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The French road to Gavarret's clinical application of probabilistic thinking Part 2: Louis-Denis-Jules Gavarret

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This article is in our series on probabilistic thinking and the evaluation of therapies, 1700–1900

The Académie des Sciences

In 1835, a statistical account of two treatments of bladder stone had been submitted for consideration by the *Académie des Sciences*. It compared the traditional extraction of the stone after cutting into the bladder to the innovative crushing of the stone by lithotripsy. A Commission of the Academy was charged with reporting to its members. It consisted of two elderly gentlemen, Napoleon's legendary surgeon Dominique-Jean Larrey (b.1766) and the physician François Double (b.1776), and two comparatively younger members, Siméon Denis Poisson (b.1781), the mathematician, and the chemist Pierre-Louis Dulong (b.1785), now the Academy's secretary.

The *Rapport* appeared on 5 October 1835.[1] It disapproved of any application of calculations to medical problems. *Rapporteur* François Double's principal objection to numerical analysis was based on the suppression of individual differences required by the method: 'In statistical matters . . . the first care before all else is to ignore that a man is an isolated individual and only to consider him as a fraction of the species'. A second point was the practical unfeasibility: The need for a large number of facts [still, how many?] could never be met. The method was 'inappropriate to elevate the human spirit to that mathematical certainty found only in astronomy'.[2] This *Rapport* was considered relevant enough to be reprinted and commented on in 2001 by the *International Journal of Epidemiology*.[1,3]

Poisson – by now a renowned mathematician – was not convinced by these objections nor by the allegedly insuperable difficulties of mathematising medicine. He was a probabilistic thinker. It was indeed only during these years that this versatile mathematician was dealing with the calculus of probabilities. In consequence, he was to publish two years later his respective contribution highlighting again the Law of Large Numbers, already described by Jacob Bernoulli and Laplace (see Parts 1 and 2/1).[a] In essence it said that more data reduces uncertainty.[2]

The *Rapport* on bladder stone was the starting point for another long discussion, in 1837, in the *Académie Royale de Médecine*. Its context and history have been analysed.[4–6] In what follows, I focus on the probability aspects.

The Académie Royale de Médecine

This time three advocates of the numerical approach, physicians of Poisson's generation and younger, were part of the Commission. They were Pierre-Charles-Alexandre Louis (b.1787), Auguste François Chomel (b.1788) and Jean Baptiste Bouillaud (b.1796). This Commission reported on a study purporting to demonstrate the superiority of repeated purges over bleeding in the treatment of typhoid fever. The report cautioned against any premature application of numbers. This would distort results, yet properly applied, numbers could be decisive. Some members of the Academy did not share this Commission's enthusiasm and asked for an enquiry into the utility of statistics applied to medicine. Thereupon a debate started a month later, in April 1837.

The main speaker in favour of statistics was Louis, a solitary Paris hospital pathologist. He had authored papers of numerical anatomo-clinical descriptions of diseases (nosographies).[7] The issue now was a study on various treatments of pneumonia previously submitted to the Academy. This had resulted in showing – was that not impossible? – the limited value of the then much favoured method of bloodletting. In this, Louis had used what came to be called 'the numerical method', although he never introduced a formal definition of it (Sheynin,[8] p. 250). In fact, it was nothing more than a statement of proportions of successes – or failures – out of total numbers of patients treated. He saw in this the only way to raise the epistemic state of medicine onto a par with that of other sciences. Unconscious, informal probabilistic thinking was behind it.

Louis's opponent, the younger clinician Benigno Risueño d'Amador (b.1802), represented the individualistic neo-hippocratic school of Montpellier. He had travelled to Paris especially for the occasion, where he droned on over seven consecutive sessions (up to July 1837) about the time-honoured *art médical*. D'Amador emphasised that it was being proposed that this art would be replaced by the counting method, 'a uniform, blind and mechanical routine' yielding only probable rather than certain results. Was medicine to become a gambling place, a lottery? If, as a consequence, one followed treatment for the majority of patients, what would happen to the minority? 'What we need is certainty', he insisted. Furthermore, biologic variability over time could not be fixed by a number.[6] On the positive side, d'Amador pleaded for the use of induction based on similarity among cases, whereas, according to him, Louis's numerical method was based on haphazardly assembled groups.

Further criticism included again the impossibility of finding sufficient numbers of comparable cases and the fact that there was no reason to abandon one time-honoured treatment – bleeding – for another – purging – since patients had also died with the latter. And finally, Risueño d'Amador formulated the essence of his conviction:

> Never, and in no instance, can a doctor judge the utility of his art by the results of large numbers. Nature preserves the species; art prolongs an individual's life as long as it can.

Maybe he formulated this as a way of articulating his fear of modernity, when medicine would 'no longer be an art, but a lottery', a warning about a utilitarian science, a wrong science, as d'Amador argued (quoted from La Berge,[6] pp. 93–96).

Results of the Paris debates

With hindsight one sees that the main question was not 'Which remedy do I prefer'? but rather 'How is competent medical judgment to be achieved'? The central point was thus rather about the concept of medicine and its epistemic status compared to that of other sciences. There were also social issues at stake: mathematicians (and other scientists) were not considered to have sufficient knowledge to evaluate medical practice. These 'strangers at the bedside' would destroy the unique nature of doctors' personal intervention in the life of an ailing patient: the doctor's prestige might be hampered. Quantification and probability were double-edged. As medical historian Andrea Rusnock[9] summarised: 'Assigning numbers to people [...] de-individualized and de-humanized, and at the same time, it leveled an unequal and hierarchical society' (p. 217). Finally, d'Alembert's old problem was a major point again: should or how could one use results obtained from a group to gain a prediction for an individual? It was the 'group-versus-single patient/case problem' – an apparently irresolvable problem?

The advocates and opponents continued quarrelling during succeeding decades. Yet confusion and vendetta were resolved with respect to three essential points.

First, henceforth the distinction was made between

(i) medical statistics, seen as indispensable for the emerging field of hygiene (that is studies of populations, public health, which adopted them in its vocabulary); and
(ii) the numerical method (*méthode numérique*) of clinical medicine, seen as dry calculations, often not based on discrete, homogenous data (an obvious fallacy of Louis's analyses).

Second, an old question had become apparent: How valuable was any of these methods? As one participant suggested:

> There is one indispensable condition for the validity of statistical results, and that is the morality of the observer, his good faith, his intelligence. Good faith is necessary, for facts have been invented or falsified in the past. (Quoted from Murphy,[4] p. 315)

How true this sentence still is!

Finally, and for us: Louis's *méthode numérique* still corresponded to Jurin's mode of unconscious, informal probabilistic thinking, whereas Risueño d'Amador, in challenging it, sometimes did so in consciously probabilistic terms. All three were pre-mathematical. This was not the case of Siméon Denis Poisson, the mathematician.

Jules Gavarret introduces the 'calculus of probabilities' to clinical medicine around 1840

Poisson was Laplace's heir in probability theory and therefore an interested attendant of the Paris debates.

Concurrently, he was working at extending Condorcet's and Laplace's work on probability theory. He had become a clear supporter of the calculus of probabilities, mainly for evaluating therapies – a formal probabilist. He developed relevant equations – specifically his Law of Large Numbers – and, after the summer break of 1837, he published his *Recherches sur les probabilités des jugements en matière civile* (Enquiries into the probabilities of judgments in civic matters, 1837). This book was to open the way to a new view of the calculus of probabilities which could be applied to clinical medicine. It was a notable step forward to applying scientific principles to the evaluation of therapies compared to the *méthode numérique*.[10]

Another follower of the 1835 discussion at the *Académie des Sciences* and of Poisson's work was Louis-Denis-Jules Gavarret (b.1809), who had studied under Poisson and graduated from the *Ecole Polytechnique* before turning to medicine.[8,11] Born in the early 19th century, he was also the first physician to be added as the next generation's link to the Bernoulli-Condorcet-Laplace-Poisson chain. And, as a young clinician, he advanced the application of their intellectual heritage in practice. First, he distinguished descriptive and inferential statistics. Second, he published the first (French) textbook on the field of statistical inference, the *Principes de Statistique Médicale: ou dévelopement des règles qui doivent présider à son employ* (Principles of medical statistics: or development of the rules governing its use, 1840), in which he gave a first concrete example of the application of such rules to clinical medicine.

Using Louis's data and Poisson's mathematics, he calculated the possible errors of averages or means. He called them '*limites d' oscillation*' (limits of possible errors). These are, however, not equivalent to today's confidence intervals, for the basis of calculation is different. He saw that

> to be able to decide in favour of one treatment over another, it is not sufficient that the method yields better results, but that the difference found must also exceed a certain limit, the value of which is a function of the number of observations. [Contrarywise he concluded, very harshly indeed, that] Each difference between two results obtained which falls within this limit, which is the smaller, the greater the number of observations, may be disregarded and considered as null. (Transl. from Gavarret, 1840, p. 158)

Gavarret further set stringent requirements of basic comparability between groups when designing a trial that would yield reliable results. From mathematical assumptions he calculated that such a trial would need 300 (or at least some 200) cases per group. Then, if the resulting probability that a difference was not due to chance should amount to 99.5%. (In the 'odds-representation' of probability this would read: odds are 212 in 213, that amounts to a probability $P = 0.9953$.) This choice of probability went back to Poisson; it was based on mathematical convenience. It was a compromise to establish probability as near to certainty as possible: 212/213 is a fraction near to unity that cannot be reduced as both nominator and denominator are near to prime numbers. If one chose fewer cases, the resulting probability would be lower, and that was not reliable in his view.

Gavarret's effort resulted in a new definition of probability, at least for medicine: determining the limits of error of two averages. Finally, someone had provided an answer to the long-standing question of '*how many* cases were needed'. But of course, there were practical difficulties.

The responses to Gavarret's book varied widely. It was translated into German (1844). However, except in Germany, it elicited little attention among physicians and was no longer cited at the end of the 19th century.[5]

This meant that discussions about the value of numbers, and different understandings about the notion of statistics, went on as trials continued. Some of these were well-designed, but many had obvious shortcomings – noticed by contemporaries. Gavarret's conscious, formally mathematical mode of probabilistic thinking surely was not mainstream.

Therapeutic reasoning in France after Gavarret

The multidisciplinary nature of the *Académie Royale de Médecine* should have provided a natural setting for deepening methodological insights in therapeutic reasoning, yet no methodological sophistication was elaborated. Numbers were used in medical debates about therapeutic innovations, but Louis's *méthode numérique* was obviously considered sufficient. These debates were characterised by disagreements and fights for exclusivity. A comparative sloppiness in observation was criticised as the weakness of this apparently precise method. Such statistics did not weigh greatly in the minds of the academicians when compared to results from morbid anatomy, experimental physiology and animal experiments, all of which were used as sources of evidence. The issue was often about the multiplicity of therapies rather than about which one was best. Furthermore, clinical statistics were not as easily collected as animal experiments, which could be repeated, or anatomical specimens, which could be demonstrated in the conference hall of the Academy. The emphasis was thus on therapeutic rationale rather than on therapeutic effects.[12]

By the mid-19th century, hospital statistics were being widely collected. In Paris, there was a statistical commission to co-ordinate the data procured. Medical historian George Weisz noted: '. . . [c]ounting was not merely occurring . . . but was providing convincing data in a limited number of cases'. Even if simple counting was frequently insufficient to provide convincing evidence, this did not mean that it was opposed in principle: its mathematical limitations were not widely understood, so it had become incorporated as an element of individual clinical judgement rather than being an alternative to it (Weisz,[12] p. 302).

This changed after the mid-1850s when, after the introduction of anaesthesia, surgical innovations became more and more frequent. One example was tracheotomy (Opinel and Gachelin, 2010), on which two debates were held in the *Académie* in 1839 and 1859, respectively, the latter comparing this surgical intervention to intubation, i.e. the insertion of a metal tube into the trachea (Opinel and Gachelin, 2010). In 1839, uncontrolled case series from various published sources were added up so that 18 'cures' of 60 operations could be claimed. Twenty years later, 27% of 446 tracheotomies performed during the previous nine years at the *Hôpital des Enfants Malades* had been successful. On the other hand, ulcerated dog larynxes after prolonged intubation were demonstrated to justify tracheotomy rather than intubation despite its low success rate. At least some children had been 'saved' by surgery (Weisz,[13] pp. 169–172).

Major surgical procedures such as amputation and lithotomy had been subjected to counting since the 18th century,[3,8] because diagnosis, prognosis and therapeutic results seemed clear cut, namely survival or death. Now removal of tumours, treatment of ovarian cysts or infectious foci continued to be reported in this simple statistical way – and compared with the presumably fatal issue of conservative therapies. There were no recognised baselines permitting comparison with other treatments or with no intervention. Some dissatisfaction about such uncontrolled statistics of operative results was voiced by French surgeons in 1873 and still three decades later in 1908 (Weisz,[13] p. 173; Verchère, 1908).

In the case of systemic therapies, however, few things remained stable during the 19th century, neither the diagnostic category, nor often the constantly evolving procedures, nor the results. George Weisz concluded from his historical study of the Paris *Académie de Médicine* that doctors attempting therapeutic evaluations

> tended to rely on case descriptions. Frequently, they avoided the issue of evaluation altogether to concentrate on whether a particular therapy "made sense". And in doing so they sometimes made use of scientific techniques that were far more sophisticated than counting. (Weisz,[12] p. 303).

Putting the numerical method into context

Medical science versus medical art

In 1828, the then young physician Armand Trousseau (b.1801) accompanied Louis to Gibraltar on a government commission to study an outbreak of yellow fever. Louis's manuscript was published a decade later in English. The translator, Dr. Cowan (whom we will meet again below), shows in his introduction shows the outdated conception of Louis's probabilistic thinking:

> In the present state of science, we must often be content with probability. M. Louis acknowledges this, whilst he insists that there is a great difference between the probable and the true, for the probable may be false. (Louis, 1839, p. XV)

So, an everlasting 'truth' was apparently in his mind and directing his research – and also Trousseau's, for he surely knew Louis's great work on the pathological anatomy of phthisis (tuberculosis) published in 1825, shortly before their common trip. Trousseau knew about the *méthode numérique* and he was certainly aware of Louis's later works, particularly on the lack of demonstrated beneficial effects of bloodletting (1835).[7]

Thirty years later, by now a prominent Parisian clinician of the day, and a brilliant orator, Trousseau published his *Clinique médicale de l'Hôtel-Dieu* (Clinical lectures delivered at the Hôtel-Dieu, 1861). In the *Introduction* he devoted eight pages to the numerical method.

For him, this was no more than the replacement of expressions such as 'sometimes', 'frequently', and 'often' by exact proportions. This might sometimes be useful, but only secondarily so, for example, when it would lead to new notions in the future. In that way, Trousseau recommended the method and admitted that he had used it himself.

As to the claimed veracity of the results, he asked, rhetorically:

> Don't you think [. . .], messieurs, that if one wants to lie, one cannot do this as well with exact numbers as with approximates [and without] fabricating details

> much labor [sic!] and with less hypocrisy? (Transl. from Trousseau, 1865, p. XLIII)

Although Trousseau had never calculated any proportions, let alone any probabilities with all their claimed rigor, he stressed their limitations, saying that they could yield only

> raw, unelaborated, elementary results [...that] are simply a pasture for the medical intelligence needed to elaborate them. I reproach [the method] to count only, [...] to stick to the rigorous result like a mathematician ....

And he continued the polemic in the style he had known from the *Academy* debate thirty years previously, sometimes quoting Risueño d'Amador:

> This [numerical] method is the scourge of intelligence. It transforms the physician into a clerk, a passive servant of numbers which he has superposed; and the maximal reproach I raise against it is to suffocate medical intelligence. (Transl. from Trousseau, 1865, pp. XL–XLII)

Observing facts, systematising them by counting, submitting an equal number of cases to two modes of treatment to decide a therapeutic question – these were the characteristics of medical science for Trousseau. But medical science was not to be confounded with medical art. He stressed

> Medicine is more of an art, and the doctor truly worthy of his ministry must above all glorify himself not to be only a learned scientist. And even when the doctor, unfortunately, errs often, one nevertheless finds more charm, more attraction in the study of an art, and [... medicine] needs a bit more intervention of intelligence [understanding and knowing] than the sciences where we are directed by certain and invariable rules. (Transl. from Trousseau, 1865, pp. 4–5)

In conclusion, Trousseau thought statistics are

> made so much noise of for such poor results that one ought not to support it to deceive young people by a kind of charlatanism of exactness and truth. (Transl. from Trousseau, 1865, p. XLIV)

Trousseau, too, was well aware of therapeutic trials and had done some himself, for example, to evaluate homeopathy in 1834.[14] To be sure, his two homeopathy trials for various illnesses were single-blinded, yet he did not report whether symptomatic improvements, if any, were more than transient. Nevertheless, he believed that these were valid tests. Later he erred again in design and inference in his own sphere of orthodox medicine, dismissing one of its most effective specifics of the day, colchicine for gout, as a placebo in the same way he had done for homeopathy (Dean,[14] pp. 142–144): Trousseau's understanding of the numerical method was absurd. Bearing this in mind, we doubt his critical acumen when we read his review of Louis's book on venesection (1835):

> ... I confess that I have been one of the most violent, one of the most unjust detractors of this [numerical] method, I did not understand it; today, having studied it, I admit that it alone will enable science to make solid progresses, that it alone will allow in future centuries the use of the works of those who shall have lived before, and to raise slowly an edifice that the dreams of a Galen or of a Paracelsus will impossibly be able to throw down. (Transl. from a quote in Bariéty,[15] p. 182)

Clearly, Trousseau and therapeutic reasoning remained unconscious, pre-mathematical, complex, messy ... and verbose.

Probability versus certainty

Trousseau's was one line of argument, medical art against medical science. Another line was probability against certainty. In France, this was articulated particularly forcefully by Claude Bernard. In 1865, when the second edition of Trousseau's *Leçons Cliniques* came out, his contemporary, Claude Bernard (b.1813), published his *Introduction à l'étude de la médecine expérimentale* (Introduction to the study of experimental medicine, 1865). At this time Bernard was already a member of the *Académie Française*, a world-famous physiologist. One of the principles underlying his work was that, in nature, every effect was due to a precise cause. This constant relationship of determinism could be discovered through animal experimentation. This was a typical line of arguments of physiologists, which we shall come across also in Germany (see Part 3/1of this series to be published).[a] Medical science was to look for certainty whereas statistics could only offer probabilities and was therefore inappropriate for physiology.

Less polemical than Trousseau, he saw empirical clinical medicine, based, as it was, on comparative experiments and statistics (in the sense of counting), as being in an intermediary stage between old 'tact and intuition' and (future) 'scientific medicine'. The latter would be rooted in (animal and other preclinical) experimentation (Morabia, 2007). In therapeutics – for the time being – one could not do without the probability of statistics; given constant progress, this was an unavoidable concession to pragmatism. Had it not been shown recently, by '*comparative experiment [...] that treatment of pneumonia by bleeding, which was believed most efficacious, is a mere therapeutic illusion*' (Transl. from Bernard, 1865, p. 273). Of course, this was a hint to the shortcomings of Louis's research design and inferences.

Outlook

Despite his important contribution based on formal, mathematical probabilistic thinking, Gavarret seems to have had no followers in 19th-century French clinical thinking. If seen at all as useful in clinical evaluation, Louis's *méthode numérique*, sensibly used, was the way to use numbers. This implied unconscious probabilistic thinking. There was much confusion about the notions of statistics, experiment and experience on one level. On other levels, there stood issues of medical science versus medical art and of probability versus deterministic certainty. Explicit probabilistic thinking was hardly considered.

Trousseau's lengthy *Introduction* containing his epistemological considerations was not included in the rapidly published translations of the *Leçons cliniques* into English (1st edition 1868), Spanish and German. There had been neither a contemporary English edition of Gavarret's book, nor was Bernard's book published in English until 1927. However, Gavarret was extensively reviewed in *The British and Foreign Medical Review*, probably by its editor, John Forbes, a very astute, critical thinker.[16] And for various reasons, partly historical, partly out of intellectual curiosity, Gavarret became influential mainly in Germany, the USA (Warner, 2003, Bartlett, 1844) and, to some extent also in Britain.

(To be continued)

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Supplementary File: The references listed below are chosen as essential to the reading of the article. However, the full list of primary and secondary references is available online both on the Journalã s website as supplementary material, and with the original publication at https://www.jameslindlibrary.org/articles/probabilistic-thinking-and-the-evaluation-of-therapies-1700-1900/. Except when otherwise mentioned, translations into English are my own.

Note

a. The series on probabilistic thinking and the evaluation of therapies, 1700–1900, will be appearing as separate articles in the forthcoming issues of *JRSM*.

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