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COMMENTARY

Editors' note: The three commentaries that follow in this issue were composed independently, but all have common themes in describing the origin and evolution of clinical epidemiology. If the present is the prologue to the future, these accounts of past events can help illuminate and clarify the current status of the field.

—A.R.F.

P. C. A. Louis and the Birth of Clinical Epidemiology

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ABSTRACT. Pierre Charles Alexandre Louis (1787–1872) has been the direct or indirect mentor of influential U.S. and English scientists in public health, epidemiology, medicine, and biostatistics during the 19th and 20th century. Louis was primarily a clinician, but his name has been more closely associated with the history of epidemiology. There is an imbalance between the fame of Louis's scientific contribution and the scarcity of in depth analyses of his work. The controversy related to the usage of bloodletting for treating inflammatory diseases is one of the most famous episodes of Louis's work. A modern analysis of Louis's data confirms his original conclusions; that is, early bloodletting seems to reduce the duration of a pneumonitis disease in patients who survive from this disease but may also increase the overall short-term mortality. Some basic algebraic mistakes in computations of means tend to attenuate the verdict against bloodletting, but these are trivial relative to the rigor of the overall demonstration and to Louis's methodological contribution to clinical observation. Louis firmly belongs to the history of epidemiology. He deserves a similar place in the history of medicine. *Copyright © 1996 Elsevier Science Inc.* J CLIN EPIDEMIOL 49;12:1327–1333,1996.

"It is truth only he loves"
(J. J. Jackson, 1836, p. XX).

Pierre Charles Alexandre Louis (1787–1872) (Fig. 1) has been the direct or indirect mentor of influential U.S. and English scientists in public health, epidemiology, medicine, and biostatistics during the 19th and 20th centuries [1,2]. According to William Osler, Louis has "special claims to remembrance . . . to have created the American school of clinical medicine through his pupils" [3]. These pupils were, among others, Oliver Wendell Holmes, George Cheyne Shattuck, and Henry I. Bowditch [4]. His seminal papers on typhoid fever or tuberculosis as well as his criticism of bloodletting in the treatment of inflammatory diseases are legendary. The influence of PCA Louis's work can also be traced to modern epidemiology. His pioneering work was recognized in Feinstein's 1967 book on "clinical judgment" [5] and has been since then regularly mentioned in textbooks of clinical epidemiology [6–9] and of epidemiology [2].

Louis was born on 14 April 1787, in Ay, France [10]. He studied medicine and went to Russia in 1814. He practiced in Odessa, where an epidemic of diphtheria occurred in 1820. "Louis was shocked by his inability to combat the disease. . . . He decided to throw up his practice and study medicine again" [11]. After returning from Russia to France at age thirty-two, Louis decided to devote himself to observation of disease as it presented itself. His motto was "Ars medica tota in observationibus" [3], that is, the medical art entirely consists of observations. During seven years at La Charité, Louis carefully recorded 2,000 clinical observations plus autopsy of patients. About this period, J. J. Jackson, an American student of Louis and editor of a translation of Louis's book on bloodletting, wrote [12]:

> So far as I have known Mr. Louis is the only physician who has devoted himself for years together, at a mature age and after sufficient education, to simple observation, without the distraction of medical practice, and without having any share in the treatment of the cases under his observation.

As a result, Louis developed a unique method of standardized data collection that Jackson summarized as follows [12]:

> First we must be careful as to our diagnosis; and second, we must be accurate as to the period of disease; third we must be minute in noting the particulars, in which amendment is produced; and fourth, we must be precise in stating the extent and the manner, in which the remedy is employed.

Louis was then able to tabulate the data collected. This approach illuminated the existence of new clinical entities such as typhoid fever. The originality of Louis was to apply to medicine a standardized method of data collection and analysis, which he called the "numerical method."

Louis's scientific contribution has never been scrutinized from a modern epidemiological perspective. What was the quality of the data Louis collected and analyzed? Do his results and conclusions resist a modern audit? In this commentary, I present, reanalyze, and discuss Louis's famous scientific contribution to the bloodletting controversy.

THE BLOODLETTING CONTROVERSY

The controversy related to usage of bloodletting for treating inflammatory diseases is a frequently quoted episode of Louis's work.

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FIGURE 1. Portrait of P. C. A. Louis.

When Louis decided to assess the efficacy of bloodletting, this treatment was not considered absurd or archaic. In 1836, J. J. Jackson wrote [12]:

> If anything may be regarded as settled in the treatment of diseases, it is that bloodletting is useful in the class of diseases called inflammatory; and especially in inflammations of the thoracic viscera.

The French Revolution had even given a new impetus to bloodletting. According to Niebyl [13] there was a "bloodletting revolution" in England and in France during the first half of the 19th century. Its origins are not clear. Leeches had become popular during the Revolution when not enough surgeons were available for venesections [13]. Ideologically, leeches and bloodletting were said to be in harmony with political liberalism because they acted by "relieving the patient from oppression," in contrast to the "medicine of symptoms" that treated nature as an "autocrats who needs supportive therapy" [14].

Around 1820, Paris still lived in the aftermath of the Revolution. Françis Joseph Victor Broussais (1772–1838) was an influential figure in medicine, known for his liberal opinions. He believed that diseases were not independent clinical entities but different manifestations of a nonspecific inflammation. Organ inflammation produced nonspecific signs, such as fever, or organ-specific symptoms such as cough or intestinal pain. But all inflammations could benefit from a universal treatment consisting of bloodletting as antiphlogistic and of light diet. Broussais therefore advocated bleeding and leeches for almost all diseases. Leeches had to be applied on the surface of the body corresponding to the inflamed organ. For example, the chest of a patient suspected of having tuberculosis was covered with a multitude of leeches. At the time of Broussais's apogee, France used tens of millions of leeches per year. In 1833, it imported 42 millions of these annelid worms.

Broussais had been the leader of Paris medicine since 1816, but after 1832, his theories rapidly lost support [13 p. 67]. What has been the influence of Louis in the progressive decline of the practice of bloodletting? To answer this question we must first review what has been Louis' scientific contribution.

LOUIS'S STUDY

There are three different publications of Louis's work on the efficacy of bloodletting. The first appeared as an article in the 1828 Annales de Médecine Générale [15]. This paper was revised and amplified to be published as a book in 1835 [16]. The book was translated and published one year later in America [17], with a preface and an appendix by J. J. Jackson.

Louis used the following rationale to determine the efficacy of bloodletting ([16], page 55; [17], pages 70–71):

> What was to be done in order to know whether bloodletting had any favorable influence on pneumonitis, and the extent of that influence? Evidently to ascertain whether, other things being equal, the patients who were bled on the first, second, third or fourth day, recovered more readily than those bled at a later period. In the same manner, it was necessary to estimate the influence of age, or any other circumstance, on the appreciable effects of bloodletting.

Louis found in his clinical records 77 patients with pneumonia who were in perfect health at the time of the first symptoms of the disease. Twenty-seven of them died. For each patient, he computed the duration of illness ([17], pages 7–8):

> I have regarded the commencement of the disease, the period when the patient has experienced a febrile affection, more or less violently, which has been followed or accompanied by pain on one side of the chest and by rusty sputa; these two symptoms appearing at the same time or nearly at the same time; and I have regarded as the time of convalescence the period at which the sick began to take some light nourishment, three days at least after the febrile action had ceased, although the local symptoms had not disappeared in every case.

Louis analyzed the duration of disease and the risk of dying according to the time of the first bleeding during the course of the disease. Because of the small sample size, he grouped those first bled during days 1 to 4 of the disease (*early bloodletting*) and those bled for the first time during days 5 to 9 after the onset of the disease (*late bloodletting*). Results were presented as in Figures 2 and 3. I have summarized them in Table 1. The two groups of patients were of comparable age. Average number of bleedings were 2.8 in those bled earlier and 2.3 in patients bled later. Duration of disease was, on average, 3 days shorter in those with early bloodletting (17.8 days) than in patients with late bloodletting (20.8 days). However, risk of death was 44% in the patients bled during the first 4 days of

1	2	3	4	5	6	7	8	9
10 3	7 3	19 3	19 3	28 2	13 1	24 2	19 2	35 1
12 2	10 2	29 3	12 2	17 3	16 2	12 4	12 1	11 2
14 2	12 2	20 2	15 2	40 2	23 3	19 2	18 1	17 2
		20	22 4	13 2	35 5	18 2	20 3	30 3
		16 3	12 4	21 2	17 2	15 2	13 2	
		17 4	21 2	13 2		27 2	21 2	
			25 3					
			28 4					
			40 2					
			16 2					
			12 4					
12 $2\frac{1}{3}$	10 $2\frac{1}{3}$	20 3	20 8	22 2	21 $2\frac{3}{5}$	19 $2\frac{1}{3}$	17 2	23 2

The figures upon the horizontal line above the columns indicate the day when the first bleeding was performed ; the figures on the left in each column mark the duration of the disease ; those on the right, the number of bleedings ; and those on the horizontal line below, show the mean duration of the disease and the average number of bleedings.

FIGURE 2. Duration of disease and number of bleedings in patients who survived, by day of the first bleeding [17]. The original legend is reproduced.

1	2	3	4	5	6	7	8	9
6 5 18	53 5 65	4 1 57	29 2 19	16 4 58	62 4 20	20 2 68	25 1 40	22 1 50
	12 3 69	16 2 54	29 4 46	8 2 63	10 2 40			
	8 2 65	6 3 30	12 1 85	9 4 24	29 3 24			
	12 1 55	6 4 47	15 3 37					
	17 7 75	47 2 75	17 1 67					
		11 4 45	20 3 22					
6 5 18	20 3 3-5 66	15 3 51	20 $2\frac{1}{3}$ 49	11 3 48	33 3 28	20 2 68	25 1 40	22 1 50

FIGURE 3. Duration of disease, number of bleedings and age in patients who died, by day of the first bleeding [17]. See Figure 1 for explanations.

TABLE 1. Age, number of bleedings, duration of illness, and risk of death according to day of first bleeding in Pierre-Charles-Alexandre Louis's "Researches on the effects of bloodletting . . . ."

Day of first bleeding	No. of subjects	Mean age (years)	No. of bleedings	Duration of disease (days)	Mortality (%)	Relative risk[a] (95% CI[b])
1–4	41	41	2.8	17.8	44	1.8 (0.9–3.5)
5–9	36	38	2.3	20.8	25	1.0 (reference)
Total	77	40	2.6	19.2	35	—

Sources: [16, 17].
[a]Not computed by Louis.
[b]CI = confidence interval.

the disease compared with 25% among those bled later. "A startling and apparently absurd result," according to Louis ([17], page 9).

When examining only those who survived, duration of disease remained, on average, shorter in those with early bloodletting (17.7 days) than in patients with late bloodletting (20.3 days). Among those who died, the average age was 51 in those bled in days 1–4 versus 43 in those first bled later.

In his interpretation, Louis took into account both the reduction in duration of disease and the increased mortality. Overall, he did not condemn bloodletting. He concluded that the effect of bloodletting was "much less than has been commonly believed" [17]. It is important to quote Louis since his conclusions are less stringent than the legend suggests ([17], page 13):

> Thus, the study of the general and local symptoms, the mortality and variations in the mean duration of pneumonitis, according to the period at which bloodletting was instituted; all establish narrow limits to the utility of this mode of treatment.

In his view, the validity of the technique was limited to severe cases pneumonia ([17], page 23):

> I will add that bloodletting, notwithstanding its influence is limited, should not be neglected in inflammations which are severe and are seated in an important organ; both on account of its influence on the state of the diseased organ; and because in shortening the duration of the disease, it diminishes the chance of secondary lesions.

Louis also thought that abundant bleeding worked better than local bleedings ([16], page 23):

> These observations seem to show that the use of the lancet should be preferred to that of leeches in the diseases which we have been considering.

The data, as reported by Louis in Figures 2 and 3 can be analyzed using life-table technique of survival analysis. Figure 4 compares the survival of patients with early or later bloodletting. The group bled during the first four days of disease had a worse survival during all the follow-up period. The *p*-value being 7%, the difference between the two curves cannot be formally viewed as statistically significant at the 5% level [18]. Thus, if the survival analysis does not provide statistically significant evidence that early bloodletting kills more than late bloodletting, it rules out a protective effect of early bloodletting.

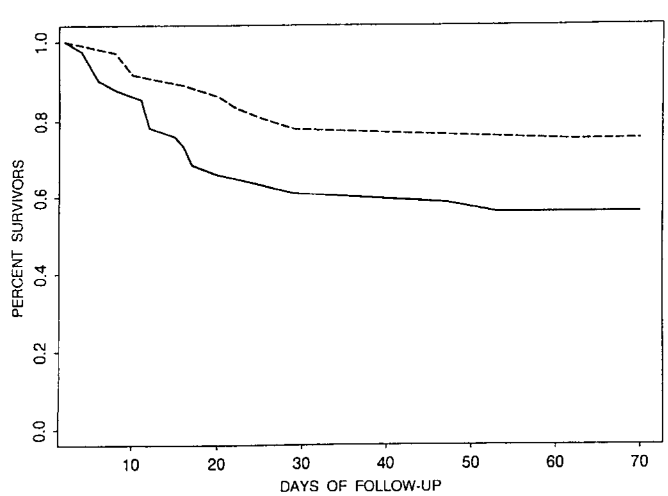

FIGURE 4. Survival by day of first bleeding, using data presented in Figures 2 and 3. Bled Days 1–4 (*solid line*), bled Days 5–9 (*dashed line*), log rank $p = 0.07$.

THE ENIGMA OF THE WRONG MEANS

Reanalysis of Louis's results on duration of disease has led to a puzzling discovery. In the original French versions of the tables, there are several mistakes in computing means. These mistakes have been corrected in the American version printed in 1836, one year after the French version of 1835. Table 2 compares the means in the original French version with those reported in the American translation. The average duration of illness is wrong in the original version for days 4, 5, and 6 in patients who died, and for days 3, 4, and 6 in patients who survived. In another table of "Recherches sur les effets de la saignée . . ." [16] describing the results from an additional series of 25 cases treated between 1830 and 1833, 6 out of 14 means are wrong in the French book [16] but correct in the American translation [17] (not shown in a table or figure).

Louis wanted to present arithmetic means. All other means computed in the book are arithmetic. In addition, Louis gave in the text the correct arithmetic mean for duration of disease in patients who survived computed on the basis of the raw data shown in Figure 2. The American translation of Louis's work reproduced in Figures 2 and 3 gives arithmetic means.

Can these wrong means be attributed to Louis's negligence? This seems very unlikely. With the exception of six additional wrong means in another table of the French edition (also corrected in the American translation), I did not find other mistakes in the many tables presented in the book. The raw data for the same patients shown in different tables were always consistent.

Some errors appear to be typos made by the printer. This is very clear when comparing the 1828 paper with the 1835 book. The number of bloodlettings of the third patient who was first bled in day 4 and survived, is missing in the book, but was 2.0 in the 1828 paper. The American version was translated from the French book since we find the same omission (see Fig. 2). But all other wrong means cannot be explained by typos and were all corrected in the American translation.

We must therefore consider the possibility that Louis did revise the observations in the tables. Louis may have deleted cases but failed to change the column means. A hint for this hypothesis is the discrepancy between the number of dead subjects analyzed and a sentence in the text introducing the "facts relative to fatal cases" ([17], page 9). Louis writes that: "Out of twenty-eight cases in question, eighteen were bled within the first days of the disease, nine from the fifth to the ninth." One case is missing since 18 + 9 = 27 and not 28. If so, means would be wrong because they have computed on the basis of a larger sample than that presented in the final tables. But this explanation can hardly be reconciled with the fact that the corresponding mean number of bloodlettings in the same tables for the same days are usually correct. As shown in Table 2, the exception is the mean number of bleedings of day 6 in patients who survived. If patients had been omitted without changing the means, both mean duration of disease and mean number of bloodletting episodes should have been wrong. Another hypothesis could be that Louis modified the duration of illness of some patients. The problem with this interpretation is that the correct means, that is, those computed from the raw data, tend to show more benefit from bleeding than do the wrong means presented in the tables. The wrong means suggest that the duration of disease *among those who survived* was 18.2 days for days 1–4 and 20.0 for days 5–9, that is, a reduction in duration of disease of 1.8 days for those bled earlier, while the correct means (supposedly after modification of the crude data) show a reduction of 2.6 days in duration of disease for those

TABLE 2. Mean duration of the disease and mean number of bleedings according to day when the first bleeding was performed in the original, French version [16] and in the American translation [17] of Pierre-Charles-Alexandre Louis's "Researches on the effects of bloodletting . . . ."

Variable	Life status	Version of the book	Day during the course of the pneumonitis in which the first bleeding was performed								
			1	2	3	4	5	6	7	8	9
Duration	Dead	Original	6	20	15	18	64	23	20	25	22
		Translation[a]	6	20	15	20	11	33	20	25	22
	Survived	Original	12	10	18	19	22	22	19	17	23
		Translation[a]	12	10	20	20	22	21	19	17	23
Bleedings	Dead	Original	5	3	3	2 1/3	3	3	2	1	1
		Translation[a]	5	3 3.5[b]	3	2 1/3	3	3	2	1	1
	Survived	Original	2/3	2 1/3	3	8	2	2 2/5	2 1/3	2	2
		Translation[a]	2 1/3	2 1/3	3	8	2	2 3/5	2 1/3	2	2

Sources: [16, 17].
[a]Data used to compute the means of the translated version are given in Figures 1 and 2.
[b]Should be 3/5 but printed 3.5 in the translation (see Figure 3).

bled earlier (17.7 versus 20.3 days). Therefore, if anything, Louis's scrutiny of the data would have finally attenuated a verdict that severely condemned bloodletting.

There is also a third explanation (beyond typos and fraud) to this enigma of the wrong means. Louis was opposed to the systematic and universal usage of bloodletting but maybe was not intimately convinced that bloodletting had to be banished from clinical practice. He may have found his results too strong in relation to his expectations and therefore tortured his observations, repeatedly checking if they were accurately reported. The process produced inconsistencies in the published tables that were spotted and corrected later either by him or by the American translator. This interpretation is tempting because such scenario is not unique in the history of medical sciences. Like Louis, Gregor Mendel (1822–1884) was a precise and meticulous recorder of data, oriented toward the study of populations rather than of the single individual, and fascinated with numerical relationships ([19], page 71). R. A. Fisher found that some of Mendel's results looked "too good" compared with what could be expected from statistical variability [20]. According to Mayr ([19], page 719), it is possible that Mendel unconsciously introduced bias in his experiments and, for example, threw away a few particularly deviant observations, thinking that they had been falsified by foreign pollen. However, there is no evidence that deliberate falsification was involved. A similar phenomenon may have occurred to Louis. However, one may argue that the errors done by Louis were relatively minor and that he could have surely done a better job had he really wanted to throw away "deviant" observations.

METHODOLOGY AND CAUSAL THINKING

A modern analysis of Louis's data confirms his original conclusions, that is, bloodletting seems to reduce the duration of disease in patients bled early during the course of a pneumonitis, but may also increase the short-term mortality. As J. J. Jackson summarized it [12]:

> The results of these observations is that the benefit derived from bleeding in the diseases, which [Louis] has here examined, are not so great and striking, as they have been represented by many teachers. If the same results should be obtained by others, after making observations as rigorous as those of M. Louis, many of us will be compelled to modify our former opinion.

Studying Louis's work leaves no doubts that he was a rigorous and meticulous scientist. The standardized data collection, the quantitative analysis and the concepts used by Louis are modern even though the statistical strategy is not. First, Louis's work is based on the principle that the effect of a cause can be observed by comparing two populations differing with respect to their exposure to the studied cause. Louis compared two groups of patients according to whether they had been bled early or later during the course of the disease.

A second modern aspect of Louis's methodology is the way he addressed the possibility that differences between the groups compared may have been introduced by what epidemiologists today would call "confounding." He checked whether subjects bled later did not differ from those bled early with respect to "causes which, independently of the period of the first bleeding, must have effected some difference in the mean duration of the disease" ([17], page 6). These were diet before bleedings, age, severity of symptoms at the beginning of the disease, and treatments other than bloodletting.

Third, Louis stated the questions related to prescribing bloodletting as a decision analysis problem. Bloodletting was considered as one of the most solid therapeutic techniques available. Louis did not refute the general opinion that bloodletting was indicated for diseases of the chest. He used observations on 77 patients to weigh its risk and its utility. He concluded that: (a) bloodletting was useful but potentially dangerous; (b) it should not be prescribed indiscriminately nor should it be completely proscribed; (c) it should be limited to patients in which the risk/benefit ratio was the largest, that is, patients with severe forms of the disease; and (d) when used, bloodletting should be abundant. These conclusions were balanced but still provocative for 1830 medicine.

On the other hand, Louis's study is premodern because allocation of treatment was not randomized. Louis was in theory aware that the validity of his methodology relied on the comparability of the treatment groups. He wrote unambiguously that ([16], page 75; [17], page 59):

> In any epidemics, let us suppose five hundred of the sick, taken indiscriminately, to be subjected to one kind of treatment, and five hundred others, taken in the same manner, to be treated in a different mode; if the mortality is greater among the first than among the second, must we not conclude that the treatment was less appropriate, or less efficacious in the first class than in the second? It is unavoidable; for among so large a collection, similarities of conditions will necessarily be met with, and all thing being equal, the conclusion will be rigorous.

This sounded like an early definition of the randomization principle introduced by Ronald A. Fisher (1890–1962) about one century later and applied to medicine for the first time in 1931 [21]. However, in his study, bloodletting was not randomized and we may wonder whether the patients bled earlier were really comparable to those bled later in the course of their disease. Patients who came rather late to see a doctor had survived the early phase of the disease. They were likely to have a better prognosis than the patients with immediate dramatic disease who managed to be brought moribund to a doctor by their relatives early in the course of the disease. The possibility of such selection bias was also addressed by Louis ([17], pages 6–7):

> Nevertheless, in regard to the foregoing remarks on the causes which, independently of the period of the first bleeding, must have effected some difference in the mean duration of the disease, it will be said perhaps that the pneumonitis was less severe in the patients bled at a late period, than in those bled on the first days of the disease: that it was undoubtedly for this reason that the former delayed application for medical aid; and that in this manner conditions, unfavorable to the rapid termination of the disease, were compensated. But having appreciated with all the exactness, of which I am capable, the symptoms experienced by patients at the commencement of their disease, and at their entrance into the hospital, I have found cases of severe or mild peripneumonia in a nearly equal proportion among the different groups of subjects; so that, supposing any mistake on my part, it could not be important enough to effect a material difference in the results stated, and to warrant us in rejecting the conclusions drawn from the analysis, which I have given. Physicians not much conversant with hospitals, or who seldom practise among the laboring classes, will not readily give credit to these remarks; but those differently situated are aware that, whether it be from indifference, or dislike to hospitals, patients seldom enter until quite late; even when their diseases have been very violent from the beginning.

Finally, Louis did not perceive the difference between misclassification bias and confounding. He considered that the virtue of group comparisons was to balance classification errors and possibly compensate them ([17], pages 59–60):

> For among so large a collection, similarities of conditions will necessarily be met with, and all things being equal, except treatment, the conclusion will be rigorous. . . . By so doing, the errors (which are inevitable) being the same in the two groups of patients subjected to different treatment, mutually compensate each other, and they may be disregarded without sensibly affecting the exactness of the results.

To my knowledge, it has taken more than a century [22] to demonstrate that balancing sources of bias across treatment group, especially if they lead to misclassification, does not necessarily remove bias from the measure of effect.

THE BIRTH OF CLINICAL EPIDEMIOLOGY

The present analysis of Louis's work sheds a new light on Louis's place in the history of medicine. Louis had apparently no mentor in public health or epidemiology. His motivations were essentially those of a clinician. After his return from Russia, he must have felt that medical observation was still in its infancy. He therefore decided to teach himself how to collect comparable observations. He was convinced—like many scientists of this time—that there were natural laws to be discovered in medicine, and that these could be derived from observation of the human body. He was probably familiar with Newtonian achievements in physics as well as with the works of Lavoisier and Condorcet [2].

The major contribution of Louis was his method of making good clinical observations rather than the algebra. The numerical method consisted of obtaining reproducible observations in order to tabulate and count them. Without standardized observations, clinicians could only discuss one case at a time. With the numerical method, it became possible to summarize information from groups or populations of patients and assign probabilities: prevalence of signs and symptoms associated with a given disease, risk associated with natural history or with treatment, etc. By analogy, Louis did to clinical medicine what William Farr (1807–1883) did later to vital statistics. Farr standardized the way mortality data was recorded and made epidemiologic analysis of this data possible. The numerical method of Louis was a standardized way of clinical data collection, it made clinical epidemiology possible. As J. J. Jackson wrote in his preface [12]:

> I have been satisfied that the physicians of Paris were laying the firmest foundation from the science of therapeutics, by studying the natural history of diseases; and by thus giving us rules for diagnosis and prognosis.

The specific contribution of Louis to this historical decline of bloodletting was to make a particular study of this therapeutics and to bring into the open its apparent inefficacy in the treatment of pneumonia ([23], page 44). The enthusiasm about bloodletting was already mitigated among Louis's contemporaries. For example, Corvisart, Laennec, and Andral were no less skeptical than Louis about Broussais's claims that letting blood through leeching was indicated for virtually all diseases ([23]; page 44). On the other hand, bloodletting may have been extremely valued for the treatment of generalized edema or "dropsy." Nowadays, we know that the fluid overload in dropsy is caused by end-stage failure of the lung, the liver, the kidney, or the heart, and we treat it with diuretics. Before diuretics were invented, a bleed of half a liter or a dozen leeches on the ankles could produce similar instantaneous relief [24]. Confusion between pneumonia and heart failure may not have been rare. Thus, doctors and their patients could reasonably hesitate to withhold phlebotomy completely. Even though the case against bloodletting was already well advanced at the time of Louis, a century of progress in medical knowledge was required to settle it completely.

There are still several unanswered questions about Louis. First of all, if Louis established the foundations of clinical epidemiology, why was he more remembered in public health rather than in medicine? One reason may be that his major contribution was more methodological than clinical. We just saw that the influence of Louis in the progressive decline of bloodletting was original but not decisive. The methods he used were later developed and sharpened by epidemiologists concerned by public health rather than clinical questions. He therefore occupied a natural place in the history of epidemiology. However, Louis was not associated with a clear-cut breakthrough in diagnosis, in contrast to his contemporaries Corvisart or Laennec, or in therapeutics. Therefore he was not retained in the mainstream of medical history. A second, more general reason has to do with the late adoption by the medical community of the epidemiological methods to investigate clinical hypotheses. The successes of bacteriology favored determinism rather than probabilism in French medicine. Claude Bernard (1813–1877), who has been an authority for French and non-French medical researchers for many years, wrote about "statistics" in his major opus ([25], pages 134 and 139):

> By destroying the biological character of phenomena, the use of averages in physiology and medicine usually gives only apparent accuracy to results. . . . In a word, if based on statistics, medicine can never be anything but a conjectural science.

These were the dominant thoughts in the mid-19th century that have hindered the growth of clinical epidemiology and statistics for many more years after Louis's death.

A second question is related to the basic algebraic mistakes in computations of means found in Louis's book that cannot be explained as consequence of negligence. Why weren't the American editor (Elisha Bartlett) or J. J. Jackson not worried by these mistakes? The most likely explanation is that they regarded them as trivial relative to the revolutionary dimension of the method of Louis. This is exemplified by Bartlett's comment on the attempt by Jackson to reproduce Louis's study in 34 patients admitted to the Massachusetts General Hospital from April 1825 to May 1834. Results were similar. Barlett editorialized that [26]:

> Dr Jackson himself, one of the most careful, and accurate, and sagacious, and matter of fact observers, did not know the results of his experience in the treatment of pneumonitis, till he adopted this system [the numerical method—AM], had counted and analyzed his cases.

In conclusion, it is reasonable to say that the scientific work of Louis has given birth to a new scientific discipline that today is referred to as clinical epidemiology. Its basic concepts, probability and population thinking, have gained popularity in medicine mostly during the second half of the 20th century. During the last 25 years, its importance has grown in medical departments and schools. Louis's contribution firmly belongs to the history of epidemiology. It is time to recognize its place in the history of medicine.

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References

1. Hinsdale G. The American medical argonauts pupils of Pierre Charles Alexandre Louis. **Transact and Studies of the College of Physicians of Philadelphia** 1945; 13: 37–43.
2. Lilienfeld AM, Lilienfeld DE. **Foundation of Epidemiology. Second Edition**. New York: Oxford University Press; 1980.
3. Massey, RU. Pierre Louis and his numerical method. **Conn Med** 1983; 53: 613.
4. Steiner WR. Dr. Pierre-Charles-Alexander Louis, a distinguished Parisian teacher of American medical students. **Ann Med Hist** 1940; 2: 451–460.
5. Feinstein AR. **Clinical Judgement**. Baltimore: Williams & Wilkins; 1967, pp. 220–224.
6. Feinstein AR. **Clinical Epidemiology: The Architecture of Clinical Research**. Philadelphia: Saunders; 1985, pp. 5–6.
7. Jenicek M, Cléroux R. **Epidémiologie Clinique. Clinimétrie**. St-Hyacinthe, Quebec: Edisem; 1985, pp. 19–20.
8. Fletcher RH, Fletcher SW, Wagner EH. **Clinical Epidemiology: The Essentials. Second Edition**. Baltimore: Williams and Wilkins; 1988, pp. 89–90.
9. Kramer MS. **Clinical Epidemiology and Biostatistics**. Berlin: Springer-Verlag; 1988, pp. 8–9.
10. Astruc T. **Pierre Charles Alexandre Louis. Les Biographies Médicales**. Paris: Librairie J.-B. Baillère; 1933, pp. 245–260.
11. Greenwood M. Louis and the numerical method. In: **The Medical Dictator and Other Biographical Studies**. London: Keynes; 1986, pp. 75–87.
12. Jackson JJ. Preface. In: **PCA Louis. Research on the Effects of Bloodletting in Some Inflammatory Diseases**. (Putnam CG, transl.) Boston: Hilliard, Gray and Company; 1836.
13. Ackerknecht EH. **Medicine at the Paris Hospital 1794–1848**. Baltimore: The Johns Hopkins Press; 1967.
14. Niebyl PH. The English bloodletting revolution, or modern medicine before 1950. **Bull Hist Med** 1977; 51, pp. 464–483.
15. Louis, PCA. Recherche sur les effets de la saignée dans plusieurs maladies inflammatoires. **Archives Générales de Médecine** 1828; 18: 321–336.
16. Louis, PCA. **Recherches sur les effets de la saignée dans quelques maladies inflammatoires et sur l'action de l'émétique et des vésicatoires dans la pneumonie.** Paris: Librairie de l'Académie Royale de Médecine; 1835.
17. Louis PCA. **Research on the effects of bloodletting in some inflammatory diseases.** (Putnam CG, transl.) Boston: Hilliard, Gray and Company; 1836.
18. Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. **Biometrica** 1982; 69: 553–566.
19. Mayr E. **The Growth of Biological Thought: Diversity, Evolution, and Inheritance**. Cambridge: Harvard University Press; 1982.
20. Fisher RA. Has Mendel's work been rediscovered? **Ann Sci** 1936; 1: 115.
21. Amberson JB, MacMahon BT, Pinner M. A clinical trial of sanocrysin in pulmonary tuberculosis. **Am Rev Tuberculosis**. 1931; 24: 401–435.
22. Newell DJ. Misclassification in 2 × 2 tables. **Biometrics** 1963; 19: 187–188.
23. Bynum WF. **Science and the Practice of Medicine in the Nineteenth Century**. Cambridge: Cambridge University Press; 1994.
24. Kiple KF. **The Cambridge World History of Human Disease**. Cambridge: Cambridge University Press; 1993, pp. 689–693.
25. Bernard C. **An Introduction to the Study of Experimental Medicine**. New York: Dover; 1957, pp. 129–140.
26. Bollet, AJ. Pierre Louis. The numerical method and the foundation of quantitative medicine. **Am J Med Sci** 1973; 266: 92–101.