit without presenting statistical analysis as such.

In September 1894, Emile Roux presented these findings to the International Congress of Hygiene, in Budapest, and this marked the introduction of widespread use of serum therapy in Europe.[20,21] In the course of the discussion which accompanied the report of Roux's lecture, the author mentioned that Hans Aronson of Berlin had reported comparable results concerning the treatment of diphtheria patients with anti-diphtheria serum prepared in Germany. Aronson mentioned a procedure for obtaining high titre serum (allegedly three times more efficient than Behring's serum), the use of which had resulted in a decrease in case fatality rate from 40% to 15% among bacteriologically-confirmed diphtheritic patients.[21–23]

The results obtained in Paris were reflected not only in Berlin, but elsewhere. For example, an American textbook[24] published soon after the French and German results had been reported concluded that the value of anti-toxin serum had been established, but, 'so that readers may themselves to a certain extent have a basis for forming their own opinions', statistics were presented showing trends in fatality among patients admitted to the Willard Parker Hospital for Contagious Diseases in New York, and the Kaiser-und-Kaiserin Friedrich Augusta Hospital in Berlin.[25]

Statistics were frequently used to assess the efficacy of anti-streptococcal and anti-diphtheritic serotherapy in Paris. In contrast, they were rarely used to assess anti-venomous, anti-tetanous and anti-tuberculous serotherapy.[26] In fact, Landouzy refers implicitly to differences in the use of statistics to define treatment effectiveness by referring to the extent to which past experience of the disease provided the basis for reliable inferences about the effects of treatments. In the case of rabies and deadly venom inoculation, the alternative facing physicians was to treat victims with inadequately tested treatments or to watch them die. Unsurprisingly, all patients with either of these two conditions were treated with vaccine or sera, with records only of the numbers of survivors and deaths. The effectiveness of these treatments was deduced from the divergence from expectation of the cumulative ratio of survival to mortality, with a discussion of possible explanations of the failures.[27]

The success of serotherapy in tetanus was sporadic and no statistical analysis was even attempted. Landouzy refers to Marmorek's clinical trials of an antiserum against streptococci, prepared in a similar way to anti-diphtheria serum.[28] Marmorek, who worked under Roux's supervision, compared the mortality rate among all streptococcal infections in the same hospital ward the year preceding the introduction of the antiserum (5.1%) and during the year of the trial (3.9%). Moreover, the serum was administered only to patients with severe erysipelas. However, no statistical protocol and no homogeneous cohort of patients were defined. The statistics to which Landouzy refers thus appear quite primitive compared with Roux's studies of serum treatment of diphtheria. This suggests that the evaluative methods applied by Roux were not in common use at the Institut Pasteur at that time, although the principles had already clearly been established and were taught to physicians at the university. In 1883 Dechambre made clear in the authoritative *Dictionary of Medicine* that reliable estimates of the value of treatments depended on studying large numbers of homogeneously defined cohorts of patients, although he did not propose any kind of protocol for carrying out trials or collecting information, and clearly preferred comparisons with historical data.[29]

Within a year of the report of Roux's observations extensive data were reported comparing the mortality of treated cases with historical control data. In 1895, GC Crandall reported that, having 'recently had access to the Library of the Royal College of Surgeons of England, I gathered as fully as possible, statistics upon the use of the anti-diphtheritic serum.' He assembled these data in what was essentially a systematic review, which included 13 comparisons of treated cases with historical controls. Unfortunately, Crandall did not provide references to his sources, but in some cases at least he considered the appropriateness of different kinds of control data. For example in the report by Washbourn and his colleagues,[30] concurrent control data from other hospitals – as used by Roux – were given. However, 'on account of the varying standards of diagnosis', Crandall decided not to lay much stress on these data by comparison with the historical control data.

The evidence from Paris and other evidence using historical controls did not convince everyone of the value of anti-diphtheritic serum, however. Apart from the fact that deaths had been attributed to the antitoxin, some of which attracted wide publicity (see Moizard and Bouchard,[31] and the responses of Roux,[32] Landouzy,[26] Weindling,[33] Hüntelmann[34]), the debate was complicated by at least two other factors, one methodological, the other more 'political'. First, interpretation of trends in mortality over time was complicated because the disease was undergoing spontaneous fluctuations, with a trend to decreased virulence. Second, some were claiming 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.[33] However, the importance of serum therapy was singled out for award of the first Nobel prize in Physiology or Medicine (1901) to Emil von Behring, implying that the beneficial effects of the therapy had become widely accepted.

Following the investigations reported by Emile Roux and his colleagues,[17] further important evaluative research on serum therapy was reported by Fibiger in Denmark[35,36] and by Bingel in Germany.[37,38] In addition, at least one controlled trial was done in France to assess the effects of calcium chloride in preventing the sometimes very unpleasant side-effects of serum treatment.[39,40] In summary, although French contributions to the development of treatments for diphtheria were undoubtedly important, it is clear that the history of the evolution and evaluation of treatments for diphtheria was a truly international endeavour.[41]

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